Outcomes of the arterial switch operation.

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Abstract

The last few decades have seen great advances in the world of paediatric cardiac surgery. In particular, the arterial switch operation (ASO) is one of the specialty's most impressive achievements. It is the procedure of choice for most children born with transposition of the great arteries (TGA).

This project aimed to expand our understanding of the long-term outcomes and prognosis of patients who have had an ASO for TGA. The ultimate goal of this work was to not only increase clinicians' knowledge of the long-term consequences of the ASO but also to allow cardiologists, cardiac surgeons and paediatricians to give the parents of patients, and patients themselves, more information about their future cardiac health.

We aimed to achieve these goals by retrospectively reviewing patients who underwent an ASO at The Royal Children's Hospital in Melbourne. This unit has performed the ASO for more than 30 years with a very low hospital mortality from the beginning. This allows for review of a large population of surviving patients from which long-term outcomes can be investigated, and makes possible the analysis of rarer subgroups of patients undergoing the ASO.

We showed that the long-term outcomes of patients undergoing the ASO are generally good extending into young adulthood. However, reintervention is common and the incidence of clinically significant neo-aortic regurgitation or the need for neo-aortic root reoperation remains an issue for survivors with more than 25 years of follow-up. In regards to the subgroups examined, we showed that patients with intramural coronaries can be operated with excellent long-term outcomes using a simple, reproducible technique. Children who are less than 2.0 kilograms at time of ASO represent one of the highest mortality risk subgroups. Female adult survivors can undergo pregnancy with a low risk of maternal cardiac complications. Patients with associated aortic arch obstruction have a higher rate of reintervention for right sided obstruction and have a low rate of recurrent arch obstruction when avoiding the use of patch material. We also demonstrated that quality of life in adult ASO survivors was comparable to the general population using a validated quality of life questionnaire.

Declaration

This is to certify that:

(i) The thesis comprises only my original work towards the PhD except where indicated in the Preface,

(ii) Due acknowledgement has been made in the text to all other material used,

(iii) The thesis is fewer than 100 000 words in length, exclusive of tables, maps, bibliographies and appendices.

Preface

This work is original, except where acknowledgements and references are made to previous work. Data collection, analysis, writing and revision of manuscripts were all performed primarily by myself.

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I would like to thank Professor Igor Konstantinov for inspiring me as a young medical student to become an academic cardiac surgeon.

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1. Intramural coronary arteries are not a risk factor for mortality in the arterial switch operation. Poster presentation. 95th Annual Meeting of American Association for Thoracic Surgery, Seattle, USA, 2015.

2. Outcomes of the arterial switch operation in adult survivors. Australian and New Zealand Society of Cardiac and Thoracic Surgeons Annual Scientific Meeting, Adelaide, Australia, 2015.

3. Outcomes of the arterial switch operation in patients with concomitant aortic arch obstruction as a single stage repair. Australian and New Zealand Society of Cardiac and Thoracic Surgeons Annual Scientific Meeting, Cairns, Australia, 2016.

4. Long-term pulmonary valve function after the Ross procedure. Australian and New Zealand Society of Cardiac and Thoracic Surgeons Annual Scientific Meeting, Noosa, Australia, 2018.

5. The impact of coronary artery anatomy on mortality after the arterial switch operation in more than 1,000 patients. 99th Annual Meeting of American Association for Thoracic Surgery, Toronto, Canada, 2019.

Awards and scholarships during candidature

1. Health Professional Scholarship, National Heart Foundation of Australia

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List of abbreviations

AAO= aortic arch obstruction

AHA= American Heart Association

AR= neo-aortic valve regurgitation

ASO= arterial switch operation

HR= hazards ratio

LV= left ventricular

LVAD= left ventricular assist device

LVOTO= left ventricular outflow tract obstruction

MCS= mechanical circulatory support

NYHA= New York Heart Association

PA= pulmonary artery

PDA= patent ductus arteriosus

PS= pulmonary stenosis

SF-36= Short Form-36

SF-6D= Short Form-Six Dimension

TBA= Taussig-Bing anomaly

TGA= transposition of the great arteries

TGA-IVS= transposition of the great arteries with an intact interventricular septum

TGA-VSD= transposition of the great arteries with a ventricular septal defect

VSD= ventricular septal defect

Chapter 1: Introduction and literature review

1.1 Transposition of the great arteries and the arterial switch operation

Surgical repair of transposition of the great arteries (TGA) is one of the successes of cardiac surgery. Fatal if untreated, TGA is a congenital heart malformation that affects approximately 4 in 10000 births in Australia (1) and constitutes approximately 5% of all congenital heart malformations (2-4). In patients with TGA, the right atrium connects to the right ventricle from which arises the aorta and the left atrium connects to the left ventricle from which arises the pulmonary artery (PA). This is described as atrioventricular concordance and ventriculoarterial discordance. As a result, the systemic and pulmonary circulations run in parallel. Survival of children with TGA depends on mixing of saturated and desaturated blood between the two parallel circulations. This occurs through a ventricular septal defect (VSD), atrial septal defect or patent ductus arteriosus (PDA). Affected children present markedly cyanosed, typically in the neonatal period. If untreated, 95% of children born with TGA will not survive their first year of life (5).

The arterial switch operation (ASO) for TGA is the procedure of choice for all TGA patients, except those presenting with single ventricle physiology or severe semilunar valvular stenosis. It represents decades of research, failed attempts and, finally, the pursuit of perfection by paediatric cardiac surgeons.

The ASO is performed at The Royal Children's Hospital in Melbourne, Australia as described herein. Access to the mediastinum is achieved via a midline sternotomy. A pericardial patch is harvested from the anterior pericardium (two patches are harvested if a VSD requires closing). The ligamentum arteriosum (or PDA) is ligated and divided. Cardiopulmonary bypass is established with aortic and bicaval cannulation and the patient is cooled to 32°C. The aorta is cross clamped proximal to the cannulation site and cardioplegic heart arrest is achieved. The aorta and pulmonary artery are transected just above the semilunar valves. The two coronary arteries are excised and are translocated into medially based J-shaped cuts in the facing sinuses of the pulmonary artery. This is referred to as the trapdoor method of coronary translocation. The pulmonary artery is then

brought forward of the aorta to become the anterior great vessel (the Lecompte manoeuvre). The aorta, now the posterior great vessel, is anastomosed to the native pulmonary root (neo-aortic root). If a VSD is present, it is closed with a pericardial patch treated with glutaraldehyde. The defects in the neo-pulmonary root, where the coronaries were excised, are repaired using a pericardial patch. Once the pulmonary artery is reconstructed, the patient is rewarmed and cardiopulmonary bypass is weaned off and discontinued.

Of particular interest is that the aorta and pulmonary artery are transected above the level of the aortic and pulmonary valves respectively. This means that the native aortic root becomes the new (neo) pulmonary root and the native pulmonary root becomes the new (neo) aortic root. As such, the native pulmonary valve becomes the neo-aortic valve and the native aortic valve becomes the neo-pulmonary valve.

If an aortic arch repair is to be performed simultaneously, this is undertaken before the ASO. The arch repair is performed end-to-side with continuous aortic and cerebral perfusion, the patient is rewarmed to 32°C and the ASO is carried out as described above.

Timing of the ASO is critical. The current policy at The Royal Children's Hospital is to operate on TGA patients with an interventricular septum (TGA-IVS) children ideally within the first two weeks of life. Pulmonary vascular resistance falls after birth and the left ventricle in TGA-IVS patients does not have to eject against as high pressures. If an ASO is delayed much beyond two weeks, the deconditioned left ventricle (which becomes the systemic ventricle after the ASO) may not be able to cope with the increased pressures of the systemic circulation subsequent to the switch (4, 6). Conversely, TGA with a ventricular septal defect (TGA-VSD) children are operated on at two months of age since they do not experience the same decrease in pulmonary pressures because of blood flow through the VSD into the pulmonary circulation.

For TGA-IVS patients presenting beyond eight weeks of age, two options remain. Traditionally a pulmonary artery band has been placed around the main pulmonary artery to increase pulmonary artery pressures. This forces the left ventricle to eject to higher pressure once again, resulting in rapid left ventricular hypertrophy. An ASO can then be performed as soon as 7-10 days later, such a strategy is called a two-stage ASO. More

recently however, the policy has been to perform an ASO and place a left ventricular assist device (LVAD) at the same time. The LVAD shares the burden of systemic pressures with the left ventricle and as soon as the left ventricle is deemed able to eject unaided, the LVAD is removed. Reports of the effectiveness of this strategy have been published by other centres (7, 8).

While it is often referred to as an anatomical repair, problems after the ASO do arise. Late complications may be even more common in more complex subgroups such as patients with Taussig-Bing anomaly (TBA), associated aortic arch obstruction (AAO) or anomalous coronary anatomy. These subgroups are discussed later in this thesis. The long-term prognosis of patients after the ASO is considered favourable, however published long-term data are limited.

1.2 Survival after the arterial switch operation

The overall early mortality of the ASO for TGA has been reported in a range of 0-11% (9-26). Mortality for TGA-IVS varies from 0-6% compared to 4.7-13% for TGA-VSD (11-14, 18-20, 24, 27).

Outcomes of the ASO in patients with AAO are limited to fewer studies. Early mortality in these patients has ranged from 1.9% to 24% (28-36). Likewise higher operative mortality rates have been reported in patients with TBA compared to TGA (18, 22, 23, 37-39). Using the van Praagh definition, TBA is a form of true double-outlet right ventricle with the semilunar valves side-by-side and approximately at the same height, a bilateral conus in which both conal free walls are muscular and approximately equally developed, and a subpulmonary VSD (40, 41). Operative mortality of 5-6% has been reported in the 2 largest studies of TBA children (37, 42).

Higher early mortality for TGA-VSD patients has led to the presence of a VSD being labelled the most important risk factor for operative death (20). However, anomalous coronary artery anatomy, in particular abnormal patterns such as single coronary arteries and intramural coronary arteries, has been the most intensely studied risk factor for mortality. This will be discussed in Chapter 1.5 (Coronary anatomy and the arterial switch operation).

Survival rates have been quite well characterised at 5 and 10 years postoperatively, with 5 year survival quoted between 80-92% (12, 17, 22, 24, 38, 43, 44) and 10 year survival reported between 88-94.9% (12, 17-19, 24). Research into survival beyond 10 years postoperatively is now coming to the fore as the earlier survivors of the ASO reach adulthood, with 15 year survival described as ranging from 81-88% (19, 24, 43, 45). Studies focussing on late mortality have also showed that the risk of death after ASO falls dramatically after the first year of life. No deaths have been reported after 1 year (15, 38, 46, 47), 2 years (12) or 5 years (19) postoperatively. Because late death is quite rare, differences in long-term survival between TGA-IVS, TGA-VSD and patients with AAO are due to the early higher mortalities of TGA-VSD and AAO patients.

1.3 Reintervention after the arterial switch operation

Most reoperations after the ASO occur after the first postoperative year. Freedom from reoperation has been reported in a range of 79-97% at 10 years (12, 15, 18, 25, 30, 48-50), 76-87% at 15 years (15, 19, 25, 50) and 86% at 25 years (49).

The most common cause of late reoperation is pulmonary stenosis (PS) (10, 12, 14, 16, 18, 19, 22, 24, 25, 45, 48, 49, 51). The majority of the stenoses occur at the suture line in the neo-pulmonary artery and proximal pulmonary artery branches (22, 43, 48, 49, 52). The precise reason for PS post ASO is unclear, but may be related to inadequate growth of the pericardium used to reconstruct the pulmonary artery, narrowing at the suture line or flattening of the pulmonary artery due to the neo-aortic root pushing it anteriorly (43).

Reintervention encompasses both reoperation and catheter reintervention. Freedom from catheter reintervention figures are rarely separated from freedom from reintervention figures. However, it is clear that PS is also the most common cause for catheter reintervention (25, 48). Catheter reintervention for PS after 17 years of follow-up has been reported in 19% of ASO survivors (25).

Risk factors for reintervention are infrequently investigated because of low power to detect them. However, the presence of a VSD or AAO have both been confirmed as risk factors on multivariate analysis in selected studies (12, 22, 52).

1.4 Neo-aortic valve dilation and regurgitation

The exact mechanism of neo-aortic root dilation after ASO is unknown but it has been postulated that dedifferentiation of smooth muscle cells in the wall of the neo-aortic root, ultimately promoting dilatation, may be a contributing factor (53). Neo-aortic root dilation can be seen in up to 50% of ASO survivors by 10-15 years of age (54, 55). Likewise, the mechanism neo-aortic valve regurgitation (AR) is also unclear and is likely to be multifactorial. It has been suggested that AR in ASO survivors may be the result of altered geometry of the neo-aortic root or turbulence caused by the differences in size between the neo-aortic root and the distal aorta, both of which have the potential to inhibit coaptation of the valvular leaflets (56, 57).

While the presence of mild neo-aortic root dilation and AR is common after ASO, the incidence of neo-aortic root or valve replacement appears low in the first 10 years after ASO. Reoperation for these reasons has been reported between 0-2.9% (16, 21, 25, 43, 54, 56, 58, 59) for studies with a mean follow-up of 5-10 years. It appears that the incidence of clinically significant AR and neo-aortic root reoperation increases as follow-up lengthens after the ASO (60, 61). For example, Koolbergen and colleagues (62) found a freedom from neo-aortic root or valve reoperation of 95% at 25 years. Likewise, van der Palen et al (63) demonstrated that the neo-aortic root increased in size with age without a stabilisation of dimension. The incidence of significant AR in their cohort of 345 patients also increased over time with a freedom from at least moderate AR of 69% at 25 years after ASO.

The long-term ability of the neo-aortic root, which is the native pulmonary root, to withstand systemic pressures is still yet to be determined.

1.5 Coronary artery anatomy and the arterial switch operation

Anomalous coronary arteries are common in patients undergoing the ASO, making up approximately one third of children operated (64, 65). The most common variant of coronary anatomy pattern is the left anterior descending artery arising from sinus 1 and right and left circumflex coronary arteries arising from sinus 2 when described using the

Leiden classification (49, 64, 65). Such variation occurs in approximately 17% of patients (28). The second most common abnormal anatomy is a single coronary artery which occurs in 6-7% of patients (49, 66).

Whether abnormal coronary artery anatomy remains a risk factor for death is controversial with conflicting reports (12, 13, 28, 38, 64-71). A meta-analysis of 1942 patients (67) reported that any variant of coronary artery anatomy doubled the risk of death compared to normal coronary anatomy. In particular, the risk of death in patients with a single coronary artery or intramural coronary artery increased almost 3-fold and 7-fold, respectively. As the patients included in this meta-analysis were operated on between 1977 and 1999, this study may not have direct clinical relevance to today's operative outcomes. The largest study of outcomes of patients with single coronary arteries undergoing the ASO was published by Gerelli and colleagues (66). They found a significant mortality of 11% in 73 children with single coronaries. All deaths except 1 occurred in patients operated before 2001, suggesting a technical learning curve which has been encountered by their institution early in its experience.

In addition to single coronary arteries, patients with intramural coronary arteries also present a surgical challenge with conflicting results in the literature. An intramural coronary artery, unlike a normal coronary artery, does not exit from the aortic sinus wall immediately from its origin but runs in the aortic wall for some distance before exiting on to the epicardial surface of the heart. New techniques to translocate intramural coronaries are still being described today (72). The largest study on patients with intramural coronaries undergoing the ASO was reported by Metton and colleagues (68). Out of 919 patients, they reviewed 46 patients with intramural coronary arteries who underwent an ASO between 1987 and 2008. They found a mortality of 28%, including 11 deaths before discharge. Nine of the 11 deaths were deemed secondary to coronary complications. Conversely, Thrupp and colleagues (71) reported one death in 18 patients with intramural coronary arteries out of 215 patients who underwent ASO between 1996 and 2006.

1.6 Low operative weight children undergoing the arterial switch operation

Low operative weight has been identified as a risk factor for mortality in paediatric cardiac surgery (73-75). These infants represent not only a technical challenge to the surgeon but also have immature organ systems which may suffer a variety of complications. These children are often premature and suffer from a higher risk of infection, renal failure, respiratory disease, cerebral haemorrhage and necrotizing enterocolitis (76). Cardiopulmonary bypass adds a significant insult to children with this type of physiology. However, there is observational data to suggest that delaying cardiac surgery in low operative weight children to allow them to gain weight can be deleterious (77-80).

Only one study has specifically addressed low operative weight as a risk factor for mortality in TGA children undergoing surgery. This study, by Roussin et al (79), examined 25 infants with TGA who underwent surgery at a weight of less than 2.0 kilograms. Of the 25, 20 underwent an ASO and the overall mortality was 16%. This is clearly a significant mortality but published data on the outcomes of these children remains scarce.

1.7 Quality of life after the arterial switch operation

Improvement in operative mortality and a low incidence of late mortality has resulted in an ever-growing number of ASO survivors reaching adulthood worldwide. As these patients begin to reach adulthood, focus is now placed on the general health of these individuals. Research into health-related quality of life in patients with repaired congenital heart disease increases our understanding of the overall effect the condition has on survivors reaching adulthood. This may allow the development of future interventions to improve physical and psychosocial issues. Quality of life outcomes studies in ASO survivors have indicated quality of life comparable to the general population but have been limited by small sample sizes (81, 82). The largest study of quality of life in ASO survivors was published by Kalfa and colleagues (83). They investigated quality of life outcomes in 67 adult ASO survivors aged 18-31 years. Part of their methodology involved using the Short Form-36 (SF-36). The SF-36 is a validated health-related quality of life questionnaire that contains 36 questions across 8 mental and physical health domains. Overall, they found that adult ASO survivors had a satisfying

quality of life but with poorer results in the physical domains of the SF-36. The summary SF-36 score, the Short Form-Six Dimension (SF-6D), was not reported.

1.8 Pregnancy outcomes in arterial switch operation survivors

An increasing number of women who have had an ASO are reaching child-bearing age. Pregnancy represents a significant physiological challenge (84, 85) and has been shown to contribute to worse outcomes in some cardiac diseases (86-89). In particular, it has been demonstrated that pregnancy may be higher risk for both mother and child in repaired congenital heart disease (90, 91).

To date, reports of outcomes in ASO survivors undergoing pregnancy have been limited to one case report (92) and two series (93, 94). This paucity of data is recognised in the guidelines for managing patients with congenital heart disease undergoing pregnancy. The 2017 American Heart Association (AHA) guidelines (95) state that "women with an arterial switch repair are anticipated to do well in pregnancy" in the absence of significant residual haemodynamic lesions but acknowledge that outcomes in women undergoing pregnancy is limited to a single series (93). The modified World Health Organisation classification of maternal risk used in the AHA guidelines do not specifically mention ASO survivors. Likewise, the 2011 European Society of Cardiology guidelines (96) references the single study on ASO survivors undergoing pregnancy and advises that the risk of pregnancy in ASO survivors is low in patients with a good clinical condition pre-pregnancy.

The effect of pregnancy on female ASO survivors has not been extensively studied and it is unknown if women who have had an ASO are at a higher risk of cardiac and obstetric complications during and after pregnancy.

1.9 Thesis outline

This thesis, focussing on patients operated at The Royal Children's Hospital in Australia, provides novel information on outcomes of patients undergoing the ASO, with a particular emphasis on subgroup populations.

Chapter objectives

Chapter 2: Determine the outcomes of the ASO in patients operated at The Royal Children's Hospital with respect to mortality, reintervention, valvular function and functional status.

Chapter 3: Report the outcomes of the ASO in patients with intramural coronary arteries.

Chapter 4: Examine the outcomes of patients less than 2.5 kilograms undergoing the ASO.

Chapter 5: Compare quality of life in adult ASO survivors with age-matched population data using the SF-36 questionnaire.

Chapter 6: Report the long-term outcomes of patients undergoing the ASO with concomitant AAO.

Chapter 7: Examine the outcomes of ASO survivors who have undergone pregnancy with respect to maternal obstetric, maternal cardiac and neonatal outcomes.

Chapter 8: Determine the impact of coronary artery anatomy on mortality in more than 1000 children undergoing the ASO at both The Royal Children's Hospital and Queensland Children's Hospital.

Chapter 2: Long-term outcomes of the arterial switch operation

2.1 Introduction

The arterial switch operation (ASO) is one of the greatest success stories in surgery of the past century and is performed with excellent early outcomes in the modern era (9, 11, 28). With the expectation that a paediatric cardiac surgery unit can achieve a low operative mortality, focus has shifted to the long-term outcomes of adult ASO survivors. After the ASO, the patient's native pulmonary root becomes their neo-aortic root and the coronaries are transferred to this newly constructed vessel. There has been concern about the ability of the neo-aortic root to withstand systemic pressures and the long-term patency of the translocated coronaries since the ASO was first performed. Indeed, neo-aortic root dilatation is a well-known feature after ASO. Although neo-aortic root reoperations has been a rare event in adolescents and young adults (15, 21, 61, 97), the fate of the neo-aortic root remains unknown in older patients. An understanding of the long-term expectations after ASO is of particular importance, as there is a worldwide rapidly increasing population of adult survivors of the ASO. We now have sufficient data to assess the outcomes of patients with more than 25 years of follow-up after the ASO.

2.2 Methods

Patients

This study was approved by The Royal Children's Hospital Human Research Ethics Committee. Follow-up information was obtained from treating hospitals and physicians, including local and interstate adult congenital heart centres. Ethics approval was obtained from each participating hospital. Valvular function and qualitative assessment of left ventricular (LV) function was determined from echocardiography reports.

Patients with a biventricular circulation who underwent an ASO at The Royal Children's Hospital, Melbourne, between May 1983 and January 2015 were identified from The Royal Children's Hospital cardiac surgery database.

Definitions

Early death or reoperation was defined as death or reoperation occurring prior to hospital discharge or within 30 days of ASO. Reintervention was defined as reoperation or transcatheter procedure. Reoperation was defined as an operation on the heart or great vessels performed after the ASO excluding exploration for bleeding, wound debridement, mechanical circulatory support (MCS) and pacemaker replacement.

Functional status was described according to the New York Heart Association (NYHA) classification.

Surgical procedures

The ASO was performed as previously described (28). Coronary translocation was undertaken using medially based trapdoors. Concomitant arch repair was via an end-to-side repair where possible.

Statistical Analysis

Data were imported into Stata Version 12 (Stata Corp, College Station, Texas). Continuous variables were reported as a median with an accompanying interquartile range. Categorical variables were presented as frequencies and percentages. Kaplan-Meier curves were constructed to display freedom from the study's outcomes. The log rank test was used to detect differences in freedom from the study's outcomes between

groups. Cox regression analysis was used to determine risk factors for an outcome. A *p* value of less than 0.05 was considered statistically significant.

2.3 Results

Eight hundred and forty-four patients with a biventricular circulation underwent an ASO during the study period. ***Table 2-1*** summarizes the perioperative and operative data of the patients.

Table 2-1. Perioperative and operative data

	Overall (n=844)	TGA-IVS (n=489)	TGA-VSD (n=228)	TBA without AAO (n=28)	All AAO (n=84)	Atrial switch to ASO conversion (n=15)
COA	62 (7.3%)	0 (0%)	0 (0%)	0 (0%)	62 (74%)	0 (0%)
HAA	46 (5.5%)	0 (0%)	0 (0%)	0 (0%)	46 (55%)	0 (0%)
IAA	10 (1.2%)	0 (0%)	0 (0%)	0 (0%)	10 (12%)	0 (0%)
LVOTO	29 (3.4%)	0 (0%)	17 (7.5%)	3 (11%)	4 (4.8%)	5 (33%)
Previous cardiac surgery	59 (7.0%)	5 (1.0%)	11 (4.8%)	5 (18%)	23 (27%)	15 (100%)
Preoperative PAB	30 (3.6%)	4 (0.8%)	4 (1.8%)	4 (14%)	7 (8.3%)	11 (73%)
Median age at ASO (days)	10 (IQR 7-23)	8 (IQR 6-11)	22 (IQR 10-58)	103 (IQR 51-424)	9 (IQR 5-34)	3759 (IQR 2564-4454)
Median weight at ASO (kilograms)	3.5 (IQR 3.1-3.5)	3.4 (IQR 3.1-3.8)	3.7 (IQR 3.2-4.3)	4.6 (IQR 3.5-6.9)	3.5 (IQR 3.2-3.9)	34 (IQR 19-39)
Less than 2.5 kilograms	35 (4.1%)	19 (3.9%)	9 (3.9%)	1 (3.6%)	5 (6.0%)	1 (6.7%)
Anomalous coronary anatomy	290 (34%)	155 (32%)	87 (38%)	13 (46%)	34 (40%)	1 (6.7%)
Single coronary artery without intramural course	29 (3.4%)	15 (3.1%)	9 (3.9%)	2 (7.1%)	3 (3.6%)	0 (0%)
Intramural coronary artery	37 (4.4%)	26 (5.4%)	7 (3.1%)	0 (0%)	4 (4.8%)	0 (0%)
Circulatory arrest used	294 (35%)	187 (38%)	68 (30%)	5 (18%)	30 (36%)	4 (27%)
Median duration of CPB (mins)	170 (IQR 129-204)	160 (IQR 121-185)	181 (IQR 139-217)	178 (IQR 153-219)	227 (IQR 166-280)	238 (IQR 200-353)
Median duration of aortic cross clamp (mins)	92 (IQR 71-116)	85 (IQR 61-105)	107 (IQR 80-132)	105 (IQR 88-125)	120 (IQR 93-168)	83 (IQR 77-90)
Mechanical circulatory support	46 (5.5%)	28 (5.7%)	9 (3.9%)	0 (0%)	9 (11%)	0 (0%)

AAO= aortic arch obstruction, ASO= arterial switch operation, COA= coarctation of the aorta, CPB= cardiopulmonary bypass, HAA= hypoplastic aortic arch, IAA= interrupted aortic arch, IQR= interquartile range, LVOTO= left ventricular outflow tract obstruction, PAB= pulmonary artery banding, TBA= Taussing-Bing anomaly, TGA-IVS= transposition with intact interventricular septum without aortic arch obstruction, TGA-VSD= transposition of the great arteries with ventricular septal defect without aortic arch obstruction

Of the 844 patients, 489 (58%, 489/844) patients had TGA-IVS without aortic arch obstruction and 228 (27%, 228/844) had TGA-VSD without aortic arch obstruction. Twenty-eight (3.3%, 28.844) had Taussig-Bing anomaly without aortic arch obstruction (TBA). Eighty-four (10%, 84.844) patients had associated AAO. Fifteen (1.8%, 15/844) had takedown of an atrial switch and conversion to ASO.

The median age at operation was 10 days (interquartile range 7-23 days) and the median weight was 3.5 kilograms (interquartile range 3.1-4.0 kilograms). Thirty-five (4.1%, 35/844) patients had an operative weight less than 2.5 kilograms.

Mortality and functional status

There were 28 (3.3%, 28/844) early deaths. Causes of early death were myocardial ischaemia (n=20), sepsis (n=5), cerebral infarction (n=1), respiratory failure (n=1) and ventricular arrhythmia (n=1).

There was no evidence of an era effect with respect to survival. Early mortality for TGA-IVS was 1.8% (9/489) compared to 3.9% (9/228) for TGA-VSD (*p=0.09*). Early mortality for TBA with or without AAO was 5.3% (3/57) and was 6.0% (5/83) in all patients with AAO.

Early mortality was 3.4% (5/148) from 1983-1989, 3.7% (11/300) from 1990-1999, 2.7% (7/263) from 2000-2010 and 3.8% (5/133) from 2010-2014.

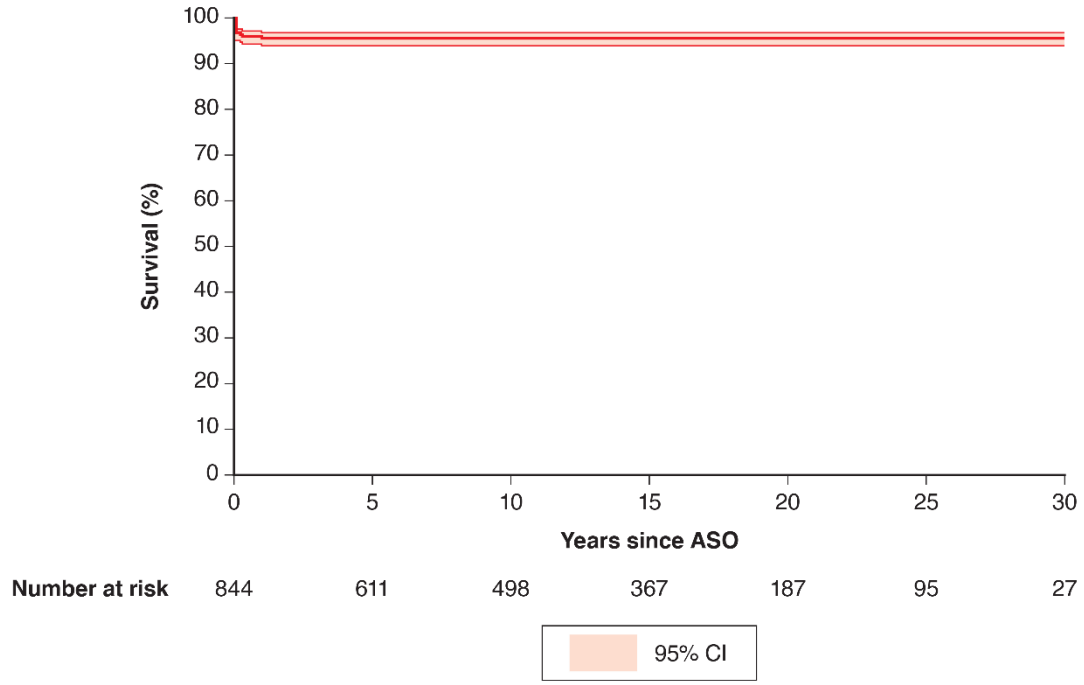
Univariate risk factors for early death were the presence of a ventricular septal defect (VSD) (*p=0.012*, hazards ratio (HR) 2.7, 95%CI 1.2-5.8), left ventricular outflow tract obstruction (LVOTO) (*p=0.047*, HR 3.4, 95%CI 1.0-11.2), previous cardiac surgery (*p=0.005*, HR 3.6, 95%CI 1.5-9.0), intraoperative PA banding (*p=0.016*, HR 5.8, 95%CI 1.4-24.5), duration of circulatory arrest (*p=0.007*, HR 1.03, 95%CI 1.01-1.06), duration of cardiopulmonary bypass *(p<0.001*, HR 1.01, 95%CI 1.007-1.012), duration of aortic cross clamp *(p<0.001*, HR 1.01, 95%CI 1.01-1.02) and concomitant arch repair (*p=0.038*, HR 2.8, 95%CI 1.1-7.3). Multivariate risk factors for early death were intraoperative PA banding (*p=0.003*, HR 7.6, 95%CI 2.0-29, duration of circulatory arrest (*p=0.006*, HR 1.03, 95%CI 1.01-1.06) and duration of cardiopulmonary bypass (*p<0.001*, HR 1.01, 95%CI 1.005-1.015).

Of the 816 survivors, 42 (5.1%, 42/816) were overseas patients who returned to their native country for follow-up. Follow-up was available for 94% (729/774) of local patients after hospital discharge. Median follow-up was 15 years (interquartile range 8-20 years).

There were 187 (26%, 187/729) patients with more than 20 years of follow-up and 95 (13%, 95/729) patients with more than 25 years of follow-up.

Overall survival was 95% (95%CI 94-97%) at 10, 20 and 25 years after ASO. There were no deaths 14 months after ASO (***Figure 2-1***).

Figure 2-1. Survival after ASO



Functional status according to NYHA class was available in 708 (91%, 708/774) survivors with follow-up. Of these patients, 695 (98%, 695/708) were in NYHA class I.

Reintervention

There were 193 catheter or surgical reinterventions in 133 patients occurring at median 1 year (interquartile range 1 month to 11 years, mean 5.3 years) after ASO. ***Tables 2-2 and 2-3*** list the reinterventions performed.

Table 2-2. Reoperation types

Reoperation type	Number of reoperations
Pulmonary artery surgery	
Branch PA stenosis repair	24
MPA repair	12
Pulmonary valve repair	8
Pulmonary valve replacement	2
Aortic surgery	
Aortic root replacement	18
Aortic valve repair	13
Aortic valve replacement	13
Aortic arch repair	8
Aortic-RA fistula repair	1
Other cardiac	
Subvalvular pulmonary stenosis resection	11
Permanent pacemaker	11
Subvalvular aortic stenosis resection	10
VSD closure	8
MV repair	5
ASD closure	5
Revision of coronary anastomosis	5
Supravalvular aortic stenosis repair	4
Implantable cardiac defibrillator	2
PA banding	2
TV repair	2
Coronary artery bypass graft surgery	2
MV replacement	1
RV-PA conduit	1
Left SVC-RA conduit	1
Other non-cardiac	
SVC stenosis repair	9
Plication of diaphragm	6
Thoracic duct ligation	4

ASD= atrial septal defect, MPA= main pulmonary artery, MV= mitral valve, PA= pulmonary artery, RA= right atrium, RV= right ventricule, SVC= superior vena cava, TV= tricuspid valve, VSD= ventricular septal defect

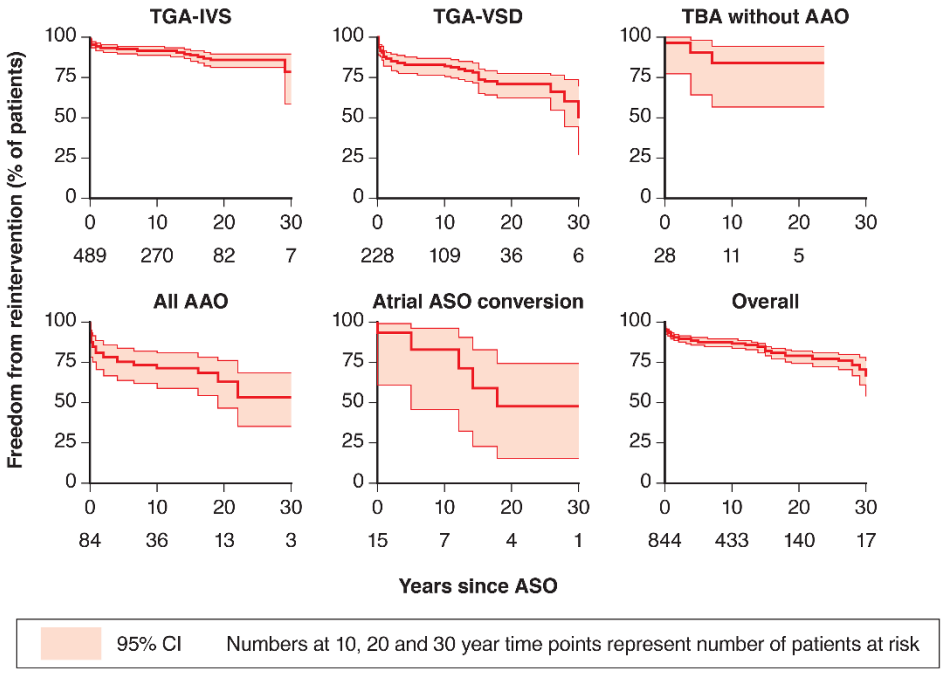
Table 2-3. Catheter reintervention types

Catheter reintervention type	Number of patients
Branch PA angioplasty or stent	21
MPA angioplasty or stent	7
Pulmonary valve angioplasty	7
Angioplasty of coarctation	5
ASD closure	3
VSD closure	2
Coiling of aortopulmonary collaterals	2
Angioplasty of SVC	2
PA band angioplasty	1
Ablation for atrial flutter	1

ASD= atrial septal defect, MPA= main pulmonary artery, PA= pulmonary artery, SVC= superior vena cava, VSD= ventricular septal defect

Freedom from any form of reintervention was 87% (95%CI 84-89%), 79% (95%CI 75-82%) and 77% (95%CI 73-81%) at 10, 20 and 25 years after ASO (***Figure 2-2***).

Figure 2-2. Freedom from reintervention



Freedom from reintervention at 20 years was 86% (95%CI 81-89%) for TGA-IVS patients and 70% (95%CI 62-78%) for TGA-VSD patients (*p<0.001*).

Univariate risk factors for reintervention were the presence of a VSD (*p<0.001*, HR 2.4, 95%CI 1.7-3.4), AAO (*p<0.001*, HR 2.2, 95%CI 1.4-3.4), LVOTO (*p<0.001*, HR 4.6, 95%CI 2.7-8.0), duration of circulatory arrest (*p<0.001*, HR 1.02, 95%CI 1.01-.1.04), duration of CPB (*p<0.001*, HR 1.007, 95%CI 1.005-1.009), duration of aortic cross clamp (*p<0.001*, HR 1.01, 95%CI 1.006-1.014) and the need for MCS (*p=0.004*, HR 3.2, 95%CI 1.5-7.1). There were no risk factors for reintervention on multivariate analysis.

There were 146 reoperations in 109 patients occurring at median 1 year (interquartile range 1 month to 11 years, mean 5.6 years) after ASO. The most common reoperation was branch PA stenosis repair (n=24). Freedom from reoperation was 89% (95%CI 86-91%, 82% (95%CI 78-86%) and 81% (95%CI 77-85%) at 10, 20 and 25 years after ASO. Freedom from reoperation at 20 years was 89% (95%CI 84-92%) for TGA-IVS patients and 76% (95%CI 68-82%) for TGA-VSD patients (*p<0.001*).

Univariate risk factors for *reoperation* were the presence of a VSD (*p<0.001*, HR 2.7, 95%CI 1.8-3.9), AAO (*p<0.001*, HR 2.5, 95%CI 1.6-3.9), LVOTO (*p<0.001*, HR 5.2, 95%CI 3.0-9.2), duration of circulatory arrest (*p=0.04*, HR 1.02, 95%CI 1.0009-1.03), duration of CPB (*p<0.001*, HR 1.008, 95%CI 1.006-1.01), duration of aortic cross clamp (*p<0.001*, HR 1.01, 95%CI 1.008-1.02) and the need for mechanical circulatory support (*p=0.003*, HR 3.5, 95%CI 1.5-8.1). The only risk factor on multivariate analysis was duration of cardiopulmonary bypass (*p=0.04*, HR 1.009, 95%CI 1.0004-1.02).

There were 44 reoperations on the neo-aortic root or neo-aortic valve in 34 patients occurring at a median 14.5 years (interquartile range 6-18 years). There was 1 (2.9%, 1/34) death associated with reoperation in these patients. Freedom from reoperation on the neo-aortic root or neo-aortic valve was 96% (95%CI 97-99%), 94% (95%CI 91-96%)

and 92% (95%CI 88-95%) at 10, 20 and 25 years after ASO. Freedom from reoperation on the neo-aortic root or neo-aortic valve at 20 years was 96% (95%CI 92-98%) for TGA-IVS patients and 94% (95%CI 88-97%) for TGA-VSD patients (*p=0.19*). Univariate risk factors for reoperation on the neo-aortic root or valve were the presence of a VSD (*p=0.03*, HR 2.2, 95%CI 1.1-4.3), LVOTO (*p<0.001*, HR 6.1, 95%CI 2.5-14.8) and previous cardiac surgery (*p=0.04*, HR 2.5, 95%CI 1.1-5.8). The only risk factor on multivariate analysis was anatomic LVOTO present prior to the ASO (*p=0.001*, HR 4.5, 95%CI 1.8-11.5).

There were 7 reoperations on the coronary arteries in 5 patients occurring at a median 12 days (interquartile range 5.5 to 55 days, mean 1.3 years) after ASO. All coronary reoperations occurred within 3 months of ASO except in 1 patient who required coronary reoperation 9 years after ASO. Two (40%, 2/5) patients died after coronary reoperation. Freedom from coronary reoperation was 99% (95%CI 98-99.7%) at 10, 20 and 25 years after ASO.

There were 47 catheter reinterventions in 38 patients occurring at a median 3 years (interquartile range 9 months to 12.5 years, mean 6.2 years) after ASO. The most common catheter reintervention was branch PA angioplasty or stent (n=21). Freedom from catheter reintervention was 96% (95%CI 94-97%), 94% (95%CI 91-95%) and 94% (95%CI 91-95%) at 10, 20 and 25 years after ASO.

Valvular function and left ventricular function

Of the 774 patients with follow-up, 713 (92%, 713/774) patients had echocardiographic assessment of the neo-aortic valve at last follow-up. Two (0.3%, 2/774) patients had moderate or severe neo-aortic valve stenosis. Twenty-two (3.1%, 22/713) patients had moderate or severe neo-aortic valve regurgitation (AR). Of the 95 patients with more than

25 years of follow-up after ASO, 6 (6.3%) had at least moderate AR and 8 (8.4%) had undergone replacement of the neo-aortic valve. The function of the other valves last follow-up is summarized in ***Table 2-4***.

Table 2-4. Valvular function at last follow-up

Valvular lesion	% patients at last follow-up
≥ moderate tricuspid regurgitation	0% (0/696)
≥ moderate tricuspid stenosis	1.4% (10/696)
≥ moderate pulmonary regurgitation	4.0% (28/688)
≥ moderate pulmonary stenosis	0.9% (6/688)
≥ moderate mitral regurgitation	0.7% (5/699)
≥ moderate mitral stenosis	0% (0/699)
≥ moderate neo-aortic regurgitation	3.1% (22/713)
≥ moderate neo-aortic stenosis	0% (0/713)

Six hundred and nine (79%, 609/774) patients had qualitative assessment of LV systolic function on echocardiography at last follow-up. Left ventricular systolic function was normal in 595 (98%, 595/609) patients.

Arrhythmia

Seven (0.9%, 7/774) patients had a known arrhythmia at last follow-up. Five of these patients had documented supraventricular tachycardia after hospital discharge and 2 patients had atrial flutter. Eleven (1.4%, 11/774) patients had a permanent pacemaker, of which 10 had VSD closure at time of ASO.

2.4 Discussion

This study represents a large cohort of ASO survivors with long-term follow-up. A particular strength of this research is the number of survivors with long-term follow-up, with 95 patients having more than 25 years of follow-up after ASO. To the best of our

knowledge, this paper has the largest number of such long-term survivors currently reported on.

Similar to others (9, 11, 18), we have demonstrated a low early mortality, especially in patients with TGA-IVS. Early mortality remained low at our institution throughout the study period and allowed a large population of ASO survivors to reach adulthood. In further examining early mortality, the need for postoperative MCS was the only risk factor on multivariate analysis. Overall, late death was a rare outcome (1.2%) as has been reported by others (19, 49, 98, 99).

Overall, reintervention was required in almost one quarter of ASO survivors by 25 years postoperatively. This finding agrees with the results of another large retrospective study by Khairy et al (49) who reported a freedom from reintervention of 75.5% at 25 years. There was a significant difference in reintervention and reoperation between patients with TGA-IVS and TGA-VSD. This difference is explained by the TGA-VSD patients undergoing reintervention for a broader scope of problems as well as more reintervention for pulmonary stenosis. Branch PA stenosis was the most common cause of both reoperation and catheter reintervention. The etiology of branch PA stenosis is not well understood but has been hypothesized to be caused by the stretched course of the arteries over a dilated neo-aortic root (100).

In contrast to reintervention for branch PA stenosis, which was common and occurred early after ASO, reoperation on the neo-aortic root or valve occurred uncommonly, but increased as follow-up increased. Koolbergen and colleagues (62) found a freedom from neo-aortic root or valve reoperation of 95% at 25 years but acknowledged that these rates of reoperation are likely to increase as follow-up lengthens. Recently, van der Palen et al (63) demonstrated that the neo-aortic root increased in size with age without a stabilisation of dimensions and the incidence of significant AR also increased over time.

One would expect that the rate of reoperation on the neo-aortic root would be higher in TGA-VSD patients in whom the neo-aortic root is generally larger from birth. In fact, we have demonstrated no significant difference between TGA-IVS and TGA-VSD patients. In our 95 patients who were more than 25 years after ASO, 15% had either at least moderate AR or had undergone neo-aortic valve replacement with or without replacement of the neo-aortic root. This is an important finding and demonstrates the significant attrition of neo-aortic valve function over time and need for ongoing surveillance of ASO survivors throughout life. How well the neo-aortic root will withstand systemic pressures as patients reach middle age is a question that only ongoing surveillance will answer.

Reoperation on the coronary arteries remained a rare event in our study. Although routine coronary angiography is not part of routine follow-up after the ASO in our hospital and the patency of individual coronary arteries could not be assessed, there were no patients with clinical or echocardiographic findings that required reintervention for coronary problems beyond 3 months after the ASO, excluding 1 patient who required late coronary reoperation. The findings from our study with regards to coronary and other reinterventions are similar to those of other late studies following the ASO (49, 98, 101). A recent meta-analysis of LV function after the ASO (102) found that LV function, as assessed by LV ejection fraction, was normal in the vast majority of ASO survivors. Similarly, qualitative assessment of LV function was normal in 98% of patients with follow-up data.

The incidence of clinically significant arrhythmia and permanent pacemaker implantation was low in our cohort in the long-term. This agrees with the reports of others (49, 98, 99, 103) and stands in contrast to late results following the atrial switch procedures for TGA (104).

A limitation of this study was its retrospective nature. We were unable to comment on the incidence of neo-aortic root dilation, outside the need for reoperation, due to lack of quantitative data on echocardiographic reports.

2.5 Conclusion

Overall long-term outcomes for ASO survivors are good with excellent late survival and functional status. However, reintervention is common particularly in patients with TGA-VSD. In patients who were more than 25 years after ASO, 15% had either at least moderate AR or had undergone neo-aortic valve replacement with or without replacement of the neo-aortic root. These findings highlight the need for ongoing surveillance of ASO survivors throughout adult life.

Chapter 3: Excellent long-term outcomes of the arterial switch operation in patients with intramural coronary arteries

3.1 Introduction

In this study, we reviewed outcomes of the ASO in patients with intramural coronary arteries. Over a study period from 1983-2009, there were 28 patients who underwent an ASO with intramural coronaries at The Royal Children's Hospital. There were no deaths and no coronary reinterventions after a mean follow-up of 16.3 years. We described a simple, reproducible technique for coronary translocation in patients with intramural coronaries. The last 25 patients in the study underwent this technique of detachment of the posterior commissure with or without unroofing of the intramural coronary and translocation of 2 separate coronary buttons to medially based trapdoors in the neo-aorta. This study represents the longest follow-up of patients with intramural coronary arteries undergoing the ASO.

3.2 Fricke TA et al. Ann Thorac Surg 2016;101:725-729

Excellent Long-Term Outcomes of the Arterial Switch Operation in Patients With Intramural Coronary Arteries

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CONGENITAL HEART

Background. Intramural coronary arteries may complicate coronary artery transfer during the arterial switch operation. We sought to determine the long-term outcomes of 28 patients with intramural coronary arteries who underwent an arterial switch operation at a single institution.

Methods. All patients who had intramural coronary arteries and underwent an arterial switch operation were identified from the hospital database and retrospectively reviewed.

Results. From 1983 to 2009, 720 patients underwent an arterial switch operation at our institution. Twenty-eight (3.9%, 28 of 720) had intramural coronary arteries. Patients with intramural coronary arteries had transposition of the great arteries (96%, n = 27) or Taussig-Bing anomaly (4%, n = 1). There were no deaths. Follow-up was 100% complete. Mean follow-up was 16.3 years (median, 15.5 years; range, 5.6 to 26.9 years). No patient required reoperation or catheter reintervention on the coronary arteries. Freedom from reoperation was 93% at 10 years. No patient had more than mild aortic regurgitation at last follow-up. Nine (32%, 9 of 28) patients had coronary angiograms at median 16 months (range, 14 months to 17 years) after arterial switch operation. All patients were asymptomatic at the time of angiogram. One patient had mild stenosis of the circumflex coronary artery demonstrated on a routine coronary angiogram 14 months postoperatively. All 28 patients were asymptomatic and in New York Heart Association functional class I at last follow-up.

Conclusions. Patients with intramural coronary arteries are not at increased risk of death or coronary reinterventions and have excellent late outcomes after the arterial switch operation.

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The arterial switch operation (ASO) has excellent early outcomes with low mortality and morbidity rates in the modern era [1–5]. Intramural coronary arteries (IMCAs) may complicate coronary transfer and contribute to a mortality of up to 28% in such patients (6). A metaanalysis of 1,942 children demonstrated that an IMCA was associated with a 6.5-fold increased risk of mortality following ASO [7]. Recent studies on the outcomes of children with IMCAs who undergo the ASO demonstrated variable results [3, 6, 8] (Table 1). We have previously reported that the IMCA was not a risk factor for mortality in 618 children who underwent an ASO for transposition of the great arteries (TGA) over a 25-year period at our institution (2). Herein we describe the surgical management of IMCA and the long-term outcomes for this subgroup of patients.

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Material and Methods

Patients

The study was approved by the Royal Children's Hospital Human Research Ethics Committee. Between May 1983 and January 2009, a total of 720 patients underwent an ASO at the Royal Children's Hospital. An ASO was performed for TGA (n = 618), Taussig-Bing anomaly (TBA; n = 57), congenitally corrected TGA (n = 21), for atrial to ASO conversion (n = 15) and TGA with univentricular physiology (n = 9). All operation reports were reviewed and all patients with IMCA were identified. There were 28 (3.9%, 28 of 720) patients with IMCA. Twenty-seven (96%, 27 of 28) patients had TGA and 1 (4%, 1 of 28) patient had TBA. Twenty (74%, 20 of 27) of the patients with TGA had an intact interventricular septum (TGA-IVS).

Definitions

An IMCA was defined as any coronary pattern in which at least one coronary artery coursed through the aortic wall for a variable distance.

Early death or reoperation was defined as death or reoperation occurring prior to hospital discharge or within

Table 1. Current Studies on Outcomes of Children with Intramural Coronaries After the Arterial Switch Operation

Author	Study Period	Total No. of Patients	No. of IMCA Patients, No. (%)	Mortality						Follow-Up
				Non-IMCA			IMCA			
				Early	Late	Overall	Early	Late	Overall	
Metton et al [6]	1987–2008	919	46 (5.0)	NR	NR	3.9%	24% (11 of 46)	5.7% (2 of 35)	28% (13 of 46)	Mean, 8.3 y
Thrupp et al [3]	1996–2006	215	18 (8.4)	3.0% (6 of 197)	NR	NR	5.6% (1 of 18)	0% (0 of 16)	5.6% (1 of 18)	Median, 6.8 y
Fricke et al [2]	1983–2009	618	28 (4.5)	2.9% (17 of 590)	1.0% (5 of 536)	3.7% (22 of 590)	0% (0 of 27)	0% (0 of 27)	0% (0 of 27)	Mean, 10 y
Qamar et al [5]	1999–2005	168	12 (7.1)	6.3% (10 of 158)	4.1% (4 of 98)	8.9% (14 of 158)	0% (0 of 12)	0% (0 of 12)	0% (0 of 12)	Mean, 1.6 y
Chen [8]	2008–2012	75	7 (8.9)	4.4% (3 of 68)	0% (0 of 65)	4.4% (3 of 68)	14% (1 of 7)	0% (0 of 6)	14% (1 of 7)	Mean, 2.9 y

IMCA = intramural coronary arteries; NR = not reported.

30 days of ASO. Late death or reoperation was defined as any death or reoperation that occurred after discharge and more than 30 days after ASO. Reoperation was defined as an operation on the heart or great vessels performed after the ASO excluding exploration for bleeding, wound debridement, mechanical circulatory support and pacemaker replacement. Reintervention encompassed reoperation and catheter reintervention performed after ASO.

Functional status was described according to the New York Heart Association (NYHA) classification.

Statistical Analysis

Data were analyzed using Stata Version 10 (Stata Corp, College Station, Texas). Continuous variables were reported as a mean or median with an accompanying range. Kaplan-Meier curves were constructed to display freedom from the study's outcomes.

Results

Early Outcomes

The intramural course involved the left main coronary artery in 24 (86%, 24 of 28) patients, the left anterior descending artery in 2 (7%, 2 of 28) patients, the right coronary artery in 1 (3.5%, 1 of 28) patient, and both left and right coronary arteries in 1 (3.5%, 1 of 28) patient (Fig 1). Our approach to the IMCA (Fig 2A) was detachment of the posterior commissure of the aortic (neopulmonary) valve in 25 (89%, 25 of 28; Fig 2B) patients and unroofing of the IMCA (Fig 2C) in 16 (57%, 16 of 28) patients. Then the coronary arteries were detached and transferred either as a single button (Fig 2D) facilitated with a pericardial hood (Fig 2, D1–D3) in the first 3 (11%, 3 of 28) patients or as 2 separate buttons (Fig 2E) using the trapdoor technique (Fig 2, E1–E2) in the next 25 (89%, 25 of 28) patients. In all patients the pulmonary artery was reconstructed with a single autologous pericardial patch and the posterior neopulmonary commissure was reattached to it.

Median age at operation was 9 days (mean, 15 days; range, 2 to 81 days) and median weight at operation was 3.5 kg (mean, 3.8 kg; range, 2.6 to 10 kg). Mean cardiopulmonary bypass time was 158 min (median, 143 min; range, 93 to 275 min) and mean aortic cross clamp time was 89 min (median, 83 min; range, 49 to 149 min). Circulatory arrest was used in 50% of the patients with a mean circulatory arrest time of 9 min (median, 8 min; range, 5 to 54 min).

There were no early deaths or early reinterventions for the IMCA. There was no mechanical circulatory support in patients with IMCA before ASO. Two patients (7.4%, 2 of 28) with IMCA had TGA-IVS with poor preoperative left ventricular function and were supported with Medtronic BioMedicus (Eden Prairie, Minnesota) centrifugal left ventricular assist device. The first patient was a 5-day-old boy operated in 1994. The second patient was a 44-day-old girl operated in 2004. Both were weaned off of the left ventricular assist device in 2 days. In comparison,

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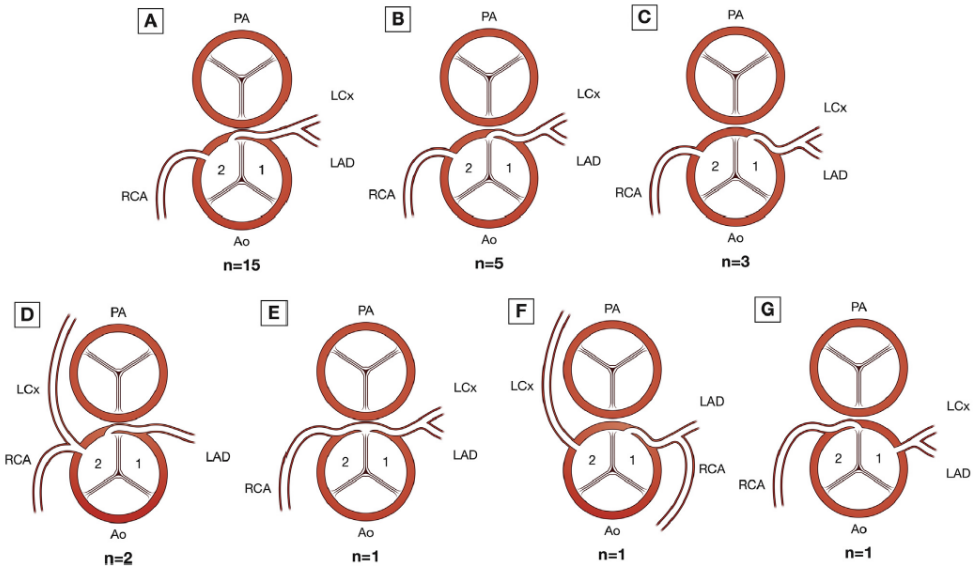

Fig 1. (A–F) Intramural course of the left coronary artery (LCA) was most common (n = 27) and in most patients (n = 17) the intramural LCA came from sinus 2 (A and D). Intramural right coronary artery (RCA) was encountered in 2 children (E and G). (Ao = aorta; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PA = pulmonary artery.)

of the remaining 647 patients, with simple TGA (n = 591) and TBA (n = 56), 4.3% (28 of 647) required mechanical circulatory support postoperatively. There were no perioperative morbidities related to the IMCA. One patient with IMCA had congenital left pulmonary artery stenosis that required early pericardial repair of the left pulmonary artery (Table 2).

Late Outcomes

Follow-up was obtained for all patients. Mean follow-up was 16.3 years (median, 15.5 years; range, 5.6 to 26.9 years). There were no late deaths. All patients were in NYHA functional class I at last follow-up.

LATE REINTERVENTION. There were 12 reinterventions in 5 patients that occurred at a mean 3 years after ASO (range, 1 day to 22 years). There were no reoperations or catheter reinterventions on the coronary arteries. Four (14%, 4 of 28) patients required reintervention including 7 reoperations and 4 catheter reinterventions. Freedom from reintervention was 89% at 5 and 10 years postoperatively and 84% at 15 and 20 years postoperatively. Freedom from reoperation was 93% at 5 and 10 years postoperatively and 88% at 15 and 20 years postoperatively (Fig 3). Reinterventions are listed in Table 2. One patient had 2 reoperations for supraaortic stenosis and an aortic-to-pulmonary artery fistula, 1 patient had mitral valve repair, and 1 patient had four reoperations for repair of left pulmonary artery stenosis.

CORONARY SURVEILLANCE. No patients required reoperation or catheter reintervention on the coronary arteries. Thirteen (46%, 13 of 28) patients had exercise electrocardiograms (ECGs). Exercise ECGs were normal in 9 (69%, 9 of 13) patients and abnormal in 4 (31%, 4 of 13) patients. Two patients with positive exercise ECGs were followed up with normal myocardial perfusion scans and normal coronary angiograms. In one patient minor ST segment depression in the inferior leads was demonstrated. The patient was otherwise asymptomatic and required no further follow-up. One patient with a positive exercise ECG was scheduled for repeat testing.

Four (14%, 4 of 28) patients had myocardial perfusion scans at a median 11.5 years (mean, 11 years; range, 7 to 16 years) after ASO. All scans were negative for inducible ischemia. Myocardial perfusion scans were performed in 2 patients as part of routine follow-up, in 1 patient after ischemic changes on exercise ECG, and in the 1 patient with a mild stenosis of the circumflex coronary artery.

Nine (32%, 9 of 28) patients had 10 coronary angiograms at median 16 months (mean, 3.8 years; range, 14 months to 17 years) after ASO. Eight of the coronary angiograms were performed as part of routine follow-up and 2 coronary angiograms were performed because of ischemic changes on exercise ECG. All patients were asymptomatic and had normal coronaries on angiogram except 1 patient who had mild stenosis of the circumflex coronary artery. This patent had an angiogram 14 months postoperatively and remained asymptomatic

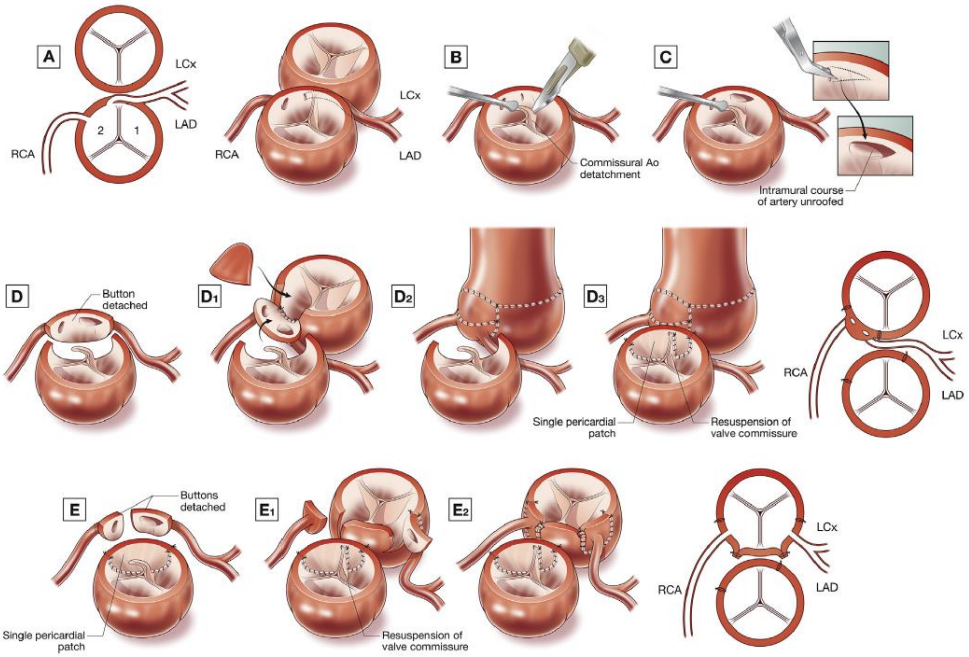

Fig 2. Surgical technique of intramural coronary artery transfer. Following identification of (A) the intramural segment, the detachment of the posterior commissure of (B) the aortic (neopulmonary) valve was performed in most patients (n = 25). The unroofing of the (C) intramural coronary artery was done in 16 patients. Then the coronary arteries were detached and transferred either as (D) a single button facilitated with a pericardial hood (D_1–D_3) in the first 3 patients or as (E) two separate buttons using the trapdoor technique (E_1–E_2) in the next 25 consecutive patients. In all patients the pulmonary artery was reconstructed with a single autologous pericardial patch and the posterior neopulmonary valve commissure was reattached to it. (Ao = aorta; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.)

with a myocardial perfusion scan negative for inducible ischemia and a CT coronary angiogram demonstrating patent coronaries at 16 and 22 years postoperatively, respectively.

Table 2. Reinterventions Following ASO

Patient	Reintervention Type	Time Since ASO (years)
1	Supravalvular aortic stenosis repair	2.1
	Closure of aorta to RPA fistula	14.1
2	Mitral valve repair	13.4
3	Lengthen LPA pericardial tube	1 day
	Reconnect LPA to MPA	3 days
	Central shunt	1.0
	LPA stenosis repair	2.7
	Balloon angioplasty LPA	3.3
	LPA stent	7.1
	Balloon angioplasty LPA	15.3
4	Coiling of aortopulmonary collateral	1.2

ASO = arterial switch operation; LPA = left pulmonary artery; MPA = main pulmonary artery; RPA = right pulmonary artery.

VALVULAR FUNCTION AND ARRHYTHMIA. Table 3 lists valvular function at last follow-up. Mild neoaortic regurgitation was reported in 9 (32%, 9 of 28) patients. No patients had more than mild aortic regurgitation. Sinus rhythm was present in all patients (n = 22) who had ECGs at last follow-up. No patients required pacemaker implantation.

Comment

Coronary transfer during the ASO in patients with IMCAs presents a surgical challenge. Few studies in the literature have looked specifically at the outcomes of this subgroup. A meta-analysis of 1,942 patients by Pasquali and colleagues [7] demonstrated that an IMCA had a 6.5-fold increased risk of mortality as compared to normal coronary anatomy. Metton and associates [6] reviewed 46 patients with IMCAs out of a cohort of 919 patients who underwent ASO between 1987 and 2008. They reported a mortality of 28%, including 11 deaths before discharge and 2 deaths at 51 and 105 days. Nine of the 11 deaths were deemed secondary to coronary complications.

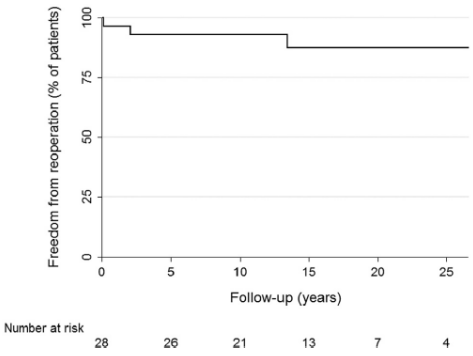

Fig 3. Freedom from reoperation.

Conversely, Thrupp and colleagues [3] reported 1 death (5.6%) in 18 patients with IMCAs out of 215 patients who underwent ASO between 1996 and 2006. They found that an IMCA was not a risk factor for mortality in their cohort of 215 patients and all survivors were asymptomatic after a median follow-up of 6.8 years. One death (14%) was reported in a smaller cohort of 7 IMCA patients operated by Chen and colleagues [8].

The results of our study demonstrate excellent early and late outcomes for patients with IMCAs who undergo an ASO. We report no deaths in 28 asymptomatic patients with a follow-up of more than 15 years. The first 3 patients in our series had a pericardial hood reconstruction of the coronaries and the next 25 underwent transfer using the trapdoor technique. The trapdoor technique for coronary transfer was first described by Brawn and Mee [9] at our institution and the modification of this technique for translocating IMCAs was first described at our institution by Asou and colleagues [10]. Our technique involves detaching the posterior commissure of the neopulmonary valve if the coronaries arise in close proximity, unroofing the IMCA if the ostium is stenotic and transferring the excised coronary button to a medially based trapdoor. We believe that a combination of wide unroofing and transfer of the IMCA using trapdoor technique is a key to successful outcomes. Thus, we advocate the use of this technique in patients with IMCAs who undergo the ASO because of its simplicity, reproducibility, and excellent long-term outcomes. Our results suggest that routine coronary angiograms in these patients during follow-up in childhood is unlikely to be useful in asymptomatic survivors.

Patients with intramural coronary arteries are not at increased risk of death or coronary reinterventions and have excellent late outcomes after the arterial switch operation.

Table 3. Valvular Function on Echocardiography at Last Follow-Up

	Mild	Moderate	Severe
Neoaortic valve regurgitation	9 (32)	0 (0)	0 (0)
Neoaortic valve stenosis	0 (0)	0 (0)	0 (0)
Pulmonary valve stenosis	7 (25)	0 (0)	0 (0)
Neopulmonary valve regurgitation	12 (43)	2 (7.1)	0 (0)
Mitral valve regurgitation	1 (3.6)	0 (0)	0 (0)
Tricuspid valve stenosis	6 (21)	0 (0)	0 (0)

Values are n (%).

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Chapter 4: Outcomes of the arterial switch operation in children less than 2.5 kilograms

4.1 Introduction

Children with a low operative weight represent one of the most challenging subgroups of patients undergoing the ASO. This is a particular subgroup for which data on outcomes is particularly scarce, with only one published study specifically looking at these patients. In this study, we examined the outcomes of the ASO in children with an operative weight of less than 2.5 kilograms. Thirty-one patients less than 2.5 kilograms who underwent an ASO were identified from The Royal Children's Hospital database. There was a significant difference ($p<0.001$) in hospital mortality in patients less than 2.5 kilograms compared to those above 2.5 kilograms (19% versus 1.9%). However, the majority of deaths occurred in children less than 2.0 kilograms. Mortality for patients less than or equal to 2.0 kilograms was 50% (5/10) compared to a mortality of 2.8% (1/21) for children greater than 2.0kg but less than 2.5kg. Despite these differences in early mortality, long-term outcomes in survivors remained excellent. The study highlighted the challenging nature of these patients and the fact that operative weight less than 2.5 kilograms is a significant risk factor for mortality.

4.2 Fricke TA et al. Ann Thorac Surg 2016;103:840-944

ORIGINAL ARTICLES: CONGENITAL HEART SURGERY

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Outcomes of the Arterial Switch Operation in Children Less Than 2.5 Kilograms

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Background. Children with body weight less than 2.5 kg who undergo the arterial switch operation (ASO) represent a challenging group. We sought to determine outcomes of patients with weight less than 2.5 kg at ASO at a single institution.

Methods. All patients who underwent an ASO with biventricular repair and weighed less than 2.5 kg at time of surgery were identified from the hospital database and reviewed retrospectively.

Results. From 1983 to 2014, 870 patients underwent an ASO with biventricular repair at our institution. At the time of ASO, 31 patients (3.6%, 31 of 870) weighed less than 2.5 kg (mean 2.1; median 2.1; range, 1.1 to 2.4). Twenty-nine patients underwent an ASO for d-transposition of the great arteries, and 2 patients had an ASO for Taussig-Bing anomaly. Mean age at operation was 16 days (median 11; range, 3 to 66). There were 6 hospital deaths (19%, 6 of 31) among patients weighing less than 2.5 kg compared with a hospital mortality of 1.9% (16 of 839) among patients weighing more than 2.5 kg ($p < 0.0001$). Mortality for children weighing 2.0 kg or less was 50% (5 of 10) compared with a mortality of 2.8% (1 of 21) for children weighing more than 2.0 kg but less than 2.5 kg. Four patients (13%, 4 of 31) required reoperation during hospital admission. Follow-up was available for 24 survivors (96%, 24 of 25). Mean follow-up was 13.2 years (median 11.9; range, 6 months to 25 years). There were no late deaths. Two patients (8%, 2 of 24) required late reoperation. No patient had more than mild neoaortic valve regurgitation, and all survivors were in New York Heart Association class I at last follow-up.

Conclusions. Early mortality for children weighing less than 2.5 kg undergoing the ASO remains high; however, most of the mortality occurred in children weighing 2.0 kg or less. Long-term outcomes for survivors are excellent.

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The arterial switch operation (ASO) has excellent early outcomes in the modern era. However, children undergoing the ASO represent a heterogeneous group with challenging subgroups. One of these subgroups includes children with low body weight (LBW) at time of surgery. Although LBW at time of surgery has been associated with poorer outcomes in pediatric cardiac surgery [1–4], it has not been closely studied with regard to the ASO. Therefore, we sought to determine outcomes of patients with weight less than 2.5 kg at time of ASO at a single institution.

Material and Methods

Patients

From 1983 to 2014, 870 patients with transposition of the great arteries (TGA) or Taussig-Bing anomaly underwent an ASO for biventricular repair at the Royal Children's Hospital. Thirty-one patients (3.6%, 31 of 870) weighed less than 2.5 kg at ASO. Mean weight at ASO for the less than 2.5 kg patients was 2.1 kg (median 2.1; range, 1.1 to 2.4). Twenty-nine patients underwent an ASO for TGA, and 2 patients had an ASO for Taussig-Bing anomaly. Mean age at operation was 16 days (median 11; range, 3 to 66). This study was approved by the

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Royal Children's Hospital Human Research Ethics Committee. All data were collected retrospectively.

Definitions

Early death or reoperation was defined as death or reoperation occurring prior to hospital discharge or within 30 days of ASO. Late death or reoperation was defined as death or reoperation occurring after discharge and more than 30 days after ASO. Reoperation was defined as an operation on the heart or great vessels performed after the ASO excluding exploration for bleeding, wound debridement, mechanical circulatory support and pacemaker replacement. Functional status was described according to the New York Heart Association classification.

Statistical Analysis

Data were imported into STATA version 12 (StataCorp, College Station, TX). Continuous variables were reported as a mean or median with an accompanying range. Kaplan-Meier curves were constructed to display freedom from the study's outcomes. Fisher's exact test was used to determine statistical significance in mortality between less than 2.5 kg and greater than 2.5 kg groups.

Results

Early Outcomes

Preoperative and operative data are summarized in Table 1.

EARLY MORTALITY. Overall early mortality was 2.5% (22 of 870) for all ASO patients. There were 6 early deaths (19%, 6 of 31 patients) among patients weighing less than 2.5 kg compared with hospital mortality of 1.9% (16 of 839 patients) among patients more than 2.5 kg ($p < 0.0001$). Of the 6 early deaths among patients less than 2.5 kg, 5 of these patients were 2.0 kg or less at time of ASO, resulting in a hospital mortality of 50% for patients 2.0 kg or less. One of the 21 patients (4.8%) more than 2 kg but less than 2.5 kg died (Tables 2 and 3). Mortality did not improve over time (Table 4). Mean weight at time of ASO was 1.8 kg (median 1.8; range, 1.1 to 2.1) for patients who died, and hospital death occurred at a median 6 days after ASO (mean 27; range, 0 to 112).

Patient 1 was born at 32 weeks' gestation and was operated on day 16 at a weight of 1.8 kg. The patient's postoperative period was complicated by bilateral chylothoraces and superior vena caval obstruction, requiring return to the operating theater. The patient was unable to be weaned from mechanical ventilation, having been

Table 1. Preoperative and Operative Data

Variables	Patients <2.5 kg (n = 31)	Patients >2.5 kg (n = 839)
Age, weight, and body surface area		
Age at operation, days	11, 16.2 (3–66)	10, 61 (1–4933)
Weight at operation, kg	2.1, 2.1 (1.1–2.4)	3.8, 3.5 (2.6–19)
Body surface area at operation, m^2	0.16, 0.15 (0.1–0.18)	0.21, 0.22 (0.16–0.79)
Previous surgeries		
Previous cardiac surgery	1 (3.2)	38 (4.5)
Previous noncardiac surgery	2 (6.5)	1 (0.1)
Associated anomalies		
Ventricular septal defect	11 (34)	317 (38)
Aortic arch obstruction	3 (9.7)	62 (7.4)
Coarctation of aorta	3 (9.7)	45 (5.4)
Hypoplastic aortic arch	2 (6.5)	31 (3.7)
Interrupted aortic arch	0 (0)	7 (8.3)
LVOTO	0 (0)	23 (2.7)
Coronary artery pattern		
Normal: 1 LAD, Cx; 2 RCA	21 (68)	469 (56)
Anatomy other than 1 LAD, Cx; 2 RCA	10 (32)	370 (44)
Intramural	0 (0)	33 (3.9)
Operative data		
Cardiopulmonary bypass time, minutes	184 (105–364)	169 (37–567)
Aortic cross-clamp time, minutes	96 (48–158)	93 (31–278)
Circulatory arrest time, minutes	8.7 (0–63)	5.7 (0–67)
Circulatory arrest used	14 (45)	455 (54)
Arch repair at time of ASO	2 (6.5)	37 (4.4)
Postoperative mechanical support	3 (9.7)	26 (3.1)

Values are median, mean (range), n (%), or mean (range).

ASO = arterial switch operation; Cx = circumflex artery; LAD = left anterior descending artery; LVOTO = left ventricular outflow tract obstruction; RCA = right coronary artery.

Table 2. Patient Deaths

Year	TGA/TBA	Age at Operation (days)	Weight at Operation (kg)	Prematurity (weeks gestation)	Cause of Death
1988	TGA-IVS	16	1.8	32	Sepsis
1990	TGA-COA-VSD	9	1.8	32	Sepsis
1998	TGA-IVS	3	1.1	31	Pulmonary hemorrhage
2008	TGA-IVS	7	2.1	37	Myocardial ischemia
2009	TGA-IVS	52	2.0	31	Sepsis
2010	TGA-IVS	22	1.9	36	Myocardial ischemia

COA = coarctation of aorta; IVS = intact interventricular septum; TBA = Taussig-Bing anomaly; TGA = transposition of the great arteries; VSD = ventricular septal defect.

become septic and requiring reintubation. The patient died after withdrawal of medical care 34 days after ASO.

Patient 2 was born at 32 weeks' gestation with numerous comorbidities including CHARGE (coloboma of eye, heart defects, atresia of nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities) syndrome and a single kidney. The patient underwent operation on day 9 at a weight of 1.8 kg. The patient's postoperative period was complicated by recurrent episodes of sepsis and the requirement of several noncardiac operations. After 3 months of hospital admission, the patient had an episode of sepsis. To prevent further suffering, the parents opted for withdrawal of medical care and the patient died 124 days after surgery.

Patient 3 was born at 31 weeks' gestation and underwent operation on day 3 at a weight of 1.1 kg. The patient became profoundly hypotensive immediately after ASO in the intensive care unit and was reopened. The patient died the next day of pulmonary hemorrhage.

Patient 4 was born at 37 weeks' gestation and underwent ASO at day 7 at a weight of 2.1 kg. The patient required a left ventricular assist device the day after ASO owing to poor hemodynamics and could not be successfully weaned from mechanical support. The patient died 5 days after ASO.

Patient 5 was born at 31 weeks' gestation. Surgery was postponed to 52 days of age to allow for the patient's weight to increase to 2 kg. Postoperatively, the patient had a cardiac arrest followed by hypotension. Hypotension persisted despite inotropic support. Five days after surgery, the patient had sepsis that was unresponsive to treatment. Withdrawal of medical treatment occurred 7 days after ASO.

Patient 6 was born at 36 weeks' gestation and underwent ASO at day 22 at a weight of 1.9 kg. The patient died of myocardial ischemia the day of ASO.

Table 3. Mortality by Weight

Weight (kg)	Mortality (n/N [%])
≤2	5/10 (50)
>2 to <2.5	1/21 (4.8)
>2.5 to <3	3/89 (3.4)
≥3.0	13/750 (1.7)

EARLY REOPERATION. Five early reoperations were performed in 4 patients (13%, 4 of 31) at a mean 16 days after ASO (median 16; range, 3 to 31). Table 5 summarizes the reoperations performed.

Late Outcomes

Follow-up was 96% complete (24 of 25). One overseas-born patient returned to his native country and was lost to follow-up. Mean follow-up time was 13.2 years (median 11.9; range, 6 months to 25 years).

LATE SURVIVAL AND FUNCTIONAL STATUS. There were no late deaths. Freedom from mortality was 80% (95% confidence interval [CI]: 61% to 90%) at 5, 10, and 20 years postoperatively (Fig 1). All patients were in New York Heart Association class I at last follow-up.

LATE REOPERATION. There were two late reoperations in 2 patients (8%, 2 of 24; Table 5). Freedom from reoperation was 92% (95% CI: 55% to 71%), 82% (95% CI: 57% to 93%), and 61% (95% CI: 29% to 82%) at 5, 10, and 20 years postoperatively, respectively (Fig 2). There were no reoperations on the coronaries or the neo-aortic root or valve in surviving patients.

VALVULAR FUNCTION AT LAST FOLLOW-UP. The echocardiographic assessment of valvular function at last follow-up is summarized in Table 6. Mild neo-aortic regurgitation was reported in 8 (33%, 8 of 24) patients. No patients had more than mild neo-aortic regurgitation.

Comment

Despite considerable progress in pediatric cardiac surgery, LBW remains a risk factor for mortality in major pediatric cardiac operations [3–5]. Low body weight infants are often premature and may have complications related to prematurity affecting various systems [6]. Organ immaturity places these infants at a higher

Table 4. Mortality by Era

Era	Mortality (n/N [%])	Mean Weight (kg)
1983–1989	1/6 (17)	2.1 kg
1990–1999	2/12 (17)	2.2 kg
2000–2014	3/13 (23)	2.0 kg

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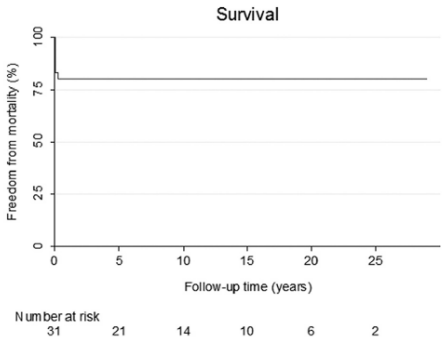

Fig 1. Kaplan-Meier curve of survival after arterial switch operation for children weighing less than 2.5 kg.

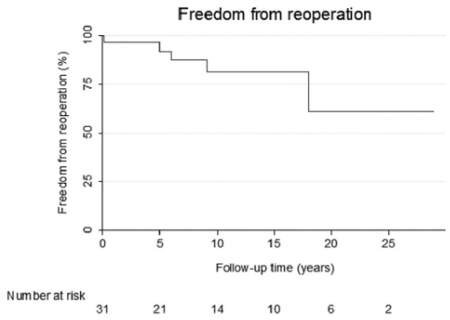

Fig 2. Kaplan-Meier curve of freedom from reoperation after arterial switch operation for children weighing less than 2.5 kg.

risk of infection, renal failure, respiratory disease, cerebral hemorrhage, and necrotizing enterocolitis, to name but a few [1]. Cardiopulmonary bypass is a significant insult to LBW infants with this type of physiology. However, delaying surgery for LBW infants with congenital heart disease is not without its own set of problems. There is evidence, albeit in heterogeneous groups without randomization, to show that delaying so they can gain weight before cardiac surgery may be deleterious [2, 6–8].

We defined LBW as an operative weight of less than 2.5 kg, as others have done [2, 9]. This definition has been identified as a risk factor for early mortality in a previous study at our institution looking at 618 children who underwent an ASO [10], and by Prandstetter and colleagues [9] in their cohort of 114 children who underwent an ASO. These patients represent an uncommon and technically challenging subgroup undergoing the ASO. We perform all vascular anastomoses (ie, aortic, pulmonary, and coronary) with 8-0 polypropylene and use an 80-degree cannula placed from the right atrial appendage into the superior vena cava to avoid direct cannulation of the superior vena cava.

Table 5. Reoperations

Patient Number	Reoperation Type	Time Since ASO (days)
1	SVC reconstruction	31
2	Subvalvular PS resection + pulmonary valvotomy	445
3	LPA + RPA stenosis repair	376
4	SVC thrombectomy, thoracic duct ligation	3, 15
5	LPA + RPA stenosis repair	20
6	SVC reconstruction	11

ASO = arterial switch operation; LPA = left pulmonary artery; PS = pulmonary stenosis; RPA = right pulmonary artery; SVC = superior vena cava.

To our knowledge, the only other published study looking specifically at weight and the ASO is by Roussin and colleagues [7]. They studied 25 infants with TGA who were operated on at a weight of less than 2 kg, 20 of whom underwent an ASO. They found an operative mortality of 16% in the LBW group, with no statistical difference in mortality when compared with their entire TGA cohort. Our mortality for children less than 2.5 kg who underwent an ASO was 19%, compared with a mortality of 1.9% in children more than 2.5 kg. Five of the 6 deaths of patients less than 2.5 kg occurred in patients who were 2.0 kg or less at time of ASO. However, only 1 of the 21 patients more than 2.0 kg but less than 2.5 kg died. It is clear from these numbers that LBW children represent a challenging group with a higher risk of early mortality after the ASO, particularly children weighing 2.0 kg or less. However, late mortality and reoperation was uncommon among children less than 2.5 kg, suggesting a late postoperative course similar to that of children more than 2.5 kg.

Study Limitations

A limitation of this study was its retrospective nature. This study covered a long period of time, and changes in

Table 6. Valvular Function at Last Follow-Up

Valvular Function	Mild (n [%])	Moderate or Severe (n [%])
Neo-AR	8 (33)	0 (0)
Neo-AS	0 (0)	0 (0)
Neo-PVS	3 (13)	0 (0)
MVR	1 (4)	0 (0)
MVS	0 (0)	0 (0)
TVR	2 (8)	0 (0)
TVS	0 (0)	0 (0)

AR = aortic regurgitation; AS = aortic stenosis; MVR = mitral valve regurgitation; MVS = mitral valve stenosis; PVS = pulmonary valve stenosis; TVR = tricuspid valve regurgitation; TVS = tricuspid valve stenosis.

management may have influenced outcomes. The small number of children weighing less than 2.5 kg also limited the level of statistical analysis performed.

Conclusion

Early mortality for children weighing less than 2.5 kg undergoing the ASO remains high; however, most of the mortality occurred in children weighing 2.0 kg or less. Long-term outcomes among survivors are excellent.

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Chapter 5: Long-term quality of life in adult survivors after the arterial switch operation

5.1 Introduction

This study investigated quality of life in adult ASO survivors using the SF-36 quality of life questionnaire. Patients who were at least 18 years of age with a contact phone number living in the state of Victoria were included. One hundred and seven patients completed the SF-36 via phone interview. Scores from the 8 domains of the SF-36 and the SF-6D summary scores for patients aged 18-24 years and 25-34 years of age were obtained. These were compared against published data from age matched controls from the Household, Income and Labour Dynamics in Australia survey. Interestingly, patients aged 18-24 ranked their health significantly higher in 3 of the 8 domains and there was no statistically significant difference in the other 5 domains. Likewise, patients aged 25-34 scored significantly higher in 4 of the 8 domains and there was no statistically significant difference in the other 4 domains. Importantly, we found that there were no statistically significant differences in SF-6D summary scores in both age groups as compared to the population data. This suggests a similar quality of life in adult ASO survivors compared to the general population. Our study represented the largest cohort of adult ASO survivors to have quality of life examined.

5.2 Fricke TA et al. Eur J Cardiothorac Surg 2016;54:1001-1003

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Long-term quality of life in adult survivors after the arterial switch operation

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Abstract

OBJECTIVES: We sought to determine the quality of life after the arterial switch operation (ASO) using the Short Form 36 questionnaire in adult survivors.

METHODS: All patients ($n = 107$) who underwent the ASO and were 18 years of age or older living in the Australian state of Victoria with a contact telephone number were identified from the hospital database. Fifty-one (48%) patients were 18–24 years old and 56 (52%) patients were 25–34 years old. Patients completed the Short Form 36 quality of life questionnaire via telephone. The results of the 8 domains of the Short Form 36 questionnaire and the derived health state summary score (Short Form 6-Dimension) were compared against mean scores from age-matched Australian population data.

RESULTS: Compared with the Australian population age-matched data, 18- to 24-year-old ASO patients ranked their health higher in 3 of the 8 domains ($P < 0.01$). The 25–34 age group ranked their health higher in 4 of the 8 domains ($P < 0.01$). No statistically significant differences in the mean Short Form 6-Dimension scores were observed in the 18–24 age group (0.769 for ASO patients vs 0.772 for Australian population, $P = 0.85$) or the 25–34 age group (0.795 for ASO patients vs 0.780 for Australian population, $P = 0.33$).

CONCLUSIONS: Young adult survivors of the ASO have similar outcomes to age-matched controls in quality of life measured by Short Form 6-Dimension.

Keywords: Arterial switch operation • Transposition of the great arteries • Quality of life

INTRODUCTION

Current outcomes after the arterial switch operation (ASO) are excellent as survivors reach adolescence and young adulthood, with an overall low incidence of late mortality and reoperation [1–9]. Limited data exist on quality of life after the ASO in those patients who reach adulthood [10, 11]. Therefore, we sought to describe health-related quality of life in adult survivors after the ASO using the Short Form 36 (SF-36) questionnaire.

MATERIALS AND METHODS

Patients

This study was approved by the Royal Children's Hospital Human Research Ethics Committee. Patients ($n = 127$) who underwent the ASO and were 18 years of age or older living in the Australian state of Victoria with a contact telephone number were identified from the hospital database. Of the 127 patients, 19 (15%) patients were unable to be contacted using hospital record contact details and 1 (0.8%) patient declined to participate in the study. This resulted in 107 patients included for this study. The clinical characteristics of the group in this study are presented in Table 1. Fifty-one (48%) patients were 18–24 years old and 56 (52%) patients were 25–34 years old. Patients were contacted via telephone and completed the SF-36 quality of life questionnaire at this time over the telephone from May 2016 to September 2016.

Definitions

The SF-36 is a validated health-related quality of life questionnaire that contains 36 questions across 8 mental and physical health domains. These domains include physical functioning (impact of health of physical activities), role limitations caused by

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physical health problems (impact of physical health on vocational and avocational activities), general health, bodily pain (frequency and impact of pain on activities), role limitations caused by emotional problems (impact of emotional problems on vocational and avocational activities), social functioning (impact of physical or emotional problems on social activities), vitality (perception of energy and fatigue) and mental health [12]. Responses to the 36 questions indicate the presence or absence of limitations and are scored and averaged so that a higher score in a domain indicates more favourably ranked quality of life. The SF-36 can be converted to a summary score, the Short Form 6-Dimension (SF-6D) score, to present a generic single-index health state that is comparable across different disease areas and the general population. The SF-6D has interval scale property, i.e. a difference between 0.2 and 0.4 is equally valued as a difference between 0.6 and 0.8, and thus is easily interpretable. The Australian population-representative scores are estimated from the Household, Income and Labour Dynamics in Australia (HILDA) survey [13].

Statistical analysis

Data were imported into Stata version 12 (Stata Corp, College Station, TX, USA). Results of the SF-36 and the SF-6D were compared against age-matched Australian population data derived from the HILDA survey [13]. The HILDA survey is an Australian government-funded longitudinal survey of more than 17 000 Australians. A 2-sample *t*-test was used to determine any statistical significant difference between the SF-36 domains and the SF-6D scores.

Table 1: Patient clinical characteristics

No. TGA, *n* (%)	97 (91)
No. TGA-IVS, *n* (%)	64 (60)
No. TGA-VSD, *n* (%)	33 (31)
No. TBA, *n* (%)	10 (9)
No. AAO, *n* (%)	13 (12)
Age at ASO (days), median (IQR)	11 (21)
Weight at ASO (kg), median (IQR)	3.5 (0.8)
No. <2.5kg at ASO, *n* (%)	2 (2)
CPB time (min), median (IQR)	130 (50)
AXCL time (min), median (IQR)	71 (28)
No. CA used, *n* (%)	75 (70)
Duration CA (min), median (IQR)	6 (16)
No. reoperation, *n* (%)	19 (18)

AAO: aortic arch obstruction; ASO: arterial switch operation; AXCL: aortic cross-clamp; CA: circulatory arrest; CPB: cardiopulmonary bypass; IQR: interquartile range; No.: number of patients; TBA: Taussig–Bing anomaly; TGA-IVS: transposition of the great arteries with intact interventricular septum; TGA-VSD: transposition of the great arteries with ventricular septal defect.

RESULTS

The mean scores of the study group in the 8 domains and the SF-6D compared with the general age-matched Australian population are presented in Table 2. Compared with the age-matched Australian population data, 18- to 24-year-old ASO patients ranked their health significantly higher in 3 of the 8 domains. The 25- to 34-year-old ASO patients ranked their health higher in 4 of 8 domains. There were no significant differences in the mean SF-6D scores in the 18–24 age group (0.769 for ASO patients vs 0.772 for the Australian population, $P = 0.85$) or the 25–34 age group (0.795 for ASO patients vs 0.780 for the Australian population, $P = 0.33$).

DISCUSSION

We have previously reported excellent long-term clinical outcomes in patients who underwent the ASO at our institution [1–7]. The hospital mortality for the ASO at Royal Children's Hospital has been reported to be 2.8% for patients operated between 1983 and 2009 and this has not changed significantly with time [2]. Late mortality is an uncommon event with a 96% survival at 15 years postoperatively [2]. This has resulted in an ever-growing number of ASO survivors reaching adulthood in recent years. Although similar results have been reported by others [8, 9], quality of life in adult survivors of the ASO has not been as well described. As these patients begin to reach adulthood, seemingly with good outcomes in the majority of patients, focus is now placed on the general health of these individuals. Investigating health-related quality-of-life outcomes in patients with repaired congenital heart disease informs our understanding of the overall effect the condition has on survivors reaching adulthood and may help to develop therapeutic interventions to address physical and psycho-social issues. To the best of our knowledge, our study represents the largest cohort of adult ASO survivors to have quality of life examined and compared with the general age-matched population. Recently, Kalfa *et al.* [10] investigated quality-of-life outcomes in 67 adult ASO

Table 2: SF-36 domain and SF6D scores

Domain	Mean 18–24 score with SD	Mean 18–24 Aus population score with SD	*P*-value	Mean 25–34 score with SD	Mean 25–34 Aus population score with SD	*P*-value
PF	92.5 ± 10.1 (95% CI 89.6–95.3)	91.1 ± 20.3 (95% CI 90.1–92.0)	0.63	92.9 ± 12.1 (95% CI 89.6–96.1)	91.6 ± 18.3 (95% CI 90.9–92.3)	0.6
RLPH	87.3 ± 27.1 (95% CI 79.6–94.9)	88.8 ± 26.4 (95% CI 87.5–90.0)	0.69	92.4 ± 20.7 (95% CI 86.9–98.0)	88.2 ± 27.7 (95% CI 87.1–89.2)	0.25
RLEP	83.0 ± 30.1 (95% CI 74.5–91.5)	82.6 ± 32.3 (95% CI 81.1.–84.0)	0.92	92.8 ± 24.4 (95% CI 86.3–99.4)	84.6 ± 31.5 (95% CI 83.4–85.7)	0.049
Vit	69.7 ± 14.7 (95% CI 65.6–73.8)	59.8 ± 19.1 (95% CI 58.6–60.4)	<0.01	68.0 ± 18.8 (95% CI 63.0–73.1)	58.3 ± 19.0 (95% CI 57.6–59.0)	<0.01
EW	81.3 ± 16.6 (95% CI 76.7–85.6)	70.4 ± 18.3 (95% CI 69.6–71.3)	<0.01	83.5 ± 14.7 (95% CI 79.6–87.4)	72.1 ± 17.0 (95% CI 71.4–72.7)	<0.01
SF	84.6 ± 21.0 (95% CI 78.7–90.5)	83.2 ± 22.2 (95% CI 82.1–84.2)	0.65	90.0 ± 18.1 (95% CI 85.1–94.8)	84.6 ± 21.4 (95% CI 83.8–85.4)	0.06
Pain	88.7 ± 17.7 (95% CI 83.7–93.7)	81.1 ± 20.5 (95% CI 80.1–82.0)	<0.01	85.2 ± 20.8 (95% CI 79.7–90.8)	78.8 ± 21.0 (95% CI 78.0–79.6)	0.02
GH	69.7 ± 18.5 (95% CI 64.5–74.9)	70.3 ± 19.6 (95% CI 69.4–71.2)	0.84	69.4 ± 18.5 (95% CI 64.4–74.3)	70.9 ± 19.0 (95% CI 70.2–71.6)	0.56
SF6D	0.769 ± 0.098	0.772 ± 0.121	0.85	0.795 ± 0.102	0.78 ± 0.116	0.33

Aus: Australian; 95% CI: 95% confidence interval; EW: emotional well-being; GH: general health; PF: physical functioning; RLEP: role limitations due to emotional problems; RLPH: role limitations due to physical health; SD: standard deviation; SF: social functioning; SF-36: Short Form 36; SF6D: Short Form 6-Dimension; Vit: vitality.

survivors aged 18–31 years using the SF-36. They found that patients overall had a satisfying quality of life but that their cohort had poorer results in the physical domains of the SF-36 and the summary SF-6D health state was not available. Ruys *et al.* [11] reported superior results in all 8 domains of SF-36 in 30 adult ASO survivors, and the health state summary of SF-6D was not reported. Görler *et al.* [14] compared SF-36 results from 24 ASO survivors above the age of 14 with 74 atrial switch survivors as well as the general population. No statistically significant differences were found between the SF-36 domains and the SF-6D scores were not reported.

Our results as summarized by the SF-6D demonstrated that adult ASO survivors have similar overall quality of life when compared with the general age-matched population. The SF-6D, derived from the SF-36 questionnaire, is a widely-used generic measure of health that can be used to describe more than 18 000 health states and generate quality-adjusted life years. It is used by health regulatory agencies around the world to compare the overall impact of interventions across disease areas to facilitate funding decisions. Although the SF-36 questionnaire is typically a written survey, telephone administration has been shown to be equivalent to the written form [15]. Absolute differences in the SF-36 domains between our ASO patients and the general population are difficult to interpret; however, ASO survivors did have similar scores in the majority of the domains and noticeably higher scores in the 2 domains of vitality and emotional well-being. Furthermore, there were no statistically significant differences in the SF-6D scores in the 2 ASO age groups compared with the Australian population. Therefore, it is reasonable to conclude that the quality of life of ASO survivors is comparable with the general public in this sample.

Limitations

One limitation of this study is that patients without a valid contact telephone number were unable to be investigated. As there could be various reasons as to why an adult ASO patient would have a contact number different from that on the hospital record, and given the excellent survival of 96% at 15 years postoperatively for this patient group [3], we believe that this would have a limited impact on our conclusion. Also, the results of our study come from a single institution and thus may not be generalizable for ASO survivors worldwide.

CONCLUSION

Young adult survivors of the ASO have similar quality-of-life outcomes to age-matched controls measured by the SF-6D.

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Conflict of interest: none declared.

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Chapter 6: Outcomes of the arterial switch operation in patients with aortic arch obstruction

6.1 Introduction

Patients with TGA or TBA with associated AAO represent a challenging subgroup undergoing the ASO. However, there are few studies examining long-term outcomes in this group of patients despite the possibility of a higher reintervention rate of the neo-aorta and the right ventricular outflow tract. As more and more of these patients are reaching adulthood, we decided to determine their long term-outcomes with an emphasis on reintervention for right sided obstruction and reintervention for recurrent AAO. In a cohort of 83 patients with a median follow-up of 13 years, we found that these patients had a higher operative mortality as well as a higher reintervention rate for right sided obstruction and a low reintervention rate for recurrent AAO. We concluded that avoidance of patch material in reconstructing the neo-aorta may lead to a lower risk of AAO recurrence. For the reasons stated above, patients who have undergone ASO and concomitant arch repair require close follow-up.

To date, this study has the longest follow-up of ASO patients with concomitant AAO repair.

6.2 Fricke TA et al. J Thorac Cardiovasc Surg 2020;159:592-599

Outcomes of the arterial switch operation in patients with aortic arch obstruction

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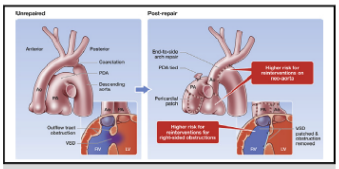
ABSTRACT

Objective: Transposition of the great arteries or Taussig–Bing anomaly with concomitant aortic arch obstruction is uncommon, with limited data on long-term outcomes after arterial switch operation and aortic arch obstruction repair. This study sought to determine outcomes of patients undergoing arterial switch operation and aortic arch obstruction repair at a single institution.

Methods: From 1983 to 2015, 844 patients underwent an arterial switch operation for biventricular repair at The Royal Children's Hospital. Eighty-three (9.8%, 83/844) patients underwent an arterial switch operation and aortic arch obstruction repair.

Results: Fifty-five (66%, 55/83) patients had transposition of the great arteries. and 28 (34%, 28/83) patients had Taussig–Bing anomaly. Fifty-nine (71%, 59/83) patients underwent arterial switch operation and aortic arch obstruction repair as a single-stage procedure, and 24 (29%, 24/83) patients underwent arterial switch operation and aortic arch obstruction repair as a 2-stage procedure. There were 5 early deaths (6.0%, 5/83). Follow-up was available for 74 (95%) of the 78 survivors. Median follow-up was 13.3 years (interquartile range, 7.3-19.3 years; range, 1-30 years). There were no late deaths. Freedom from reintervention was 77%, 71%, and 68% at 5, 10, and 20 years, respectively. Reintervention was more common compared with patients without aortic arch obstruction ($P < .001$). Reintervention for right-sided obstruction was more common compared with patients without aortic arch obstruction ($P = .006$).

Conclusions: Patients with transposition of the great arteries or Taussig–Bing anomaly with associated aortic arch obstruction have a higher reintervention rate, especially for right-sided obstruction. Closer monitoring of this subgroup of patients is warranted. (J Thorac Cardiovasc Surg 2019;■:1-8)



Transposition with AAO represents a subgroup of patients who may be at a higher risk of reintervention for right-sided obstruction and reintervention on the neo-aorta.

Central Message

Patients with dTGA or TBA with associated AAO represent a higher-risk subgroup undergoing the ASO with a higher operative mortality and reintervention rate, particularly for right-sided obstruction.

Perspective

Transposition of the great arteries or TBA with concomitant AAO is repaired by an ASO with an aortic arch repair. An increasing number of survivors are now reaching adulthood. These patients are at a higher risk of late reintervention, particularly for right-sided obstruction, and therefore require closer follow-up.

See Commentary on page XXX.

CONG

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D-transposition of the great arteries (dTGA) and Taussig–Bing anomaly (TBA) with associated aortic arch obstruction (AAO) are uncommon anomalies. Approximately 5% of patients with dTGA have associated AAO,[1,2] and up to 50% of patients TBA have AAO.[3,4] Although 2-stage repair can be performed and can yield good results, it has largely been abandoned in favor of single-stage repair at most pediatric cardiac centers worldwide.[5-7] We have previously demonstrated that the need for AAO repair was a risk factor for mortality after the arterial switch operation (ASO) at our institution,[1,2] and others have also observed a higher mortality in this group.[3,8-13] Furthermore, a higher rate of reintervention has been reported.[8,14] However, there is a paucity of data on the long-term outcomes in these patients. To the best of our knowledge, there

Abbreviations and Acronyms

AAO = aortic arch obstruction
ASO = arterial switch operation
CI = confidence interval
dTGA = D-transposition of the great arteries
ECMO = extracorporeal membrane oxygenation
LV = left ventricular
MCS = mechanical circulatory support
NYHA = New York Heart Association
PA = pulmonary artery
TBA = Taussig–Bing anomaly
VSD = ventricular septal defect

are no currently studies specifically looking at the outcome of these patients with a mean or median follow-up greater than 9 years. Despite the rarity of TGA or TBA with associated AAO, there is an increasing number of survivors reaching adolescence and young adulthood. Therefore, it seems timely to define the long-term expectations in this challenging subgroup of patients.

MATERIALS AND METHODS

Patients

This study was approved by The Royal Children's Hospital Human Research Ethics Committee. All data were collected retrospectively from hospital records. Valvular function and qualitative assessment of left ventricular (LV) function were determined from echocardiography reports.

Between May 1983 and January 2015, 844 patients underwent an ASO for biventricular repair at The Royal Children's Hospital. A total of 761 (90.2%, 761/844) patients underwent ASO without AAO repair and 83 (9.8%, 83/844) patients underwent an ASO and AAO repair as a single-stage or 2-stage repair. Patients who underwent 2 stage repair were included if they survived until ASO.

Definitions

Early death or reoperation was defined as death or reoperation occurring before hospital discharge or within 30 days of ASO and AAO repair. Late death was defined as death occurring after discharge and more than 30 days after ASO. Reintervention was defined as reoperation or transcatheter procedure. Reintervention for right-sided obstruction was defined as reintervention for obstruction at the branch pulmonary artery (PA), main PA, neopulmonary valve, or subvalvular level. Reoperation was defined as an operation on the heart or great vessels performed after the ASO excluding exploration for bleeding, wound debridement, mechanical circulatory support (MCS), and pacemaker replacement. Functional status was described according to the New York Heart Association (NYHA) classification.

Surgical Procedures

This study represents an operative experience of more than 30 years. At the beginning of the experience, patients underwent a 2-stage repair with an initial arch repair followed by an ASO at a later date. Our current preferred approach to TGA or TBA with associated AAO is single-stage procedure with an end-to-side repair of the AAO. The end-to-side repair involves the dissection and division of the first 3 pairs of intercostal arteries, longitudinal incision in the inner curvature of the ascending aorta opposite to the origin of the innominate artery, and anastomosis of the descending aorta to the ascending aorta as previously reported.[2,15] A triangular resection of the noncoronary sinus is performed to reduce the diameter of the sinotubular junction if there is a large size discrepancy between the neo-aorta and neopulmonary root. Our technique of the ASO involves the creation of medially based rectangular flaps in the neoaortic sinuses for coronary translocation as described earlier.[16-18]

Statistical Analysis

Data were imported into Stata Version 12 (StataCorp LP, College Station, Tex). Continuous variables were reported as a median with an accompanying interquartile range. Categoric variables were presented as frequencies and percentages. Kaplan–Meier curves were constructed to display freedom from the study's outcomes. Statistical significance in differences between groups for freedom from reintervention was compared using the log-rank test. In patients with AAO, Cox regression analysis was used to determine risk factors for overall reintervention and reintervention for right-sided obstruction.

RESULTS

Of the 83 patients, 55 (66%, 55/83) had dTGA and 28 (34%, 28/83) had TBA. Sixty-one patients (73%, 61/83) had coarctation of the aorta, of whom 34 had associated hypoplasia of the aortic arch. Twelve (14%, 12/83) patients had a hypoplastic aortic arch without a discrete coarctation, and 10 (12%, 10/83) patients had an interrupted aortic arch. Fifty-nine (71%, 59/83) patients underwent a single-stage procedure, and 24 (29%, 24/83) patients underwent ASO and AAO repair as a 2-stage procedure. Of these 24 patients, 21 (88%, 21/24) had arch repair before ASO and 3 (12%, 3/24) had arch repair after ASO. The median age at operation was 9 days (interquartile range, 5.2-33), and the median weight was 3.5 kg (interquartile range, 3.2-3.9). AAO most commonly was repaired with end-to-side anastomosis without any patch material (45%, 37/83). Ten (12%, 10/83) patients had right ventricular outflow tract resection at time of ASO. Table 1 summarizes the perioperative and operative data of the patients.

Mortality and Functional Status

There were 5 early deaths (6.0%, 5/83), all in patients with dTGA. Four (6.8%, 4/59) deaths occurred in patients undergoing single-stage repair, and 1 (4.2%, 1/24) death occurred in a patient undergoing 2-stage repair. The early mortality for patients undergoing single-stage repair with end-to-side arch repair was 5.4% (2/37). Causes of death were myocardial ischemia (n = 3), respiratory failure after extracorporeal membrane oxygenation (ECMO) support (n = 1), and sepsis (n = 1).

Patient 1 had dTGA, ventricular septal defect (VSD), and coarctation of the aorta with a hypoplastic aortic arch. The patient underwent subclavian flap repair of the AAO at day 8 of life and ASO 7 weeks later at a weight of 4.0 kg in 1990. The patient had a cardiac arrest day 1 postoperatively and was placed on ECMO. The patient was unable to be weaned from ECMO and died 9 days after ASO.

TABLE 1. Preoperative and operative data

	Overall (n = 83)	dTGA (n = 55)	TBA (n = 28)
Median age at operation (d)	9 (IQR, 5.2-33)	9 (IQR, 5.0-31)	9 (IQR, 5.7-33)
Median weight at operation (kg)	3.5 (IQR, 3.2-3.9)	3.5 (IQR, 3.3-3.9)	3.4 (IQR, 3.2-3.6)
VSD (no. of patients)	71 (86%)	43 (78%)	28 (100%)
Coarctation of the aorta (no. of patients)	61 (74%)	43 (78%)	18 (64%)
Hypoplastic aortic arch (no. of patients)	46 (55%)	30 (55%)	16 (57%)
Interrupted aortic arch (no. of patients)	10 (12%)	4 (7.3%)	6 (21%)
Normal coronary anatomy (no. of patients)	49 (59%)	36 (65%)	13 (46%)
Abnormal coronary anatomy (no. of patients)	34 (41%)	19 (35%)	15 (54%)
Intramural coronary (no. of patients)	3 (3.6%)	2 (3.6%)	1 (3.6%)
Single coronary (no. of patients)	4 (4.8%)	4 (7.3%)	0 (0%)
Single-stage repair (no. of patients)	59 (71%)	38 (69%)	21 (75%)
2-stage repair (no. of patients)	24 (29%)	17 (31%)	7 (25%)
Median CPB time (min)	227 (IQR, 165-279)	212 (IQR, 157-279)	238 (IQR, 182-277)
Median AXCL time (min)	120 (IQR, 92-169)	120 (IQR, 91-169)	120 (IQR, 105-151)
CA used (no. of patients)	29 (35%)	20 (36%)	9 (32%)
Median CA time (min)	29 (IQR, 23-45)	28 (IQR, 16-39)	39 (IQR, 29-47)
End-to-side arch repair (no. of patients)	37 (45%)	20 (36%)	17 (61%)
End-to-end arch repair (no. of patients)	19 (23%)	15 (27%)	4 (14%)
End-to-end, augmented with a patch (no. of patients)	8 (10%)	7 (13%)	1 (3.6%)
Subclavian flap arch repair (no. of patients)	18 (22%)	13 (24%)	5 (18%)
Interposition graft arch repair (no. of patients)	1 (1.2%)	0 (0%)	1 (3.6%)
Postoperative mechanical support (no. of patients)	9 (11%)	6 (11%)	3 (11%)

dTGA, Transposition of the great arteries; *TBA*, Taussig–Bing anomaly; *IQR*, interquartile range; *VSD*, ventricular septal defect; *CPB*, cardiopulmonary bypass; *AXCL*, aortic crossclamp; *CA*, circulatory arrest.

Patient 2 was born at 31 weeks with dTGA, VSD, coarctation of the aorta with a hypoplastic aortic arch, and severe bronchopulmonary dysplasia. The patient was ventilated for 7 weeks before surgery to gain weight. The patient underwent single-stage ASO and end-to-end repair on day 52 of life at a weight of 2.0 kg in 1990. The postoperative period was complicated by sepsis of unclear etiology, and the patient died on day 6 postoperatively.

Patient 3 had dTGA, multiple VSDs, and coarctation of the aorta with a hypoplastic aortic arch. The patient underwent single-stage ASO and end-to-end repair on day 3 of life at a weight of 3.4 kg in 1992. The patient had a cardiac arrest the following day and could not be resuscitated.

Patient 4 had situs inversus, dTGA, VSD, and coarctation of the aorta with a hypoplastic aortic arch. The patient underwent single-stage ASO and end-to-end repair with patch augmentation on day 8 of life at a weight of 3.6 kg in 2009. The postoperative period was complicated by a bronchopleural fistula and wound infection. The patient died of respiratory failure on day 47 postoperatively.

Patient 5 had dTGA, VSD, and interrupted aortic arch. The patient underwent single-stage ASO and end-to-side repair on day 13 of life at a weight of 3.3 kg in 2010. Intraoperative revision of the left coronary button was required, and ECMO was instituted in the operating room. The patient was unable to be weaned from ECMO and died on day 42 postoperatively.

Follow-up after hospital discharge was available for 74 (95%) of the 78 survivors. Median follow-up was 13.3 years (interquartile range, 7.3-19.3 years; range, 1-30 years). There were no late deaths. Overall survival was 94% (95% confidence interval [CI], 86-97) at 20 years postoperatively. Seventy-three (99%, 73/74) patients were in NYHA class I, and 1 (1.0%, 1/74) patient was in NYHA class II.

Reintervention

There were 36 reinterventions (30 reoperations and 6 catheter reinterventions) in 23 patients that occurred at a median 2.2 years after ASO (interquartile range, 5 months to 9 years). Freedom from reintervention was 77% (95% CI, 65-85), 71% (95% CI, 59-81), and 68% (95% CI, 54-78) at 5, 10, and 20 years, respectively. Freedom from reintervention in patients without AAO operated over the same period of time was 89% (95% CI, 86-91), 89% (95% CI, 86-91), and 81% (95% CI, 76-84) at 5, 10, and 20 years, respectively (Figure 1). The difference in

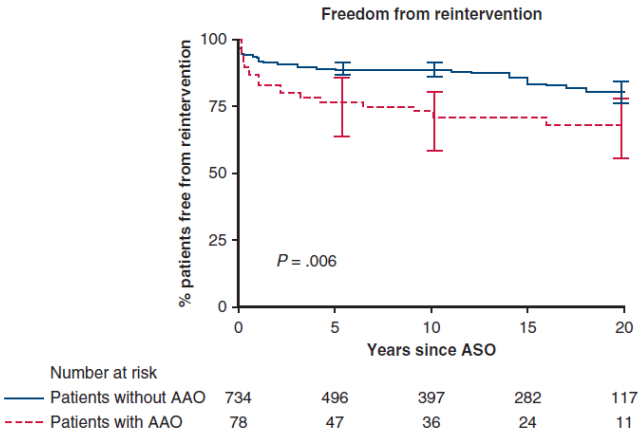

FIGURE 1. Freedom from reintervention. Freedom from reintervention was 77% (95% CI, 65-85), 71% (95% CI, 59-81), and 68% (95% CI, 54-78) at 5, 10, and 20 years, respectively. Freedom from reintervention in patients without AAO was 89% (95% CI, 86-91), 89% (95% CI, 86-91), and 81% (95% CI, 76-84) at 5, 10, and 20 years, respectively. *ASO*, Arterial switch operation; *AAO*, aortic arch obstruction.

reintervention between patients with AAO and patients without AAO was statistically significant ($P = .006$). Twelve (43%, 12/28) patients with TBA required reintervention compared with 11 (22%, 11/50) surviving patients with dTGA with follow-up. TBA was not a risk factor for reintervention on Cox regression (Table 2). Freedom from reintervention for patients undergoing single-stage repair with end-to-side arch repair was 74% at 5, 10, and 20 years. Postoperative MCS was a risk factor for reintervention on univariate analysis (HR, 4.4; $P = .008$) (Table 2).

The most common cause for reintervention was right-sided obstruction in 11 (15%, 11/74) surviving patients with follow-up. Stenosis occurred at the branch PA level (n = 6), main PA (n = 6), neopulmonary valve (n = 5), or subvalvular level (n = 6). Stenosis was repaired surgically in all patients except 1 with valvular stenosis who required both catheter reintervention and reoperation, 2 with main PA stenosis who required both catheter reintervention and reoperation, and 1 with branch PA stenosis who required both catheter reintervention and reoperation. Freedom from reintervention for right-sided obstruction was 88% (95% CI, 78-94), 86% (95% CI, 76-92), and 83% (95% CI, 71-91) at 5, 10, and 20 years, respectively. Freedom from reintervention for right-sided obstruction in patients without AAO operated over the same period of time was 98% (95% CI, 96-99), 97% (95% CI, 96-98), and 95% (95% CI, 93-97) at 5, 10, and 20 years, respectively (Figure 2). This difference was statistically significant ($P < .001$). Seven (25%, 7/28) patients with TBA required reintervention for right-sided obstruction compared with 4 (8%, 4/50) surviving patients with dTGA with follow-up. TBA was not a risk factor for reintervention for right-sided obstruction in patients with AAO on Cox regression (Table 2). Freedom from

TABLE 2. Risk factor analysis for overall reintervention and reintervention for right-sided obstruction in patients with aortic arch obstruction

Variable	HR (95% CI)	*P* value
Risk factor analysis for overall reintervention		
RVOTO resection at time of ASO	2.2 (0.82-6.0)	.12
TGA	0.52 (0.23-1.2)	.11
TBA	1.9 (0.85-4.4)	.11
COA	0.51 (0.21-1.2)	.13
HAA	1.3 (0.56-3.0)	.55
IAA	1.8 (0.62-5.5)	.27
Operative weight <2.5 kg	0.97 (0.13-7.3)	.98
Single coronary artery	0.61 (0.08-4.6)	.63
Intramural coronary artery	1.5 (0.20-12)	.67
Postoperative MCS	4.4 (1.5-13)	.008
Risk factor analysis for reintervention for right-sided obstruction		
RVOTO resection at time of ASO	1.5 (0.33-7.1)	.59
TGA	0.35 (0.10-1.2)	.09
TBA	2.9 (0.84-9.8)	.09
COA	0.38 (0.12-1.3)	.12
HAA	0.72 (0.22-2.4)	.59
IAA	3.1 (0.81-12)	.10
Operative weight <2.5 kg	-	-
Single coronary artery	1.79 (0.22-13)	.62
Intramural coronary artery	3.1 (0.39-25)	.28
Postoperative MCS	1.3 (0.16-10)	.81

HR, Hazard ratio; *CI*, confidence interval; *RVOTO*, right ventricular outflow tract obstruction; *ASO*, arterial switch operation; *TGA*, transposition of the great arteries; *TBA*, Taussig–Bing anomaly; *COA*, coarctation of aorta; *HAA*, hypoplastic aortic arch; *IAA*, interrupted aortic arch; *MCS*, mechanical circulatory support.

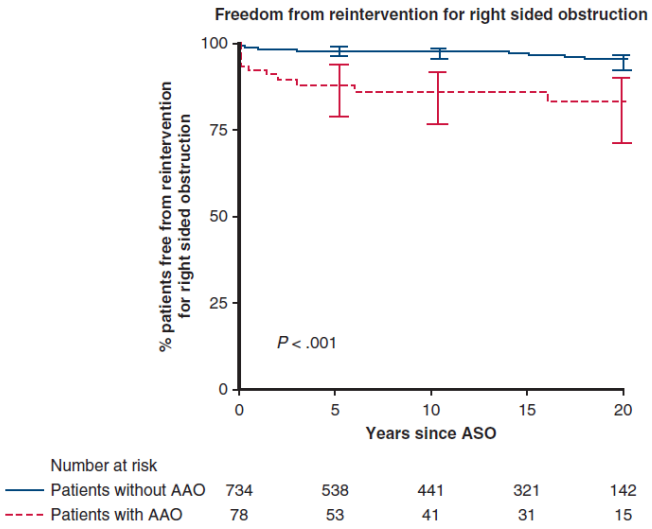

FIGURE 2. Freedom from reintervention for right-sided obstruction. Freedom from reintervention for right-sided obstruction was 88% (95% CI, 78-94), 86% (95% CI, 76-92), and 83% (95% CI, 71-91) at 5, 10, and 20 years, respectively. Freedom from reintervention for right-sided obstruction in patients without AAO was 98% (95% CI, 96-99), 97% (95% CI, 96-98), and 95% (95% CI, 93-97), at 5, 10, and 20 years, respectively. *ASO*, Arterial switch operation; *AAO*, aortic arch obstruction.

reintervention for right-sided obstruction in patients undergoing single-stage repair with end-to-side arch repair was 89% (95% CI, 72-96) at 5, 10, and 20 years.

Four (5.4%, 4/74) patients required 5 reinterventions (2 reoperations and 3 catheter reintervention) for recurrent AAO at a median of 2.1 years after ASO (interquartile range, 0.5-2.2 years). Of these 4 patients, 2 (5.7%, 2/35) had undergone a single-stage repair with end-to-side arch repair and later required balloon angioplasty for recurrent AAO. Two (5.7%, 2/35) patients who underwent single-stage repair with end-to-side arch repair required reoperation for supravalvular aortic stenosis.

Five (6.8%, 5/74) patients required reoperation on the neoaortic valve for neoaortic regurgitation at a median of 8 years after ASO (interquartile range, 4-16 years). This included 3 neoaortic valve repairs, 1 neoaortic valve replacement, and 1 Bentall procedure. Of these 5 patients, 2 (5.7%, 2/35) had undergone a single-stage repair with end-to-side arch repair.

Valvular and Left Ventricular Function

Three (4.1%, 3/74) patients had more than mild neo-aortic valve regurgitation. Five (6.8%, 5/74) patients had more than mild tricuspid regurgitation, 2 (2.7%, 2/74) patients had more than mild mitral regurgitation, and 1 (1.4%, 1/74) patient had more than mild neopulmonary regurgitation. One (1.4%, 1/74) patient had more than mild neopulmonary valve stenosis.

Qualitative assessment of LV function was available in 60 survivors (81%, 60/74). Fifty-eight patients (97%, 58/60) had normal LV function, and 2 patients (3%, 2/60) had mild LV dysfunction.

Arrhythmia

One patient (1.4%, 1/74) had a known arrhythmia at last follow-up (Wolf–Parkinson–White syndrome). No patients required permanent pacemaker insertion.

DISCUSSION

Despite an ever-increasing number of survivors, only a few studies specifically report the outcomes of ASO with associated repair of AAO.[3,8-13,19] To the best of our knowledge, the current study has the longest follow-up of the patients who underwent ASO with AAO repair (Table 3). Operative mortality in patients undergoing ASO and AAO repair is substantially higher than that expected for simple ASO as reported by most institutions (Table 3) and has ranged widely from 1.9% to 24%.[3,9-13] Overall operative mortality in our patients was 6.0% (5/83). Operative mortality was 6.8% (4/59) for patients undergoing single-stage repair and 5.4% (2/37) for patients undergoing single-stage repair with end-to-side arch repair without patches. Thus, operative mortality in our patients compares favorably to that of most others studies. Encouragingly, our study demonstrated no late mortality

TABLE 3. Studies specifically on outcomes of repair of D-transposition of the great arteries/Taussig–Bing anomaly with aortic arch obstruction

Author	Study period	No. patients	Follow-up	Early mortality	Reintervention	Reintervention for PS	Reintervention for recurrent AAO	Reoperation for neoaortic valve regurgitation
Bokenkamp and colleagues[8]	1977-2015	36 single stage 9 two stage	Median 6 y	13%	Freedom from reoperation 49.9% at 10 y	Freedom from reoperation for RVOTO 66.5% at 10 y	7 (20%, 7/35) patients	No reoperations
Choi and colleagues[9]	2003-2015	19 single stage	Mean 3.4 y	11%	Freedom from reintervention 55% at 5 y	NR	1 (6.3%, 1/16) patient	No reoperations
Gontijo Filho and colleagues[10]	1998-2005	14 single stage, 7 two stage	NR	24%	NR	NR	NR	NR
Hirata and colleagues[19]	1991-2006	53 single stage	Mean 7.8 y	1.9%	Freedom from reintervention 74% at 10 y	Freedom from reoperation for right-sided obstruction 80% at 10 y	NR	No reoperations
Huber and colleagues[11]	1999-2009	22 single stage	Mean 4.8 y	14%	Freedom from reintervention 50% (TGA) and 54% (TBA) at 10 y	4 (22%, 4/18) patients	8 (44%, 8/18) patients	No reoperations
Luo and colleagues[3]	2006-2015	39 single stage	Mean 3.2 y	7.7%	Freedom from reoperation 77% at 5 y	4 (11%, 4/36) patients	4 (11%, 4/36) patients	No reoperations
Mohammadi and colleagues[12]	1983-2002	67 single stage 42 two stage	Mean 8.1 y	9.2%	50 (46%, 50/109) patients reoperated	NR	10 (17%, 10/109) patients	10 (9.2%, 10/109) patients
Pocar and colleagues[13]	1990-1998	38 single stage	Mean 8.3 y	24%	Freedom from reintervention 72% at 10 y	3 (10%, 3/29) patients	3 (10%, 3/29) patients	No reoperations

PS, Pulmonary stenosis; *AAO*, aortic arch obstruction; *RVOTO*, right ventricular outflow tract obstruction; *NR*, not reported; *TGA*, transposition of the great arteries; *TBA*, Taussig–Bing anomaly.

and excellent long-term functional status in this subgroup of patients.

As in previous reports,[8,13] we found a relatively high reintervention rate in children with AAO (Figure 3). Freedom from reintervention was 68% at 20 years in patients with AAO compared with 81% in those without AAO. Freedom from reintervention for patients undergoing single-stage end-to-side arch repair was similar to the overall reintervention rate at 74% at 20 years. Reintervention was most commonly for right-sided obstruction. Reintervention for right-sided obstruction is more common in patients with AAO or TBA.[8,13,19-22] Right-sided obstruction occurred at all levels from the branch pulmonary arteries to the subvalvular level in almost equal frequency. In particular, patients with AAO may be at a risk of right-sided obstruction because the native aortic annulus is often relatively small with or without subvalvular obstruction.[2,8,19] It is important to relieve any subvalvular obstruction at the time of ASO in these patients to reduce the risk of late reoperation, although routine resection of the conal septum was not performed at our institution. This is especially important for patients with TBA. Although TBA was not a risk factor for reintervention for right-sided obstruction, likely because of small numbers, conal malalignment may further contribute to subvalvular obstruction necessitating reoperation for recurrent right-sided obstruction.

Reintervention for recurrent AAO was uncommon in our patients, with only 4 (5.4%, 4/74) requiring reoperation or catheter reintervention. More specific to our current practice today, only 2 patients (5.7%, 2/35) after end-to-side repair required reintervention for recurrent AAO. Reintervention for recurrent AAO has been reported from 6.3% to 44% in ASO AAO survivors[3,8,9,11-13] with the adoption of different initial arch repair techniques. Although arch repair techniques varied over the 30-year

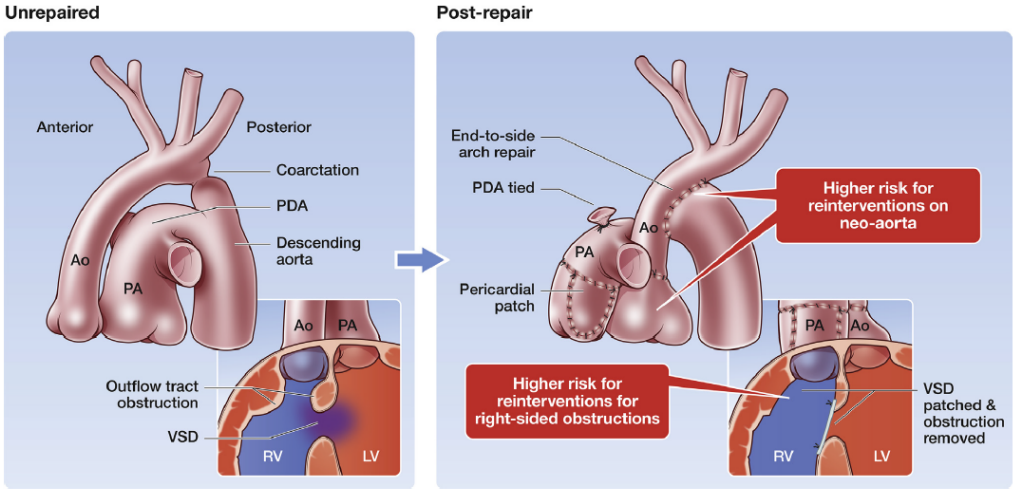

FIGURE 3. Transposition with AAO represents a subgroup of patients who may be at a higher risk of reintervention for right-sided obstruction and reintervention on the neo-aorta. *PDA*, Patent ductus arteriosus; *AO*, aorta; *PA*, pulmonary artery; *VSD*, ventricular septal defect; *RV*, right ventricle; *LV*, left ventricle.

experience of our institution, the current preferred technique at our institution is an end-to-side repair without patch augmentation as a single-stage procedure.[15] Two-stage repair of dTGA or TBA with AAO is now rarely performed at our institution. Others have advocated the use of patch augmentation of the arch with good results and a low rate of reintervention for recurrent AAO.[13,23] In particular, Pocar and colleagues[13] reported outcomes in 38 patients who underwent single-stage repair at a single institution. Their arch repair of choice for most patients involved the used of a pericardial patch to enlarge the curvature of the aortic arch. Despite an operative mortality rate of 24%, only 3 of their 28 survivors required balloon angioplasty for recoarctation after a mean follow-up of 8.3 years. We think that arch repair without the use of patch material leads to a low rate of recurrent AAO. Because of the small number of patients who developed recurrent AAO in our study, we were unable to statistically analyze any differences in recurrent AAO between arch repair techniques. In most cases, the size discrepancy between the aorta and the main PA can be corrected with a small triangular resection of the main PA without the use of patching. However, we acknowledge that 2 patients in our study who underwent end-to-side arch repair did develop supravalvular aortic stenosis that required reoperation.

Reoperation on the neoaortic valve occurred in 5 patients (6.8%, 5/74). This is higher than in most other published series (Table 2). This finding can be explained by the fact that reoperation for neo-aortic valve regurgitation was a late complication occurring at a median 8 years after ASO in our study. Other series have not seen this need for reoperation because of shorter follow-up periods. Encouragingly, although enlargement of the native pulmonary trunk is part of the pathology (13), only 1 patient (1.4%, 1/74) in our study required neoaortic root replacement with a Bentall procedure.

In view of the higher need for reintervention, particularly because of right-sided obstruction, this subgroup of patients should not be considered to be cured and require lifelong follow-up.

Study Limitations

A limitation of this study was its retrospective nature. This study covered a lengthy period of time, and changes in management may have influenced our outcomes. Because of patient numbers, we were unable to statistically determine any significant differences in outcomes between different arch repair techniques.

CONCLUSIONS

Patients with dTGA or TBA with associated AAO represent a higher-risk subgroup undergoing the ASO. These patients have a higher reintervention rate, particularly for right-sided obstruction. Reintervention for recurrent AAO is uncommon. Ongoing follow-up is important as these patients progress through adulthood.

Conflict of Interest Statement

Dr Brizard has a financial relationship with Admedus. Dr d'Udekem has a financial relationship with Actelion and MSD. All other authors have nothing to disclose with regard to commercial support.

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Key Words: arterial switch operation, transposition of the great arteries, aortic arch obstruction

Chapter 7: Pregnancy outcomes in women after the arterial switch operation

7.1 Introduction

An increasing number of women who have had an ASO are reaching child-bearing age. Data on women who have had an ASO undergoing pregnancy are limited. This is reflected in American and European guidelines for managing congenital heart disease in pregnancy (95, 96). Considering that pregnancy represents a considerable physiological challenge and few studies exist, we sought to determine maternal cardiac, obstetric and fetal outcomes in ASO survivors undergoing pregnancy.

In 11 women who underwent 17 pregnancies, there were 2 maternal cardiac complications. There were 15 maternal obstetric complications in 10 women. This was a relatively high and unexpected number of obstetric complications that we were unable to explain. There was 1 neonatal complication in a child who was premature and no child was born with congenital heart disease. As such, we concluded that pregnancy in female ASO survivors appears to be safe in the majority of women.

This study represents only the third published series on pregnancy outcomes after the ASO and the first published in Australian patients.

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ORIGINAL ARTICLE

Pregnancy Outcomes in Women After the Arterial Switch Operation

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Background Pregnancy outcomes after the arterial switch operation (ASO) are rare. We sought to determine outcomes of ASO survivors who underwent pregnancy.

Methods Female patients who had an ASO and underwent pregnancy were identified from the congenital heart disease pregnancy clinic at The Royal Melbourne Hospital. All follow-up data were collected retrospectively by medical record review.

Results Eleven (11) women were identified as having undergone medical care during pregnancy, from the adult congenital database, at The Royal Melbourne Hospital. There were 17 successful pregnancies, and nine women have been followed post pregnancy. Of the 17 successful deliveries, eight were delivered by Caesarean section, seven were vaginal deliveries and two were instrumented vaginal deliveries. Of the eight Caesarean sections, five were emergency and three were elective. The indications for emergency Caesarean section were obstructed labour (n = 2), abnormal cardiotocography (n = 1), obstructed labour and abnormal cardiotocography (n = 1) and congestive cardiac failure (n = 1). There was one neonatal complication (respiratory distress requiring intubation) in a child born at 31 weeks. There were maternal obstetric complications in 10 patients. There were two maternal cardiac complications during pregnancy (heart failure and rapid atrial fibrillation/flutter). There was no change in left ventricular function post-pregnancy. There was progression of severity of neo-aortic valve regurgitation in two patients post pregnancy (trivial to mild and moderate-severe to severe respectively).

Conclusion Pregnancy post ASO appears to be safe in the majority of women. Maternal cardiac complications are uncommon in patients without residual significant haemodynamic lesions, although maternal obstetric complications may be common.

Keywords Pregnancy • Arterial switch operation • Transposition of the great arteries

Abbreviations: AHA, American Heart Association; AR, neo-aortic valve regurgitation; ASO, arterial switch operation; BSA, body surface area; LV, left ventricular; PR, neo-pulmonary regurgitation; RV, right ventricular; TGA, transposition of the great arteries; TTE, transthoracic echocardiography; WHO, World Health Organization; AHA/ACC, American Heart Association/American College of Cardiology; VSD, ventricular septal defect; ESC, European Society of Cardiology; PPH, postpartum haemorrhage; NYHA, New York Heart Association; PAB, pulmonary artery banding

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Introduction

The arterial switch operation (ASO) is the procedure of choice for most children born with transposition of the great arteries (TGA) and has excellent early and midterm outcomes [1–6]. Survival at 25-year follow-up has been reported to be as high as 97% [7]. As such, an increasing number of women who have had an ASO are reaching child-bearing age. Whilst the majority of ASO survivors reach young adulthood, the potential for problems post ASO remains. These include neo-aortic root dilatation, neo-aortic valve regurgitation (AR), pulmonary stenosis and coronary artery stenosis. Pregnancy represents a significant physiological challenge [8,9] and may contribute to worse outcomes in some cardiac diseases [10–13]. The effect of pregnancy on female ASO survivors has not been extensively studied and it is unknown if women who have had an ASO are at a higher risk of cardiac and obstetric complications during and after pregnancy. Thus, we sought to determine outcomes of ASO survivors who underwent pregnancy.

Methods

This study was approved by The Royal Children's Hospital Human Research Ethics Committee and The Royal Melbourne Hospital Human Research Ethics Committee. Female patients who had an ASO at The Royal Children's Hospital in Melbourne and experienced a pregnancy were identified from the congenital heart disease pregnancy clinic at The Royal Melbourne Hospital. All follow-up data were collected retrospectively. Follow-up of patients was obtained from medical records of The Royal Children's Hospital, The Royal Melbourne Hospital and obstetric hospitals. Available pre-pregnancy and post-pregnancy transthoracic echocardiograms were reviewed by a cardiologist and re-reported. Maternal and fetal complications during pregnancy were obtained from outpatient clinic notes and discharge summaries. The Wilcoxon signed-rank test was used to determine any statistically significant difference between pre-pregnancy and post-pregnancy left ventricular (LV) size, LV size/body surface area (BSA), right ventricular (RV) size and neo-aortic root size.

Results

Eleven (11) women were identified as having undergone successful pregnancy, from the adult congenital database at The Royal Melbourne Hospital (Table 1).

Six patients underwent ASO in the first 2 weeks of life. Of the five patients operated later, two patients initially underwent atrial switch repairs. These two patients developed right ventricular dysfunction, underwent pulmonary artery banding (PAB) and subsequent takedown of the atrial switch repair with concomitant ASO at 3 years and 10 years of age, respectively. One patient was born with Taussig-Bing anomaly and underwent PAB during infancy with ASO at 4 years of age. One patient was born with multiple ventricular septal defects (VSD) and left ventricular outflow tract obstruction and underwent ASO at 21 months of age. One patient underwent ASO and VSD closure at 3 months of age after a delayed presentation.

There were 17 successful pregnancies. Mean gestation was 38.5 ± 2.2 weeks and mean birth weight was 3.6 ± 0.3 kg. Mean maternal age at time of delivery was 29.3 ± 3.4 years. Of the 11 women who have delivered, nine have been followed at The Royal Melbourne Hospital post pregnancy. Eight (8) patients had both pre-pregnancy and postpartum transthoracic echocardiography (TTE) data available (Table 2). Two (2) patients did not have pre-pregnancy TTE data either due to a failure to attend a clinic appointment (n = 1) or being lost to follow-up following transition from paediatric to adult care (n = 1, i.e. one patient attended her first adult appointment whilst pregnant) and two patients did not have post-pregnancy TTE data either due to a failure to attend a clinic appointment (n = 1) or relocation to a different state of the country (n = 1). Pre-pregnancy TTE was performed a mean of 22 months (range 6 months to 65 months) before delivery and postpartum TTE was performed a mean of 18 months (range 2 months to 44 months) postpartum.

Mode of Delivery and Neonatal Complications

Of the 17 successful deliveries, eight were delivered by Caesarean section, seven were vaginal deliveries and two were instrumented vaginal deliveries. Of the eight Caesarean sections, five were emergency and three were elective. The indications for emergency Caesarean section were largely obstetric: obstructed labour (n = 2), abnormal cardiotocography (n = 1), obstructed labour and abnormal cardiotocography (n = 1). There was a single maternal cardiac indication for emergency Caesarean section being congestive cardiac failure (n = 1). The indications for elective Caesarean section were mechanical aortic valve (n = 2), to facilitate anticoagulation management, and patient preference (n = 1).

There was one neonatal complication, in a neonate born at 31 weeks after emergency Caesarean section for maternal congestive heart failure. Respiratory distress necessitated intubation on day 1 of life. The neonate was treated with surfactant and extubated the following day.

No child was diagnosed with congenital heart disease.

Maternal Complications

Of the 17 successful pregnancies, there were maternal obstetric complications in 10. Complications included postpartum haemorrhage (PPH) (n = 5), obstructed labour (n = 3), gestational diabetes mellitus (n = 2), pre-eclampsia (n = 2), third degree perineal tear (n = 2) and bladder injury during Caesarean section (n = 1).

There were two maternal cardiac complications during pregnancy. One patient entered pregnancy with moderate to severe AR and experienced symptomatic deterioration, requiring admission for management of worsening heart failure at 31 weeks and emergency Caesarean section.

Table 1 Patients.

Year of ASO	Operations before ASO	Age at ASO (days)	Pathology	Reintervention since ASO	Gravida parity	Anticoagulation at pregnancy	No. successful pregnancies	Age at pregnancy (years)	Mode of delivery	Cardiac complication	Obstetric complication
1987	-	644	TGA VSD	pacemaker	G1P1	nil	1	32	emergency CS	nil	obstructed labour
1986	-	13	TGA IVS	-	G3P1 (1 miscarriage, 1 termination)	nl	1	29	V	nil	nil
1985	Senning atrial switch, pulmonary artery banding	1,264	TGA VSD	-	G2P2	nil	2	29, 33	V, V	nil, nil	PET + PPH, PET + GDM
1990	Senning atrial switch, pulmonary artery banding	3,684	TGA VSD	aortic valve replacement	G2P2	warfarin (mechanical AVR)	2	32, 36	elective CS, elective CS	nil, atrial fibrillation/ flutter	bladder damage during CS, PPH
1986	Pulmonary artery banding + patent ductus closure	9	TGA VSD	-	G2P1 (1 miscarriage)	nil	1	29	emergency CS	nil	PPH
1987	-	8	TGA IVS	-	G2P2	nil	2	27, 30	V, V	nil, nil	nil, nil
1994	Pulmonary artery banding	1,484	TBA	residual VSD closure, aortic root replacement + RVOTO resection, ICD	G2P1 (1 miscarriage)	nil	1	22	emergency CS	nil heart failure (moderate-severe AR)	nil
1986	-	11	TGA IVS	-	G2P2	nil	2	26, 28	IV, V	nil, nil	3rd degree tear, PPH
1988	Subclavian flap coarctation repair	10	TGA VSD	RVOTO resection, pulmonary valve replacement	G1P1	nil	1	26	emergency CS	nil	GDM + obstructed labour
1987	-	9	TGA IVS	-	G2P2	nil	2	25, 27	IV, elective CS	nil, nil	3rd degree tear + PPH, nil
1983	-	104	TGA VSD	LVOTO resection	G2P2	nil	2	27, 31	V, emergency CS	nil, nil	nil, obstructed labour

Abbreviations: AR, neo-aortic regurgitation; ASO, arterial switch operation; CS, Caesarean section; GDM, gestational diabetes mellitus; ICD, implantable cardiac defibrillator; IV, instrumented vaginal; IVS, intact interventricular septum; LVOTO, left ventricular outflow tract obstruction; PET, preclampsia; PPH, postpartum haemorrhage; RVOTO, right ventricular outflow tract obstruction; TBA, Taussig-Bing anomaly; TGA, transposition of the great arteries; V, vagina; VSD, ventricular septal defect.

Table 2 Transthoracic echocardiography data pre and post-pregnancy.

Pre-Pregnancy						
Patient	LV function	LV size (cm)	LV size/BSA	AR	Neo-aortic root size (cm)	PR
1	Normal	5.2	3	Mild	4.4	Trivial
2	Normal	5.2	3.3	Mild	3.9	Nil
3	Normal	5.4	2.6	Nil	4	Moderate
4	Normal	5.5	3.2	Mild	Not available	Trivial
5	Normal	5.7	3	Trivial	3.5	Mild
6	Normal	5.0	2.8	Mod-severe	4.6	Moderate
7	Normal	5.1	3.2	Trivial	3.4	Mild
8	Normal	5.7	3.2	Trivial	3.6	Trivial
Post-pregnancy						
LV function	LV size (cm)	LV size/BSA	AR	Neo-aortic root size (cm)	PR	
Normal	6.1	3.4	Trivial to mild 1.5	4.5	Trivial	
normal	5.1	2.8	Trivial to mild	3.5	Nil	
Normal	5.3	2.3	Nil	4.2	Trivial	
Normal	4.9	2.7	Trivial	3.4	Trivial	
Normal	5.8	3	Mild 2	3.6	Trivial	
Normal	5.2	2.9	Severe 4	4.7	Moderate	
Normal	4.7	2.2	Trivial 1	3.7	Trivial	
Normal	6	3.3	Trivial 1	3.5	Trivial	

Abreviations: AR, neo-aortic valve regurgitation; BSA, body surface area; cm, centimetres; LV, left ventricular; PR, neo-pulmonary valve regurgitation.

Another patient experienced rapid atrial flutter and fibrillation 2 days after delivery, which was treated with a beta blocker.

Ventricular Function

Left ventricular function, assessed by TTE, was normal in all patients with TTE data both pre-pregnancy and post-pregnancy. Mean LV size was 5.4 cm (range 5.0–5.7 cm) pre-pregnancy and 5.3 cm (4.7–6.1 cm) post-pregnancy. Paired statistical analysis did not demonstrate any statistically significant difference in either LV measurement or LV indexed to BSA when pre-pregnancy data was compared with post-pregnancy data.

Pre-pregnancy RV function qualitatively assessed by TTE was normal in all eight patients with TTE data. Postpartum RV function was normal in seven patients and mildly reduced in one patient. Mean basal RV size was 4.6 cm (range 4.2–5.0 cm) pre-pregnancy and 4.7 cm (range 4.1–5.1 cm) post-pregnancy. Paired statistical analysis did not demonstrate and statistically significant difference in RV size when pre-pregnancy data was compared with post-pregnancy data.

Neo-Aortic Valve Regurgitation and Neo-Aortic Root Dilatation

Eight (8) patients had the severity of AR assessed on TTE pre and post pregnancy. The severity of AR was moderately-severe in one patient, mild in three patients, trivial in three patients and nil in one patient pre-pregnancy. There was progression of degree of AR in two of these patients post pregnancy (trivial to mild and moderate-severe to severe). The patient who developed severe AR underwent an aortic root replacement 22 months after delivery.

Mean neo-aortic root size was 4.0 cm on TTE both pre and post-pregnancy. Paired statistical analysis did not demonstrate any statistically significant difference in neo-aortic root size when pre-pregnancy data was compared with post-pregnancy data.

Neo-Pulmonary Valve Regurgitation

Eight (8) patients had the severity of neo-pulmonary regurgitation (PR) assessed on TTE pre and post pregnancy. The degree of PR was moderate in two patients, mild in two patients, trivial in three patients and nil in one patient pre-pregnancy. There was no progression of PR severity in any patients post pregnancy.

New York Heart Association Class

New York Heart Association (NYHA) class was I in nine patients pre-pregnancy and II in two patients. There was no change in NYHA class in the patients followed post-pregnancy.

Discussion

This study represents only the third published series on pregnancy outcomes after the ASO and the first published in Australian patients. It is well known that pregnancy may be higher risk for both mother and child in repaired congenital heart disease [14,15]. Pregnancy outcomes in TGA

women who underwent an atrial switch operation during childhood have been reported [11] but pregnancy outcomes after the ASO are scarce. The expectation would be that pregnancy post ASO would have a lesser likelihood of cardiac complications, as the systemic ventricle in these women is a left ventricle (unlike post atrial switch) and these individuals appear to not have the atrial arrhythmia risks seen post atrial baffle [16,17]. The 2017 American Heart Association (AHA) guidelines [18] state that "women with an arterial switch repair are anticipated to do well in pregnancy" in the absence of significant residual haemodynamic lesions but acknowledge that outcomes in women undergoing pregnancy is limited to a single series [19]. The modified World Health Organisation (WHO) classification of maternal risk used in the AHA guidelines do not specifically mention ASO survivors. Likewise, the 2011 European Society of Cardiology (ESC) guidelines [20] references the single study on ASO survivors undergoing pregnancy and advises that the risk of pregnancy in ASO survivors is low in patients with a good clinical condition pre-pregnancy.

To date, reports of outcomes in ASO survivors undergoing pregnancy have been limited to one case report [21] and two series [19,22]. In their paper of nine patients, Tobler and colleagues [19] reported one case of postpartum valve thrombosis, one case of recurrent non-sustained ventricular tachycardia and one patient with progression of supravalvular pulmonary stenosis who required balloon angioplasty 12 months following pregnancy. More recently, Stoll et al. [22] published their experience of pregnancy outcomes in 15 women after ASO. They found no significant maternal cardiac complications with only one woman having a decline in LV function from normal to mildly impaired and one woman having progression of degree of AR from none to mild. Maternal obstetric complications were not reported so no comparison with our observed rate is possible.

We found a low incidence of maternal cardiac complications during pregnancy but an unexpected incidence of maternal obstetric complications. In 10 of the 17 pregnancies, the mother experienced an obstetric complication. Seven (7) of these complications were either PPH or third degree perineal tear. Theoretically, the increased frequency of these specific complications could be explained by a prolonged second stage of labour as a result of avoidance of Valsalva, as has been postulated by others [23]. Avoidance of Valsalva may prevent its associated reduction in preload and increased myocardial oxygen demand. However, this may come at the cost of a prolonged second stage of labour leading to uterine atony as well as increasing the likelihood of an instrumented delivery. Both atony and instrumented delivery are recognised risk factors for PPH [24,25]. Avoidance of Valsalva was not documented in any cardiology obstetric plan for these women. Although a short second stage was recommended for four women (seven pregnancies), only one of those required an instrumented delivery and was complicated by a PPH. The increased rate of PPH in this cohort remains unexplained.

The cardiac safety of the obstetric plans in these ladies is supported by Cauldwell and colleagues [26] who studied a cohort of 73 women with cardiac disease who underwent pregnancy. Twenty-five (25) (34%), including 18 (25%) patients who were a modified WHO class I or II, pushed for longer than was recommended at an institutional multidisciplinary antenatal delivery plan. No adverse cardiac complications were noted in these women. Avoidance of Valsalva is unlikely to be necessary in repaired TGA patients without significant residual haemodynamic lesions, including no more than moderate neo-aortic root dilatation, who have undergone anatomic correction with an ASO.

Overall, pregnancy remained reasonably low risk in the majority of women who had undergone ASO as a child. In the absence of residual haemodynamic significant lesions, these women can undergo vaginal delivery safely and would be considered a class II in the modified WHO classification of maternal risk. Women who have undergone ASO in childhood and are considering pregnancy should have preconception counselling that includes an assessment by and discussion with an adult congenital heart disease cardiologist as recommended by 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease [27]. As a minimum, an electrocardiogram, echocardiogram and stress echocardiogram should be performed pre-pregnancy. The rest and stress echocardiographic imaging will allow assessment of exercise capacity, ventricular function and its augmentation with exercise, valvular function, neo-aortic root size and infer normal coronary supply by normal ventricular wall function. Clearly in women with significant haemodynamic lesions, such as our patient with moderate to severe AR pre-pregnancy, closer monitoring and consideration of intervention pre-pregnancy should occur.

Limitations

The main limitations of this study are its retrospective nature and the small number of patients included. The retrospective nature of this study has limited the imaging data to what was ordered in routine care. Larger studies are needed to examine risk factors for adverse pregnancy outcomes in this patient group.

Conclusion

Pregnancy post ASO appears to have a better risk profile than in women with the prior operative repair for TGA, an atrial switch procedure. Maternal cardiac complications seem to be uncommon in patients without residual significant haemodynamic lesions, although maternal obstetric complications were common.

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Chapter 8: The impact of coronary artery anatomy on mortality after the arterial switch operation

8.1 Introduction

Patients with abnormal coronary artery patterns represent a challenging subgroup undergoing the ASO. In this study, we combined patients operated at The Royal Children's Hospital with patients operated at The Queensland Children's Hospital over the same time period of 1983-2013. This resulted in 1033 patients from which we retrospectively examined the effect of anomalous coronary anatomy on mortality and coronary reintervention after the ASO.

There was a higher early mortality in patients with abnormal coronary anatomy compared to patients with normal coronary anatomy (3.9% vs 3.0%) but this was not statistically significant. Likewise, higher early mortalities were observed in TGA-IVS and TGA-VSD patients with abnormal coronary anatomy. Overall, the need for postoperative mechanical circulatory support was higher in patients with abnormal coronary anatomy and this difference was statistically significant. Coronary reoperation was necessary in only 6 patients.

We concluded that, while neither anomalous coronary anatomy or a specific coronary pattern was a statistically significant risk factor for mortality, these patients had higher early mortalities and a higher risk for postoperative mechanical circulatory support. Statistical significance may be difficult to achieve since mortality is an uncommon event and many anomalous coronary patterns are rare.

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The impact of coronary artery anatomy on mortality after the arterial switch operation.

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CENTRAL MESSAGE: Patients with anomalous coronary anatomy had higher rates of early mortality after the ASO but this was not statistically significant and coronary reoperation was rare.

56

57 **PERSPECTIVE STATEMENT:** Patients with anomalous coronary anatomy
58 undergoing the arterial switch operation are a challenging subgroup. These patients may
59 be at a higher risk of mortality as well as a higher risk for postoperative mechanical
60 circulatory support and coronary reintervention.

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63 **CENTRAL FIGURE LEGEND**: Patients with abnormal coronary anatomy
64 undergoing the arterial switch have a higher early mortality and need for postoperative
65 mechanical circulatory support but abnormal coronary anatomy is not a statistically
66 significant risk factor for mortality.
67 LAD= left anterior descending artery
68 LCx= left circumflex artery
69 MCS= mechanical circulatory support
70 RCA= right coronary artery
71

ABBREVIATIONS

ASO= arterial switch operation

IQR= interquartile range

MCS= mechanical circulatory support

NYHA= New York Heart Association

TGA= transposition of the great arteries

TGA-IVS= transposition of the great arteries with an intact ventricular septum without aortic arch obstruction

TGA-VSD= transposition of the great arteries with a ventricular septal defect without aortic arch obstruction

OBJECTIVE: We sought to determine the impact of coronary artery anatomy on mortality in more than 1000 children undergoing the arterial switch operation (ASO).

METHODS: All patients who underwent an ASO were identified from two hospital databases and reviewed retrospectively. Coronary anatomy was recorded from operative reports using the Leiden classification.

RESULTS: An ASO was performed in 1033 children between 1983 and 2013. Coronary anatomy was normal in 697 (67%, 697/1033) patients. The most common type of anomalous coronary anatomy was the circumflex coronary artery arising from sinus 2 (15%, 152/1033). Forty-seven (4.5%, 47/1033) patients had all coronary arteries arising from a single sinus. Of these 47 patients, 34 (3.3%, 34/1033) patients had a true single coronary artery. Fifty-two (5.0%, 52/1033) patients had an intramural coronary artery. Overall early mortality was 3.3% (34/1033) over the 30-year period. Early mortality was 3.0% (21/697) for patients with normal coronary anatomy and 3.9% (13/336) for any type of anomalous coronary anatomy. Early mortality was 3.3% (5/152) for patients with the circumflex coronary artery arising from sinus 2, 6.4% (3/47) for patients with all coronary arteries arising from a single sinus and 5.9% (2/34) for patients with a true single coronary artery. Early mortality for patients with intramural coronaries was 1.9% (1/52). No coronary pattern was found to be a risk factor for mortality.

CONCLUSION: Patients with anomalous coronary artery anatomy had higher rates of early mortality after the ASO but this was not statistically significant. Coronary artery reoperations were rare.

The arterial switch operation (ASO) has excellent early and late outcomes in the modern era (1-5). Technical complexity of the operation may increase in the presence of coronary artery anomalies, which occur in approximately one third of patients (1, 2, 6-8). In particular, single coronary arteries and intramural coronary arteries have been associated with a higher mortality (9-11). Therefore, we sought to determine the impact of coronary artery anatomy on mortality in more than 1000 children undergoing the ASO.

MATERIALS AND METHODS

Patients

This study was approved by The Royal Children's Hospital Human Research Ethics Committee and The Children's Health Queensland Human Research Ethics Committee. All data were collected retrospectively from hospital records for patients operated at The Royal Children's and Queensland Children's Hospitals between 1983 and 2013. Data for patients who were 18 years of age or older were collected from hospital records of adult congenital cardiac services and general practitioners. Coronary anatomy was recorded from operative reports using the Leiden classification.

Definitions

Early death or reoperation was defined as death or reoperation occurring prior to hospital discharge or within 30 days of ASO. Late death was defined as death occurring after discharge and more than 30 days after ASO. Coronary reintervention was defined as reoperation or transcatheter procedure on the coronary arteries. Normal coronary anatomy was defined as the left anterior descending artery and circumflex

coronary arteries arising from sinus 1 and the right coronary artery arising from sinus 2. All patterns other than this were considered abnormal or anomalous.

Statistical Analysis

Data were imported into Stata Version 12 (Stata Corp, College Station, Texas). Continuous variables were reported as a median with an interquartile range (IQR). Kaplan-Meier curves were constructed to display freedom from the study's outcomes. Cox regression analysis was used to determine risk factors for statistical significance. Fisher's exact test was used to detect significant differences in early mortality between groups. The Mann Whitney U test was used to detect any significant differences in medians of continuous variables between groups. A p value of less than 0.05 was considered statistically significant.

RESULTS

An ASO was performed in 1033 children between 1983 and 2013 at The Royal Children's and Queensland Children's Hospitals. The trapdoor technique for coronary translocation was used at both institutions consistently since the inception of their programs in almost all patients. ***Table 1*** summarizes the perioperative and operative data of the patients. Eight hundred and eight patients (78%, 808/1033) underwent ASO at The Royal Children's Hospital between 1983 and 2013. Two hundred and twenty-five patients (22%, 225/1033) underwent ASO at the Queensland Children's Hospital between 1995 and 2013. Nine hundred and fifty (92%, 950/1033) had transposition of the great arteries (TGA) ,67 (6.5%, 67/1033) patients had Taussig-Bing anomaly and 16 (15%, 16/1033) patients had a previous atrial switch operation with takedown and conversion to ASO. In the patients with TGA, 282 (30%, 282/950) patients had a

ventricular septal defect without aortic arch obstruction (TGA-VSD), 613 (65%, 613/950) patients had an intact interventricular septum without aortic arch obstruction (TGA-IVS) and 55 (5.3%, 55/1033) patients had TGA with aortic arch obstruction. Median age of operation was 10 days (IQR 7-20 days) and median weight at operation was 3.5kg (IQR 3.1-3.9 kilograms). Thirty-six (3.5%, 36/1033) patients were less than 2.5 kilograms at time of operation.

Anomalous coronary anatomy occurred in 336 (33%, 336/1033) patients. Anomalous coronary anatomy was more common in patients with a ventricular septal defect compared to those with an intact interventricular septum (37% versus 30%, *p=0.03*). The most common type of anomalous coronary anatomy was the circumflex coronary artery arising from sinus 2 (15%, 152/1033). Forty-seven (4.5%, 47/1033) patients had all coronary arteries arising from a single sinus. Of these 47 patients, 34 (3.3%, 34/1033) patients had a true single coronary artery. Fifty-two (5.0%, 52/1033) patients had an intramural coronary artery. Follow-up after hospital discharge was 92% (947/1033). Median follow-up was 14.3 years (IQR 8.3-18.8 years).

Mortality

There were 34 (3.3%, 34/1033) early deaths. *Table 2* lists the early mortality for each coronary pattern. Early mortality was 3.0% (21/697) for patients with normal coronary anatomy and 3.9% (13/336) for patients with anomalous coronary anatomy. Early mortality was 3.3% (5/152) for patients with the circumflex coronary artery arising from sinus 2, 6.4% (3/47) for patients with all coronary arteries arising from a single sinus and 5.9% (2/34) for patients with a true single coronary artery. Early mortality for patients with intramural coronaries was 1.9% (1/52). There were no significant differences in early mortality between patients with normal coronary

anatomy compared with anomalous coronary anatomy by decade operated (***Table 3***). Causes of death were coronary ischemia (n=22), sepsis (n=7), respiratory failure (n=2), unknown cause (n=2) and brain death (n=1). Late mortality occurred in 9 (0.9%, 9/999) patients, 2 of whom had anomalous coronary anatomy.

There was no statistically significant difference in early mortality between normal coronary anatomy and abnormal coronary anatomy in TGA-IVS patients *(1.2% vs 2.7%, p=0.17)*, TGA-VSD patients *(3.9% vs. 5.8%, p=0.56)* or overall *(3.0% vs. 3.9%, p=0.46)*. No coronary pattern was found to be a risk factor for mortality on Cox regression analyzed for the entire cohort, for TGA-IVS patients alone and TGA-VSD patients alone.

Survival at 20 years was 96% for both normal and abnormal coronary artery anatomy patients (***Figure 1***).

In patients whom New York Heart Association (NYHA) class was available at last follow-up, 98% (587/598) of patients with normal coronary anatomy were in NYHA class I and 98% (277/283) of patients with abnormal coronary anatomy were in NYHA class I.

Postoperative mechanical circulatory support (MCS) was more common in patients with abnormal coronary artery anatomy compared to those with normal coronary anatomy (6.5% vs 2.9%, *p=0.007*) as well as in patients with intramural coronary arteries (9.6%, *p=0.02*). Patients who required MCS had longer median cardiopulmonary bypass (235 minutes vs 109 minutes, *p<0.001*) and longer median aortic cross clamp times (170 minutes vs 92 minutes, *p<0.001*). Patients who required MCS had more associated ventricular septal defect repairs (48% vs 39%, *p=0.27*) and more associated aortic arch obstruction repairs (17% vs 7.9%, *p=0.07*). More patients

who required MCS were less than 2.5 kilograms at time of ASO (9.5% vs 3.2%, *p=0.05*).

Reintervention for coronary stenosis

Six (0.6%, 6/1033) patients required 8 reinterventions, all reoperations, on the coronaries at a median 11 days (IQR 6-33 days, range 1 day to 9 years) after ASO. Three (0.4%, 3/697) patients with normal coronary anatomy required reintervention for coronary stenosis and 3 (0.9%, 3/336) patients with abnormal coronary anatomy. The difference was not statistically significant (*p=0.40*).

Patient 1 underwent an uneventful ASO for TGA IVS at 8 days of age with coronary anatomy of 1LAD; 2RCA, Cx and end to end coarctation repair at 11 days of age. The patient had a very small doubly committed VSD that was missed during the ASO. The patient developed chest pain 9 years after ASO and transthoracic echocardiography demonstrated partial occlusion of the LAD by the distorted cusp of the aortic valve. Aortic valve repair was performed, the VSD was closed and LAD was reimplanted. The patient is in NYHA class I at 17 years of age.

Patient 2 underwent an ASO for TGA IVS at 8 days of age with normal coronary anatomy. The patient's immediate postoperative period was complicated by bradycardia and blood pressure dependent electrocardiogram changes. A coronary angiogram was performed demonstrating patent coronaries however there was concern for ongoing coronary ischemia. The patient returned to theatre and underwent relocation of the RCA button. The patient is in NYHA class I at 13 years of age.

Patient 3 underwent ASO for TGA IVS at 18 days of age with coronary anatomy of 1LAD, RCA; 2Cx. Immediately after coming of bypass, there was ischemia of the posterior ventricular wall. The Cx button was repositioned and the child was supported

with ECMO. Unfortunately, the patient had cerebral embolism while on ECMO and died on day 12 after ASO.

Patient 4 underwent ASO and end to side arch repair for TBA with coarctation at 6 days of age with normal coronary anatomy. The patient had a cardiac arrest in the intensive care unit and was placed on ECMO. The coronary angiogram demonstrated severe stenosis of the left coronary artery and the left coronary button was relocated lower into the sinus of Valsalva. The patient is alive and well at 7 years of age.

Patient 5 underwent ASO for TGA VSD at 11 days of age with normal coronary anatomy. The patient went into ventricular tachycardia the day after ASO. Because of concern for right coronary ischemia, the patient returned to theatre for reimplantation of the right coronary button. The patient is in NYHA class I at 16 years of age.

Patient 6 underwent ASO for TGA IVS at 11 days of age with coronary anatomy of 1LAD, RCA; 2Cx. The patient was unable to be successfully weaned from cardiopulmonary bypass at time of ASO and was placed on ECMO. A coronary angiogram demonstrated obstruction at the level the circumflex coronary artery and this was revised with a patch on day 9 postoperatively. Repeat coronary angiography demonstrated residual obstruction at the level of the circumflex patch and the coronary was relocated to the non-facing sinus. The patient was unable to be weaned off ECMO and died day 23 postoperatively.

DISCUSSION

The anomalous coronary anatomy may represent a technical challenge during the ASO. The most common abnormal anatomy is the circumflex coronary artery arising from sinus 2 (1-3, 6, 7). Single coronary artery, or all coronaries arising from the same sinus, are usually the next most common anomaly (1, 3, 11). Single coronary

artery and intramural coronary arteries are uncommon coronary patterns and, thus, a large cohort of patients is necessary to analyze risk factors for mortality.

Technical experience with complex coronary anomalies has improved the results of many institutions over the years. However, despite this improvement contradictory results still exist in the literature. The meta-analysis by Pasquali and colleagues (10) on the effect of coronary anatomy on mortality after the ASO has been referenced by many papers on this topic (6, 7, 9, 11-16). In this meta-analysis of 1942 patients, any variant of coronary artery anatomy doubled the risk of death. Furthermore, the same meta-analysis demonstrated that risk of death in patients with a single coronary artery was 3 times higher and in those with an intramural coronary artery 7 times higher compared to those with normal coronary anatomy. This meta-analysis, however, was limited to studies of patients operated between 1977 and 1999. A more recent study by Trezzi and colleagues investigated the effect of anomalous coronary anatomy in 283 children undergoing the ASO between 2000 and 2015 and found it not to be a risk factor for operative mortality (6). Outcomes for intramural coronaries have been particularly varied with operative mortality ranging from 0-24% in recent studies (9, 17, 18). Likewise, single coronary arteries have also been a focus. The largest series of such patients comes from Gerelli and colleagues who published results of 73 children with single coronary arteries undergoing the ASO (11). Mortality was 11%. However, all deaths except 1 occurred in their patients operated before 2001. In our cohort of 1033 patients across 2 institutions, there were 2 (5.9%, 2/34) operative deaths in patients with a single coronary artery and 1 (1.9%, 1/52) operative death in patients with intramural coronaries. Both anomalies were not statistically significant risk factors for mortality. The technique for coronary translocation across both our institutions is the trapdoor technique, which has been previously described in several publications,

and has been consistently used since its introduction by Roger Mee in Melbourne in the 1980s (2, 18-20). We have previously published a detailed description of our technique to translocate intramural coronary arteries (18).

Interestingly, we observed higher early mortalities in TGA-IVS and TGA-VSD patients with abnormal coronary anatomy compared to normal coronary anatomy (1.2% vs. 2.7% and 3.9% vs. 5.8%) in the current study . Despite higher early mortality in children with anomalous coronary patterns, these differences between the groups were not statistically significant nor was anomalous coronary anatomy or any specific anomalous coronary pattern a risk factor on Cox regression analysis ***(Figure 2)***.

We found that the need for postoperative MCS was more common in patients with abnormal coronary artery anatomy and intramural coronary arteries compared to those with normal coronary. However, this finding must be tempered by the fact that patients who required MCS had longer cardiopulmonary bypass and aortic cross clamp times, more concomitant ventricular septal defect and aortic arch obstruction repairs and were more likely to be less than 2.5 kilograms. Those factors, leading to more complex repairs and longer ischemic times, may be responsible for the higher need for MCS in these patients.

Encouragingly, reinterventions for coronary stenosis were rare in patients (0.6%, 6/1033). Our 2 institutions do not perform routine coronary angiogram in patients after the ASO and do not have set protocols for coronary surveillance after ASO. However, most patients at both institutions undergo exercise stress testing before transfer to adult care. Stress testing that is suggestive of ischemia is followed with myocardial perfusion imaging or coronary angiography. Although currently, no data exists on the ideal form of surveillance, it would be reasonable to routinely do an exercise test in asymptomatic patients with abnormal coronary arteries on transition to

adult congenital service. All patients with exercise induced chest pain or those unable to complete exercise test should undergo CT scan assessment of the coronary arteries. Coronary events are generally reported to be low late after ASO (1, 3), but may be more common in institutions where routine follow-up coronary angiography is performed (21, 22). Asymptomatic stenosis has been reported in approximately 10% of patients on coronary angiography or CTCA (15, 23) and abnormal coronary artery patterns have been identified as risk factors for coronary obstruction (22, 24, 25). When late coronary ischemia does occur, surgical coronary revascularization can be performed with a low mortality (16, 21, 26-28). The role of percutaneous coronary intervention in growing children is less well-defined (14, 29) but may play a larger role in adult patients in the future.

Our results demonstrate that anomalous coronary arteries are not a risk factor for the ASO. Reports of successful ASOs in even the most difficult coronary anatomy have been published including a single coronary artery from the non-facing sinus (30) and bilateral intramural coronaries from a single sinus (13, 31). Despite this, myocardial ischemia is the most common cause of early mortality and, while rare, late death is also coronary-related in many instances (32). Furthermore, the demonstration of early atherosclerosis by intravascular ultrasound in coronaries after the ASO (33) highlights need for ongoing coronary surveillance throughout adulthood despite good outcomes.

LIMITATIONS

A limitation of this study was its retrospective nature. Differences in mortality may not be statistically significant due to small number of early deaths. Routine coronary angiography was not performed in our patients and therefore we cannot comment on the potential for coronary stenosis in asymptomatic patients. The rarity of

certain types of anomalous coronaries as well as the low early mortality means significant differences in mortality are difficult to detect.

CONCLUSION

Anomalous coronary artery anatomy was not a statistically significant risk factor for mortality after the ASO. However, patients with anomalous coronary anatomy had higher early mortality after the ASO.

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454

455 **FIGURES**

456

457 Figure 1. Survival by coronary artery anatomy.
458 Survival for patients with normal coronary arteries was 96% (95% confidence interval
459 94-97%) at 5, 10 and 20 years after ASO.
460 Survival for patients with anomalous coronary arteries was 96% (95% confidence
461 interval 92-98%) at 5, 10 and 20 years after ASO.
462 Survival for patients with single coronary arteries was 91% (95% confidence interval
463 74-97%) at 5, 10 and 20 years after ASO.

Survival for patients with intramural coronary arteries was 98% (95% confidence interval 87-100%) at 5, 10 and 20 years after ASO.

CA= coronary arteries

Abnormal CA= abnormal coronary arteries (excluding single and intramural coronaries)

Figure 2. Normal and abnormal coronary artery outcomes

Abnormal coronary artery anatomy associated with a higher early mortality but was not statistically significant and was still had a low rate of coronary reoperation.

ASO=arterial switch operation, LAD= left anterior descending artery, LCx= left circumflex artery, MCS= mechanical circulatory support, RCA= right coronary artery

Figure 1 revised

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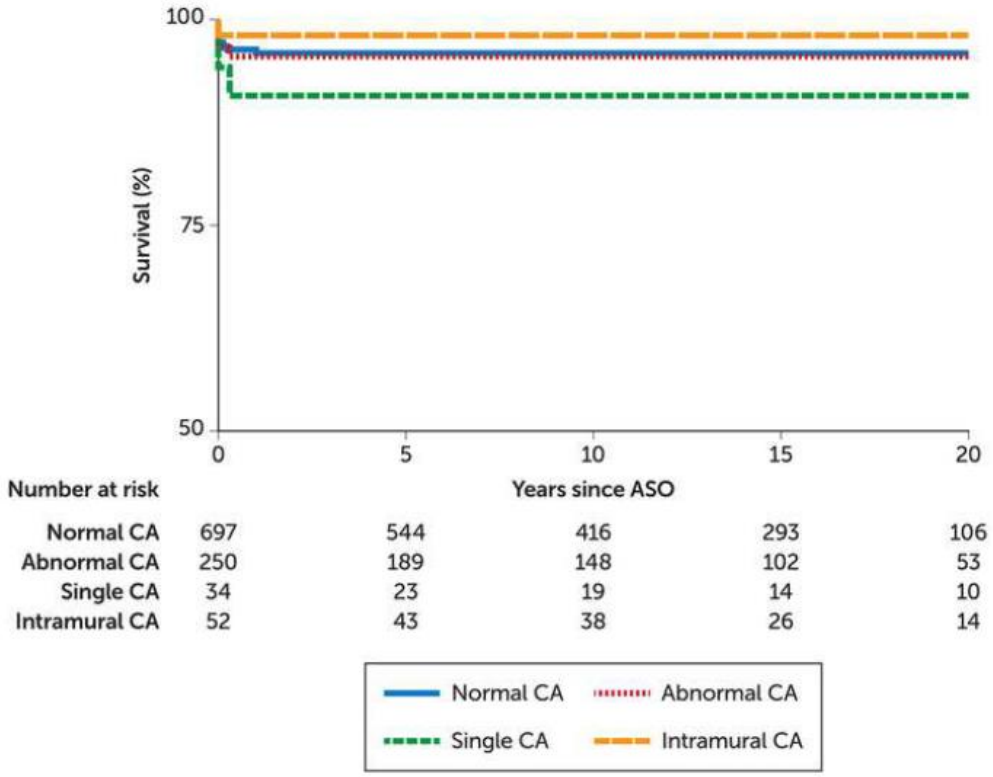

Number at risk					
Normal CA	697	544	416	293	106
Abnormal CA	250	189	148	102	53
Single CA	34	23	19	14	10
Intramural CA	52	43	38	26	14

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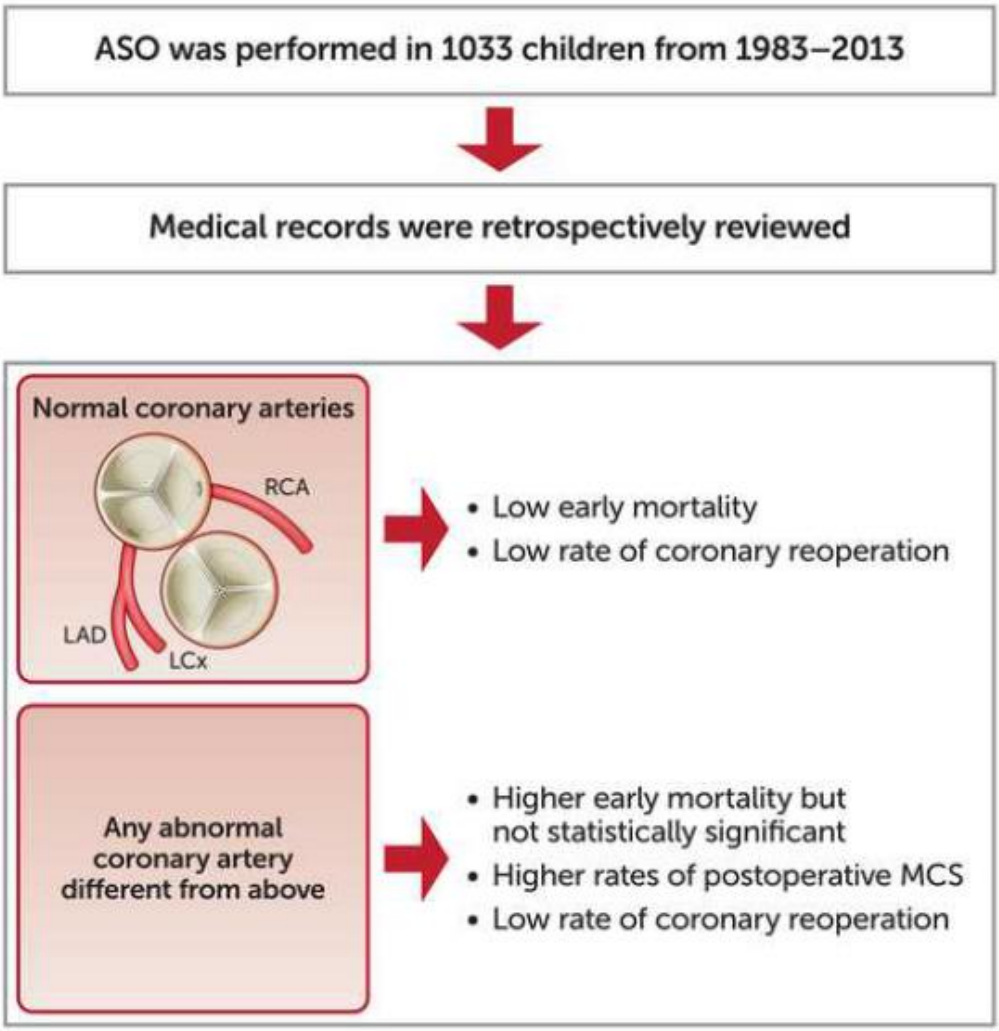

Table 1

Table 1. Perioperative and operative data

	Normal CAs (n=697)	Anomalous CAs (n=336)	*p* value
TGA	645 (93%)	305 (91%)	NS
TGA-IVS	430 (62%)	183 (54%)	0.03
TGA-VSD	178 (26%)	104 (31%)	NS
TGA-AAO	37 (5.3%)	18 (5.4%)	NS
TBA	37 (5.3%)	30 (8.9%)	0.03
TBA without AAO	23 (3.3%)	15 (4.5%)	0.04
TBA AAO	14 (2.0%)	15 (4.5%)	0.04
Atrial switch to ASO conversion	15 (2.2%)	1 (0.3%)	0.03
Median age at operation (days)	10, IQR 7-19	10, IQR 7-22	-
Median operative weight (kg)	3.1, IQR 3.1-3.9	3.5, IQR 3.2-3.9	NS
Operative weight <2.5kg	24 (3.4%)	12 (3.6%)	NS
Coronaries from single sinus	-	47 (14%)	
Coronaries from single sinus, single ostium (true single CA)	-	34 (10%)	
Coronaries from single sinus, separate ostia	-	13 (3.9%)	
1LAD; 2RCA, CX	-	152 (45%)	
1LAD, RCA; 2CX	-	35 (10%)	
1RCA; 2LAD, CX	-	24 (7.1%)	
1CX; 2LAD, RCA	-	2 (0.6%)	
Intramural CA	-	52 (15%)	
1conal branch; 2LAD, CX, RCA	-	16 (4.8%)	
1accessory RV branch; 2LAD, CX, RCA	-	2 (0.6%)	
1LAD, CX, RCA; 2sinoatrial node branch	-	2 (0.6%)	
1accessory LAD, 2LAD, CX, RCA	-	2 (0.6%)	
1LAD, CX, RCA; 2accessory RCA	-	1 (0.6%)	
1LAD, CX; 2RCA, accessory LAD	-	1 (0.6%)	
Median CPB time (minutes)	164, IQR 137-198	175, IQR 134-214	NS
Median aortic cross clamp time (minutes)	88, IQR 71-112	97, IQR 76-120	NS
Postoperative MCS	20 (2.9%)	22 (6.5%)	<0.001

AAO= aortic arch obstruction, ASO= arterial switch operation, CA= coronary artery, CPB= cardiopulmonary bypass, CX= circumflex coronary artery, IQR= interquartile range, kg= kilograms, IVS= intact interventricular septum, LAD= left anterior descending coronary artery, MCS= mechanical circulatory support, NS= non significant, RCA= right coronary artery, RV= right ventricular, TBA= Taussig-Bing anomaly, TGA= transposition of the great arteries, TGA-VSD= transposition of the great arteries with ventricular septal defect without aortic arch obstruction

Table 2. Early mortality

				Early mortality			
Coronary pattern	**Overall**	**TGA-IVS**	**TGA-VSD**	**TGA-AAO**	**TBA without AAO**	**TBA-AAO**	**Atrial switch to ASO conversion**
1LAD, CX; 2RCA	3.0% (21/697)	1.2% (5/430)	3.9% (7/178)	11% (4/37)	13% (3/23)	0% (0/14)	13% (2/15)
Abnormal coronary anatomy	3.9% (13/336)	2.7% (5/183)	5.8% (6/104)	11% (2/18)	0% (0/15)	0% (0/15)	0% (0/1)
Coronaries from single sinus	6.4% (3/47)	4.5% (1/22)	11% (2/18)	0% (0/5)	0% (0/2)	0% (0/0)	0% (0/0)
Coronaries from single sinus, single ostium (true single CA)	5.9% (2/34)	5.9% (1/17)	8.3% (1/12)	0% (0/3)	0% (0/2)	0% (0/0)	0% (0/0)
True single CA from sinus 1	0% (0/16)	0% (0/10)	0% (0/4)	0% (0/1)	0% (0/1)	0% (0/0)	0% (0/0)
True single CA from sinus 2	13% (2/16)	17% (1/6)	14% (1/7)	0% (0/2)	0% (0/1)	0% (0/0)	0$ (0/0)
True single CA from non-facing sinus	50% (1/2)	100% (1/1)	0% (0/1)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)
Coronaries from single sinus, separate ostia	7.7% (1/13)	0% (0/5)	17% (1/6)	0% (0/2)	0% (0/0)	0% (0/0)	0% (0/0)
1LAD; 2RCA, CX	3.3% (5/152)	2.4% (2/85)	2.1% (1/47)	29% (2/7)	0% (0/6)	0% (0/6)	0% (0/1)
1LAD, RCA; 2CX	8.3% (3/36)	11% (2/19)	10% (1/10)	0% (0/1)	0% (0/3)	0% (0/3)	0% (0/0)
1RCA; 2LAD, CX	4.3% (1/23)	0% (0/6)	11% (1/9)	0% (0/1)	0% (0/4)	0% (0/3)	0% (0/0)
1CX; 2LAD, RCA	0% (0/2)	0% (0/1)	0% (0/1)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)
Intramural CA	1.9% (1/52)	0% (0/37)	11% (1/11)	0% (0/3)	0% (0/0)	0% (0/1)	0% (0/0)
1conal branch; 2LAD, CX, RCA	0% (0/16)	0% (0/9)	0% (0/6)	0% (0/0)	0% (0/0)	0% (0/1)	0% (0/0)
1accessory RV branch; 2LAD, CX, RCA	0% (0/2)	0% (0/0)	0% (0/1)	0% (0/1)	0% (0/0)	0% (0/0)	0% (0/0)
1LAD, CX, RCA; 2sinoatrial node branch	0% (0/2)	0% (0/1)	0% (0/1)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)
1accessory LAD, 2LAD, CX, RCA	0% (0/2)	0% (0/2)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)
1LAD, CX, RCA; 2accessory RCA	0% (0/1)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/1)	0% (0/0)
1LAD, CX; 2RCA, accessory LAD	0% (0/1)	0% (0/1)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)	0% (0/0)

CA= coronary artery, CX= circumflex coronary artery, LAD= left anterior descending artery, RCA= right coronary artery, RV= right ventricular, TBA= Taussig-Bing anomaly, TBA-AAO= Taussig-Bing anomaly with aortic arch obstruction

TGA-AAO= transposition of the great arteries with aortic arch obstruction, TGA-IVS= transposition of the great arteries with intact interventricular septum without aortic arch obstruction

TGA-VSD= transposition of the great arteries with ventricular septal defect and no aortic arch obstruction

Table 3. Early mortality by decade

Era		Early mortality
1983-1989	Overall	3.4% (5/148)
	Normal CA anatomy	4.9% (4/82)
	Abnormal CA anatomy	1.5% (1/66)
1990-1999		
	Overall	3.4% (12/352)
	Normal CA anatomy	3.5% (9/254)
	Abnormal CA anatomy	3.1% (3/98)
2000-2013		
	Overall	3.2% (17/533)
	Normal CA anatomy	2.2% (8/361)
	Abnormal CA anatomy	3.1% (9/272)

CA= coronary artery

Chapter 9: Conclusions

9.1 Overview

Characterising the long-term outcomes of patients who undergo the ASO allows us to improve our understanding of the prognosis and treatment of this important patient group. This thesis detailed outcomes of patients undergoing the ASO as an entire cohort, as well as investigating outcomes in challenging subgroups.

9.2 Key findings

In *Chapter 2*, we determined the long-term outcomes of patients who underwent an ASO for TGA over a period of more than 30 years. We demonstrated excellent late survival, functional status and a very low rate of coronary reoperation. Despite this, reintervention was reasonably common overall and the incidence of clinically significant AR, particularly in patients with more than 25 years of follow-up, was significant. These findings highlight the need for ongoing follow-up of these patients as they reach their third and fourth decades of life.

In *Chapter 3*, we showed that patients with intramural coronary arteries undergoing the ASO can be operated with excellent long-term outcomes. We reported no deaths and no coronary reinterventions in 28 patients. Of these 28, the last 25 consecutively operated patients underwent the same technique for coronary translocation which this study describes in detail. This demonstrates that patients with intramural coronary arteries can safely undergo the ASO using a simple, reproducible technique, with the longest follow-up reported in this patient group.

In *Chapter 4*, we analysed the outcomes of children with an operative weight of less than 2.5 kilograms undergoing the ASO. In only the second published and largest study to specifically examine this subgroup, we showed a significant difference in hospital mortality in patients less than 2.5 kilograms compared to those above 2.5 kilograms (19% versus 1.9%). In this chapter, we showed that the majority of mortality occurred in children less than 2.0 kilograms. However, long-term outcomes for these patients appear reasonable and comparable to normal operative weight children undergoing the ASO.

In *Chapter 5*, we investigated quality of life in adult ASO survivors. As assessed by the SF-36 quality of life questionnaire, patients had similar health related quality of life compared to published population data from Australian age-matched controls. This is a powerful and hopeful message to patients and clinicians, particularly as the adult population of ASO survivors continues to grow. This study is the largest published quality of life study in ASO patients published to date.

Chapter 6 detailed the long-term outcomes of a challenging subgroup of patients undergoing the ASO, those with associated AAO. We showed that these patients have a significantly higher reintervention rate, particularly for right sided obstruction. However, we were able to show a low rate of reintervention for recurrent AAO by avoiding the use of patch material in arch repair at the time of ASO. This study has the longest follow-up of such patients published in the literature to date.

Pregnancy outcomes in female survivors of the ASO was investigated in *Chapter 7*. With little published data on women undergoing pregnancy after the ASO, we aimed to further add to the understanding and management of these women. We found that pregnancy was reasonably low risk in the majority of the 17 successful deliveries. There was a low rate of neonatal complications and maternal cardiac complications but, unexpectedly, a high rate of maternal obstetric complications. This study was the first to be published on Australia women undergoing pregnancy after the ASO.

The impact of coronary anatomy on mortality after the ASO was examined in *Chapter 8*. Data from two institutions, The Royal Children's Hospital and the Queensland Children's Hospital, were combined in order to obtain a large number of patients for which abnormal coronary patterns could be analysed as risk factors for mortality. Despite higher early mortalities in patients with abnormal coronary anatomy as compared to those with normal coronary anatomy, abnormal coronary anatomy was not a statistically significant risk factor for mortality. The rarity of specific coronary patterns makes analysis of their contribution to mortality difficult, even in such a large patient population. Using the trapdoor technique for coronary translocation during the ASO results in a low rate of coronary reintervention.

9.3 Future directions

The true long-term success of the ASO will be assessed by the ongoing follow-up of these patients into mid and late adulthood. While we have demonstrated good outcomes overall in patients entering adulthood, the fate of the neo-aortic root and of the translocated coronaries remains to be determined. One would expect that patients with clinically significant AR in their twenties would require neo-aortic valve replacement at some point in their lives. Likewise, while there are no reports in the literature of dissection or rupture, patients with large neo-aortic roots will need close surveillance. Similarly, it is yet unknown how atherosclerotic disease will affect the coronary arteries of these patients. As such, continuing data collection of ASO survivors followed at adult congenital centres is key in order to improve current and future management strategies.

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Appendix A: Additional manuscripts authored or co-authored during candidature

A.1: Naimo PS et al. Semin Thorac Cardiovasc Surg 2016;28:500-511.

ORIGINAL SUBMISSION

Outcomes of Truncus Arteriosus Repair in Children: 35 Years of Experience From a Single Institution

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We evaluated the long-term outcomes following repair of truncus arteriosus (TA) from a single institution. We conducted a retrospective review of children ($n = 171$) who underwent TA repair between 1979 and 2014. Early mortality rate was 11.7% (20/171). There were 19 late deaths. Most deaths (74%, 29/39) occurred within the first year following surgery. The 1-year mortality rate in 1979-2004 was 18% (25/136) and decreased to 11% (4/35) in 2005-2014. The overall survival rate was 73.6% at 30 years. Multivariate analysis identified postoperative extracorporeal membrane oxygenation ($P = 0.003$), operative weight <2.5 kg ($P = 0.012$), prior surgical intervention ($P = 0.018$), and coronary artery anomaly ($P = 0.037$) as risk factors for early mortality. A Cox regression model identified DiGeorge syndrome ($P = 0.008$) as a risk factor for late mortality. Freedom from right ventricular outflow tract reoperation was 4.6% at 20 years. Concomitant truncal valve (TV) repair or replacement was undertaken in 20 patients. Additionally, 14 patients underwent late TV repair or replacement. The overall survival rate in patients who underwent TV operation was 76.9% at 20 years. A total of 19 patients had concomitant interrupted aortic arch with a survival rate of 89.5% at 20 years. Median follow-up was 19 years (mean = 17 years, range: 1-34 years). All patients were in New York Heart Association Class I/II at last follow-up. Following repair of TA, patients had good long-term functional status but had high reoperation rates. Repair of interrupted aortic arch and TV were not risk factors for mortality. Postoperative extracorporeal membrane oxygenation, operative weight <2.5 kg, prior surgical intervention, and coronary artery anomaly were risk factors for early death. DiGeorge syndrome was associated with late death, most commonly from infection.

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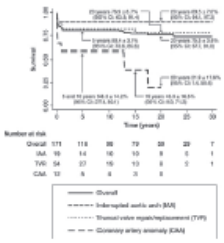

Kaplan-Meier overall survival following truncus arteriosus repair.

Central Message

Postoperative extracorporeal membrane oxygenation, operative weight <2.5kg, prior surgical intervention, and coronary artery anomaly were risk factors for early death. Truncal valve repair and interrupted aortic arch are no longer risk factors for death.

Perspective

Postoperative ECMO, weight of less than 2.5 kg at the time of TA repair, surgical intervention prior to TA repair and coronary artery anomalies were risk factors for early death. Truncal valve surgery and interrupted aortic arch repair were not risk factors for mortality. Patients with DiGeorge syndrome require long-term follow-up to prevent post-infection complications that may result in late death.

See Editorial Commentary on pages 512-513.

Keywords: truncus arteriosus, common arterial trunk, conotruncal, surgery, congenital heart disease

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Dr. Weintraub reports receiving consulting fees from Actelion. Drs. Brizard, Bullock, d'Udekem, Fricke, Kelly, Konstantinov, Naimo, Radford and Yong have no commercial interest to disclose

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INTRODUCTION

Truncus arteriosus (TA) is a rare anomaly in which a common arterial trunk supplies both systemic and pulmonary circulations.[1,2] Large single-institution studies with long-term follow-up are limited. We aimed to determine the mortality, morbidity, and risk factors for adverse outcomes in patients after TA repair at a single institution.

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METHODS

Patients

The Human Research Ethics Committee at the Royal Children's Hospital approved the study. Between 1979 and 2014, 171 patients underwent repair of TA. Data were obtained retrospectively by review of medical records from initial admission until last cardiology follow-up.

Definitions

Early mortality was defined as death occurring within 30 days of surgery or before hospital discharge. All other deaths were considered late. A modified Van Praagh classification for TA was used[3]: Type 1: TA with a main pulmonary artery (PA) giving rise to the branch PAs. Type 2: TA with separate PA orifices. Type 3: TA with one PA originating from the TA and a ductal or aortic origin of the other PA, or dual ductal origins of the PAs. Type 4 of the Van Praagh classification was described into the 3 types mentioned and the types of interrupted aortic arch (IAA) specified. The presence (type A) or absence (type B) of a ventricular septal defect (VSD) was also specified. As a VSD is commonly a part of the TA complex, it was not considered a concomitant anomaly. A coronary artery anomaly (CAA) was defined as an abnormal coronary origin or course with or without the CA crossing the right ventricular (RV) outflow tract (RVOT).

Operative Technique

Surgery was performed with cardiopulmonary bypass in all patients. The PAs were detached from the TA and subsequently connected to the RVOT. Continuity between the RV and the PA was established by a conduit or direct anastomosis of the main PA to the RVOT with or without a monocusp valve. The remaining defect in the TA was closed directly ($n = 169$) or with a patch ($n = 2$). The VSD was closed directly ($n = 4$) or with a patch ($n = 165$). Single-staged repair of concomitant anomalies was undertaken in most patients.

Data Analysis

Data were analyzed using Stata version 12 (StataCorp LP, College Station, TX). Continuous data were expressed as means ± standard deviations (range), and skewed continuous data are expressed as medians (interquartile range). Categorical data were summarized as frequencies and percentages. Univariate and multivariate logistic regression and Cox proportional hazard modeling were used to determine risk factors for mortality and reoperation. Kaplan-Meier actuarial survival curves were used to analyze and plot time-related end points. Non-normally distributed data were log transformed before analysis. Statistical significance was set at $P < 0.05$.

RESULTS

Median age at surgery decreased from 67 days (1979-2004; $n = 136$) to 20 days (2005-2014; $n = 35$). Patient characteristics and operative data are summarized in Tables 1 and 2. Continuity between the RV and the PA was established using a conduit in 160 patients and direct RV-PA anastomosis in 11 patients without ($n = 7$) and with Gore-Tex ($n = 2$) or autologous pericardial ($n = 2$) monocusp valves. Patients who underwent direct RV-PA anastomosis underwent type 1 TA repair. One patient underwent TA repair with truncal valve (TV) replacement and VSD closure with fenestrated patch owing to hypoplastic PAs. One patient had TA with intact ventricular septum, mitral atresia, hypoplastic left ventricle, and an IAA and underwent a univentricular staged repair that resulted in the Fontan operation and was doing well 4 years after the Fontan operation.

Surgical interventions before TA repair were performed in 17 patients. Most staged procedures (13 of 17 patients) occurred before 1990. Before this period, PA banding was performed for failure to thrive ($n = 5$). The only remaining PA banding was done in a patient on extracorporeal membrane oxygenation (ECMO) ($n = 1$) in 2010. A modified Blalock-Taussig shunt was done in 2 patients with hypoplastic branch PAs. Other prior repairs were PA reconstruction ($n = 5$), major aortopulmonary collateral artery ligation ($n = 2$), repair of esophageal atresia with tracheoesophageal fistula ($n = 2$), and IAA repair ($n = 1$).

Mortality

The early mortality rate was 11.7% (20/171). There were 19 late deaths (12.6%, 19/151). Most deaths (74%, 29/39) occurred within the first year following surgery. The 1-year mortality rate in 1979-2004 was 18% (25/136) and decreased to 11% (4/35) in 2005-2014, although this trend did not reach statistical significance ($P = 0.15$). Excluding patients who required postoperative ECMO, the highest overall mortality occurred in patients with CAA (Fig. 1). One patient with CAA required postoperative ECMO. The Kaplan-Meier overall survival rate was 80.4 ± 3.1% (95% CI: 73.6-85.6) at 10 years and 73.6 ± 4.0% (95% CI: 64.8-80.5) at 30 years (Fig. 2).

Risk factors for early and late mortality are summarized in Table 3. A total of 14 patients required ECMO for a mean of 5 days after TA repair, 71% (10/14) of them died. Weight of <2.5 kg at the

OUTCOMES OF TRUNCUS ARTERIOSUS REPAIR

Table 1. Patient Characteristics

Variable	
Total patients	$n = 171$
Neonates	29.8% (51/171)
Male	52% (89/171)
Median age at repair	52 days (range 1 day to 8.7 years)
Median weight at repair	3.62 kg (range: 1.70-23.0 kg)
Classification	
Type A1	30.4% (52/171)
Type A2	61.4% (105/171)
Type A3	7.6% (13/171)
Type B3	0.6% (1/171)
Truncal valve insufficiency	
Mild	34.5% (59/171)
Moderate-to-severe	10.5% (18/171)
Truncal valve stenosis	
Mild	4.7% (8/171)
Moderate-to-severe	3.5% (6/171)
Tricuspid regurgitation†	8.8% (15/171)
Mitral regurgitation†	5.8% (10/171)
DiGeorge syndrome	17.5% (30/171)
Other syndromes	5.8% (10/171)
VATER syndrome	2.3% (4/171)
Pierre Robin syndrome	1.2% (2/171)
Goldenhar syndrome	0.6% (1/171)
Holt-Oram syndrome	0.6% (1/171)
Klinefelter syndrome	0.6% (1/171)
Triple X syndrome	0.6% (1/171)
Concomitant anomalies	48.5% (83/171)*
ASD	52.6% (90/171)
IAA	11.1% (19/171)
CAA	7.0% (12/171)
Hypoplastic PA	4.7% (8/171)
PDA	2.9% (5/171)
MAPCA	2.3% (4/171)
CoA	1.2% (2/171)

ASD, atrial septal defect; CAA, coronary artery anomaly; CoA, coarctation of aorta; IAA, interrupted aortic arch; MAPCA, major aortopulmonary collateral artery; PA, pulmonary artery; PDA, patent ductus arteriosus; TA, truncus arteriosus; VATER, syndrome involving vertebral anomalies, imperforate anus, tracheoesophageal fistula with esophageal atresia, cardiac anomalies, renal dysplasia, and limb defects; VSD, ventricular septal defect.

*Excluding ventricular septal defects.

†Mitral and tricuspid regurgitation rated as moderate or severe.

time of TA repair and surgical intervention before TA repair were risk factors for early mortality. CAA (Fig. 3) was associated with increased early mortality (Table 4). It is noteworthy that a CA crossed the RVOT in 4 patients—of whom, 3 died and 1 was doing well at 2 years of follow-up.

DiGeorge syndrome was clinically diagnosed in 30 patients. Diagnosis was confirmed with fluorescence in situ hybridization in 70% (21/30) of patients. DiGeorge syndrome was a risk factor for late mortality. There were 8 late deaths in this subgroup of patients: 5 patients with DiGeorge syndrome died of infection (respiratory failure due to respiratory virus, $n = 2$; disseminated fungal osteomyelitis, $n = 1$; methicillin-resistant *Staphylococcus aureus* sepsis, $n = 1$; and pneumonia, $n = 1$), 1 patient died of arrhythmia, and the cause of death was unknown in 2 patients.

Reoperations

There have been 207 reoperations in 114 patients. Freedom from any reoperation was 23.3 ± 3.7% (95% CI: 16.3-31.0) at 10 years and 3.2 ± 1.8% (95% CI: 0.9-8.2) at 20 years. Freedom from reoperation for RVOT obstruction, aortic arch obstruction, and TV insufficiency is shown in Figure 4.

Table 2. Operative Data

Variable	
Mean CPB duration	139 ± 67 min (33-417 min)
Mean aortic cross-clamp time	77 ± 37 min (31-263 min)
Mean circulatory arrest time	13 ± 17 min (1-85 min)
Direct RV-PA anastomosis	6.4% (11/171)
RV-PA conduit	93.6% (160/171)
Conduit type	
Aortic homograft	31.9% (51/160)
Hancock	26.9% (43/160)
Pulmonary homograft	19.4% (31/160)
Contegra	6.8% (11/160)
Tascon	6.3% (10/160)
Gore-Tex	5.0% (8/160)
Dacron	3.8% (6/160)
Median size of conduit	12 mm (range: 5-20 mm)
Concomitant truncal valve operation	
Truncal valve repair	11.1% (19/171)
Truncal valve replacement	0.6% (1/171)
Concomitant repairs	
VSD closure	99.4% (170/171)
ASD closure	50.3% (86/171)
PA reconstruction	12.3% (21/171)
Aortic arch reconstruction	11.7% (20/171)
PDA ligation	2.9% (5/171)
MAPCA ligation	2.3% (4/171)
Right pneumonectomy	0.6% (1/171)

ASD, atrial septal defect; CPB, cardiopulmonary bypass; MAPCA, major aortopulmonary collateral artery; PA, pulmonary artery; PDA, patent ductus arteriosus; RV, right ventricle; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

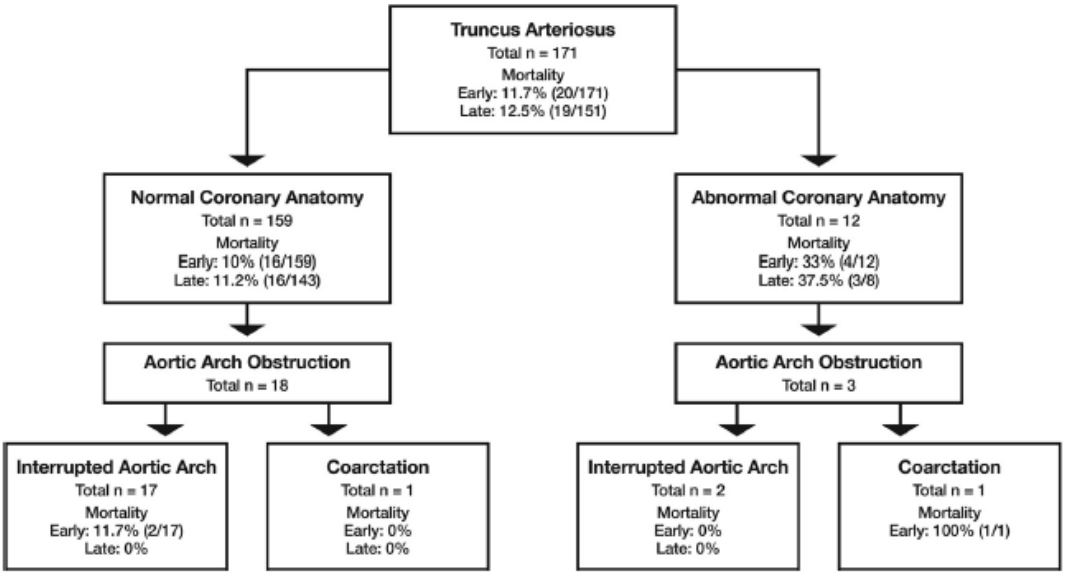

Figure 1. Outcomes of patients with and without coronary artery anomalies and aortic arch obstruction.

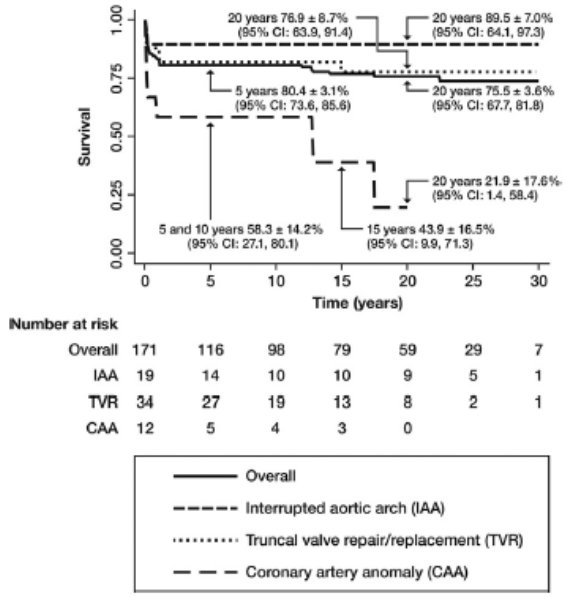

Figure 2. Kaplan-Meier overall survival following truncus arteriosus repair.

Table 3. Risk Factors for Mortality

Early Mortality

Variable	Mortality (%)	Univariate		Multivariate Regression	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Moderate-to-severe TVI	22% (4/18)	2.44 (0.71-8.33)	0.153		NS
IAA	14% (3/21)	1.30 (0.34-4.89)	0.694		NS
Initial truncal valve repair	20% (4/20)	2.10 (0.63-7.09)	0.227		NS
Coronary artery anomaly	33% (4/12)	4.46 (1.21-16.51)	0.025	5.27 (1.11-25.07)	0.037
DiGeorge syndrome	17% (5/30)	1.68 (0.56-5.04)	0.355		NS
Prior surgical intervention	29% (5/17)	3.86 (1.20-12.46)	0.024	5.31 (1.33-21.11)	0.018
Neonate at repair	22% (11/51)	3.39 (1.31-8.79)	0.032		NS
Operative weight < 2.5 kg	33% (4/12)	4.46 (1.21-16.51)	0.025	6.95 (1.52-31.61)	0.012
Postoperative ECMO	50% (7/14)	11.08 (3.36-36.47)	<0.001	11.01 (2.90-41.76)	0.003

Late mortality

Variable	Mortality (%)	Univariate		Cox proportional hazard	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Moderate-to-severe TVI	14% (2/14)	1.43 (0.33-6.29)	0.630		NS
IAA	0% (0/18)	Inestimable	Inestimable		NS
Initial truncal valve repair	13% (2/16)	1.12 (0.26-4.90)	0.879		NS
Coronary artery anomaly	38% (3/8)	4.10 (1.18-14.26)	0.026		NS
DiGeorge syndrome	32% (8/25)	5.02 (1.99-12.68)	0.001	3.72 (1.40-9.84)	0.008
Prior surgical intervention	8% (1/12)	0.53 (0.07-4.03)	0.544		NS
Neonate at repair	10% (4/40)	0.81 (0.27-2.44)	0.702		NS
Operative weight <2.5 kg	13% (1/8)	1.04 (0.14-7.80)	0.969		NS
Postoperative ECMO	43% (3/7)	5.20 (1.46-18.43)	0.011		NS

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; IAA, interrupted aortic arch; NS, not significant; OR, odds ratio; RVOT, right ventricular outflow tract; TVI, truncal valve insufficiency.

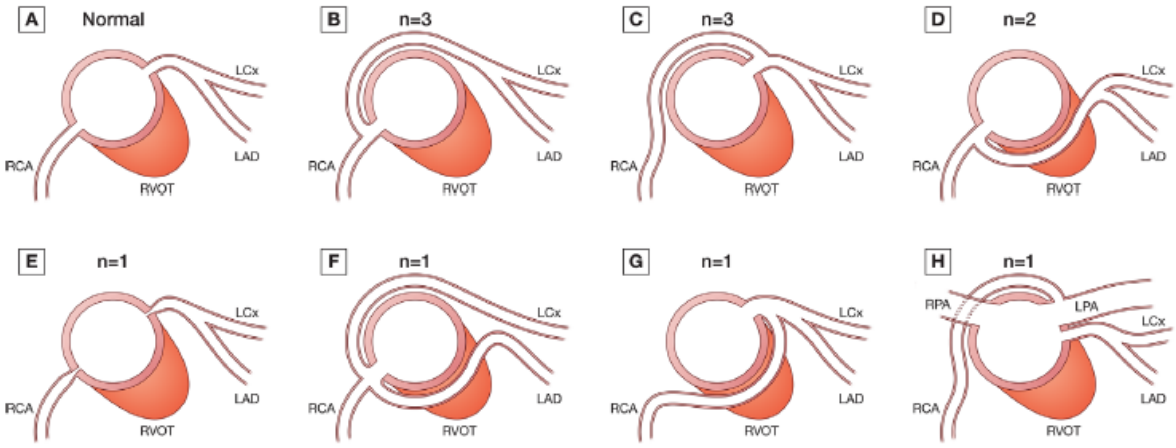

Figure 3. Coronary artery anomalies. Most patients had normal coronary anatomy (A). Most common coronary anomaly was a single coronary orifice (B-D, F, and G). One patient had narrow coronary ostia immediately on top of the commissures of a bicuspid truncal valve (E). In 1 patient, the right coronary artery originated from the left pulmonary artery (H). LAD, left anterior descending; LCA, left coronary artery; LCx, left circumflex artery; LPA, left pulmonary artery; RCA, right coronary artery; RPA, right pulmonary artery; RVOT, right ventricular outflow tract. (Color version of figure is available online at http://www.semthorcardiovascsurg.com.)

RVOT Reoperation

There have been 156 RVOT reoperations in 106 patients, which included conduit insertion for 3 patients who had direct RV-PA repair. Of these reoperations, 45 patients have had at least 2 conduit replacements, and 7 patients have had 3 conduit replacements. Median time to RVOT reoperation was 4.25 years (2.1-8.1 years). Freedom from RVOT reoperation was 29.2 ± 4.4% (95% CI: 20.9-38.0) at 10 years and 4.6 ± 2.4% (95% CI: 1.4-10.9) at 20 years (Fig. 4). Cox regression models identified a conduit size of less than 16 mm (hazard ratio [HR] = 2.14; 95% CI: 1.23-3.75; $P = 0.007$) as a risk factor for early RVOT reoperation. Freedom from RVOT reoperation in patients who underwent direct RV-PA anastomosis was 70.7 ± 14.3% (95% CI: 33.7-89.5) at 5 years and 47.1 ± 21.5% (95% CI: 8.5-79.5) at 10 years. Most conduit insertions ($n = 3$) in these patients occurred within 1 month of TA repair; an additional patient underwent conduit insertion at 6.5 years. Catheter-based interventions were 33 in the conduit group (21%, 33/160) and 2 in the direct RV-to-PA anastomosis group (18%, 2/11). There was no statistically significant difference in reoperation or catheter-based reintervention rates between patients who underwent conduit repair and those who underwent direct RV-PA anastomosis.

Aortic Arch Obstruction

A total of 19 patients had a TA with concomitant IAA. The IAA was type A in 3 patients, type B in 15 patients, and type C in 1 patient. IAA repairs were performed by end-to-side anastomosis in 15 patients, patch augmentation in 2 patients, and implantation of an aortic homograft and Gore-Tex graft in 1 patient. One patient underwent IAA repair before TA repair. There were 2 early deaths and no late deaths in these patients. The overall survival rate of patients with TA-IAA was 89.5±7.0% (95% CI: 64.1-97.3) at 20 years (Fig. 2).

An additional 2 patients underwent aortic arch patch augmentation repair because of coarctation of the aorta. One of these patients died on postoperative day 4 due to cardiac failure, and the other is currently alive and well after 4 years of follow-up.

Overall, 5 patients underwent 9 aortic reoperations. Freedom from aortic reoperation was 70.1 ± 11.5% (95% CI: 41.5-86.7) at 10 and 20 years (Fig. 4). Of these reoperations, 3 patients underwent aortic reoperations during their initial hospital stay. These were an implantation of an 8-mm Gore-Tex interposition graft into the aorta to relieve left bronchial compression by reconstructed aortic arch in 2 patients and pericardial patch enlargement of residual aortic arch obstruction in 1 patient. There were 5 late aortic reoperations in 4 patients. These were replacement of the aforementioned 8-mm Gore-Tex interposition graft with 18-mm Gore-Tex grafts in 2 patients and aortic arch reconstructions for reobstruction in 3 patients.

TV Operation

Initial TV operation was undertaken in 20 patients (repair, $n = 19$ and replacement with a 10-mm aortic

Table 4. Characteristics and Outcomes of Patients With Concomitant Coronary Artery Anomaly

Year of Repair	Age at Repair (d)	Coronary Artery Anomaly	Course of Coronary Artery	Additional Concomitant Anomalies	Outcome	Cause of Death	Follow-up Time
1984	68	Single CA	LCA from RCA and crossed RVOT	Right PAPVC	Late death	Sudden VF following pressure load on RV	17.5 years
1986	386	RCA from LPA	RCA ostium on LPA as it arises just above sinus of Valsalva	RPA from descending aorta and DGS	Late death	Sepsis	11 months
1988	42	Abnormally positioned coronary ostia	Abnormally narrow coronary ostia closely related to bicuspid truncal valve commissures	PFO	Early death	Cardiac arrest	12 hours
1988	27	LAD from RCA	LAD arises from RCA and crosses RVOT	RPA from left side of TA and hypoplastic LPA from left subclavian artery	Early death	Severe tracheobronchomalacia	77 days
1996	164	Single CA with an intramural course	Intramural LCA, normal course	Hypoplastic LPA and left lung	Survived	–	17.9 years
1998	69	Single CA	Normal epicardial course	–	Late death	Sudden cardiac arrest; emergency ECMO that could not be weaned	12.8 years
1998	3	Single CA	RCA from LCA and crosses RVOT	CoA, PDA, and VATER complex	Early death	Cardiac failure; no improvement on ECMO	4 days
1999	178	Single CA	LCA from RCA and crosses RVOT	Goldenhar syndrome	Survived	–	1.7 years
2001	44	Single CA	Normal epicardial course	TV repair	Survived	–	13.3 years
2006	9	Single CA	Normal epicardial course	IAA type C, PDA, ASD, aberrant right subclavian artery, and DGS	Survived	–	6 years
2012	3	Single CA	Normal epicardial course	IAA type B, PDA, and PFO	Survived	–	1 years
2013	6	Single CA	Normal epicardial course	PFO	Early death	Sepsis	26 days

ASD, atrial septal defect; CA, coronary artery; CoA, coarctation of aorta; CVA, cerebrovascular accident; DGS, DiGeorge Syndrome; ECMO, extracorporeal membrane oxygenation; IAA, interrupted aortic arch; LAD, left anterior descending artery; LCA, left coronary artery; LPA, left pulmonary artery; LV, left ventricle; MI, myocardial infarction; PAPVC, partial anomalous pulmonary venous connection; PDA, patent ductus arteriosus; PFO, patent foramen ovale; RCA, right coronary artery; RPA, right pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract; TV, truncal valve; VF, ventricular fibrillation.

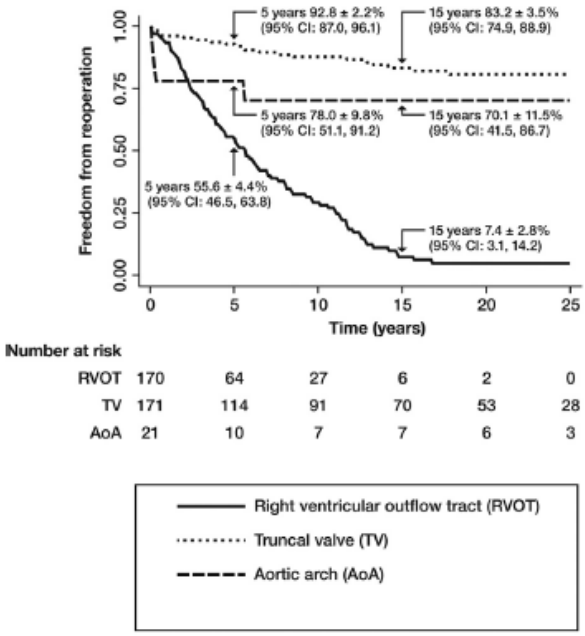

Figure 4. Freedom from reoperation following truncus arteriosus repair.

homograft, $n = 1$). There were 6 deaths (4 early and 2 late) in this group of patients. Overall, 9 patients underwent TV reoperation (repair, $n = 4$ and replacement with bileaflet mechanical prostheses, $n = 5$) at a median time of 2.0 years (235 days to 5.6 years). Freedom from TV reoperation was 51.4 ± 12.2% (95% CI: 25.8-72.3) at 10 years and 25.8 ± 19.1% (95% CI: 1.8-62.9) at 20 years (Fig. 5).

Of the remaining 151 patients, 14 underwent TV surgery (repair, $n = 6$ and replacement with bileaflet mechanical prosthesis, $n = 8$) at a median time of 7.1 years (4.7-13.2 years) (Fig. 5). One patient underwent 2 TV replacements. Overall freedom from any late TV operation was 92.6 ± 2.4% (95% CI: 85.9-96.3) at 10 years and 86.5 ± 3.6% (95% CI: 77.5-93.0) at 20 years.

There have been 7 deaths in the 34 patients who have undergone TV operation (4 early deaths and 3 late deaths). The overall survival rate in patients who underwent TV operation was 82.4 ± 6.5% (95% CI: 64.9-91.7) at 10 years and 76.9 ± 8.7% (95% CI: 63.9-91.4) at 20 years (Fig. 2). Neither TV

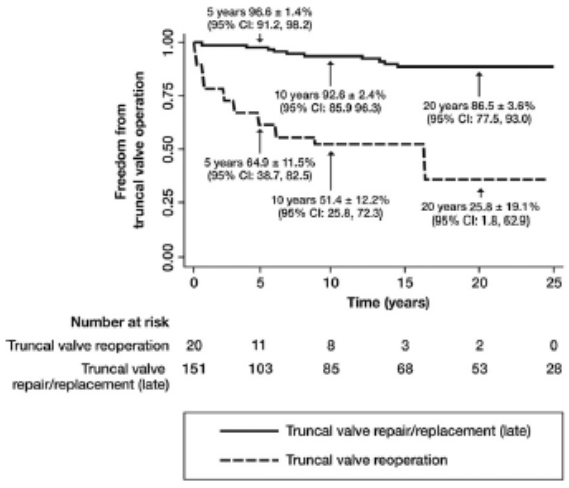

Figure 5. Freedom from truncal valve operation in those ($n = 20$) who had concomitant truncal valve repair during the initial complete repair of the truncus (dashed line) and those ($n = 151$) who did not (solid line).

Table 5. Follow-up Characteristics of Late Survivors

Variable	
RV function	
Normal	81.1% (107/132)
Mildly reduced	17.4% (23/132)
Unknown	1.5% (2/132)
RVOT characteristics	
Mean maximum velocity	2.8 m/s
Mean maximum gradient	44.2 mmHg
Mean gradient	21.3 mmHg
Degree of obstruction	
None	27.3% (36/132)
Mild	49.2% (65/132)
Moderate	15.2% (20/132)
Severe	6.8% (9/132)
Unknown	1.5% (2/132)
Pulmonary valve regurgitation	
None	61.4% (81/132)
Mild	22.0% (29/132)
Moderate	6.1% (8/132)
Severe	15.2% (20/132)
Unknown	1.5% (2/132)
Truncal valve stenosis or insufficiency	
Mean maximum velocity	2.2 m/s
Mean maximum gradient	24.9 mmHg
Degree of insufficiency	
None or trivial	74.2% (98/132)
Mild	22.7% (30/132)
Moderate-to-severe	1.5% (2/132)
Unknown	1.5% (2/132)

RV, right ventricle; RVOT, right ventricular outflow tract.

operation nor TV insufficiency was a risk factor for mortality.

Long-term TV status in surviving patients who did not undergo TV operation was good, with 79.0% (83/115) of patients having no or trivial TV insufficiency. In those 115 patients, preoperative TV insufficiency severity had decreased in 38 patients. However, there was newly developed TV insufficiency in 12 patients (mild TV insufficiency, $n = 10$ and moderate-to-severe insufficiency, $n = 2$).

Follow-up Status

Follow-up was 98.5% (130/132) complete for survivors; 2 patients were lost to follow-up. Median follow-up was 19 years (mean = 17 years, range: 1-34 years). At last follow-up, all patients were in New York Heart Association Class I/II. Follow-up characteristics are summarized in Table 5.

DISCUSSION

Mortality

To our knowledge, this is the largest study of children who underwent TA repair in a single institution. It is now accepted that a complete surgical repair of TA should be performed within the first months of life, including single-staged repair of concomitant anomalies.[4-8] Currently, we perform single-staged repair of concomitant cardiovascular anomalies. Postoperative ECMO was a risk factor for early mortality. Of all patients requiring ECMO, 50% (7/14) died before hospital discharge. ECMO was electively used in only 3 patients, whereas the remaining patients required emergent ECMO cannulation. DiGeorge syndrome was a risk factor for late mortality. Of operative survivors with DiGeorge syndrome, 32% (8/25) died late and 6 of them died of infection. The proportion of late deaths due to infection in this cohort may be because of lymphopenia associated with DiGeorge syndrome. Thus, these patients must have an ongoing immunology follow-up.

We have previously described outcomes of TA repair between 1979 and 1995 with a policy of elective TA repair between 2 and 3 months of age.[8] Over that period, median age at operation was 71 days and the early mortality rate was 13.4% (11/82) and the late mortality rate was 15.5% (11/71).[8] Over the most recent decade, the median age at repair decreased to 20 days, with an early mortality rate of 11.8% (4/35) and a late mortality rate of 6.5% (2/31). Overall, the early mortality rate was 11.7% (20/171) in 171 children who underwent TA repair and the late mortality rate was 12.5% (19/151). Interestingly, 52.6% (10/19) of late deaths occurred within the first year of TA repair. Rajasinghe et al[9] also noted that 56% (13/23) of late deaths occurred within the first year following repair. Similarly, Tlaskal et al[6] reported 8 late deaths, 7 of them occurring within the first year after TA repair. We observed a decrease in the 1-year mortality rate over the study period from 18% (25/136) in 1979-2004 to 11% (4/35) in 2005-2014. Surgical outcomes of previous studies are summarized in Table 6.

Coronary Artery Anomalies

CAAs are reported in approximately 5%-20% of patients with TA[10-12] and have been associated with a high mortality rate following TA repair.[13-15] Schreiber et al[13] reported on 106 patients with TA between 1976 and 1998, with 13 patients having a CAA. They concluded that a CAA was associated with poorer surgical outcomes, with 5 early deaths and 2 late deaths being related to compression or distortion of the anomalous CA.[13] Danton et al[14] described their experience with 61 patients with TA between 1988 and

Table 6. Reported Outcomes of Truncus Arteriosus Repair

Study	Year	Study Period	Patients (*n*)	Age at Repair (Median, d)	Early Mortality	Late Mortality	Follow-up (Mean, y)
Lacour-Gayet et al[28]	1996	1988-1995	56	41	16% (9/56)	4.3% (2/47)	3.2
Rajasinghe et al[9]	1997	1975-1995	165	106	Not reported	13.9% (23/165)	10.5†
Urban et al[8]	1998	1987-1997	46	62	4.3% (2/46)	2.3% (1/44)	3
Williams et al[29]	1999	1953-1997	148	38	50% (74/148)	14.9% (11/74)	Not reported
Jahangiri et al[16]	2000	1992-1998	50	14	4% (2/50)	0% (0/48)	1.9†
Schrieber et al[13]	2000	1976-1998	106	134	17.9% (19/106)	26.4% (23/87)	6
Alexiou et al[30]	2001	1974-1994	23	51	17.4% (4/23)	5.3% (1/19)	14.8
Brown et al[15]	2001	1978-2000	60	76*	16.7% (10/60)	2% (1/50)	9.4
Danton et al[14]	2001	1988-2000	61	34	13% (8/61)	15.1% (8/53)	4.2
Thompson et al[25]	2001	1992-1999	65	10	4.6% (3/65)	3.2% (2/62)	2.7†
Kalavrouziotis et al[31]	2006	1993-2005	29	28	3.4% (1/29)	3.6% (1/28)	6.2
Henaine et al[32]	2008	1986-2003	153	35	17.0% (26/153)	4.7% (6/127)	8.1
Raisky et al[33]	2009	2000-2006	32	74*	15.6% (5/32)	22.2% (6/27)	3.3
Hawkins et al[24]	2010	1999-2008	42	31	9.5% (4/42)	10.5% (4/38)	5
Tlaskal et al[7]	2010	1981-2009	83	54	23% (19/83)	12.5% (8/64)	10.9
Vohra et al[23]	2010	1964-2008	32	14	9.4% (3/32)	3.4% (1/29)	24.5†
Xu et al[34]	2010	2000-2006	23	350	8.7% (2/23)	0% (0/21)	4.1
Total		1953-2009	1174		16.3% (191/1174)	8.3% (98/983)	

*Mean age at repair
†Median follow-up times.

2000, 9 of whom had a CAA that included intramural CA ($n = 3$), major branch CA crossing the RVOT ($n = 3$), and abnormally positioned coronary ostia ($n = 3$). Among these patients, 2 deaths were directly associated with a CA injury, and it was concluded that the presence of a CAA was a risk factor for death.[14] The study by Brown et al[15] of 60 patients with TA conducted between 1978 and 2000 identified 6 patients with a CAA, with a single death. Though a CAA was not statistically significant, they suggested that owing to the variable pattern of the CAs in patients with TA, it must be considered a risk factor.[15]

A major CA crossed the RVOT in 4 patients, of whom 3 died and 1 was well at 2 years of follow-up. A major branch CA crossing the RVOT is of particular importance, as this exposes the CA to damage during a right ventriculotomy, as well as postoperative compression from the conduit.[10,11] Particular attention must be given to conduit position so as to allow it to bridge over the anomalous CA without causing compression.

This study demonstrated that a CAA carries significant risk for death after repair of TA. Over the recent decade (2005-2014), a CAA did not emerge as a risk factor for death. However, it must be noted that there have only been 4 patients with CAA over this time, with 1 early death, and importantly, none of these patients had a CA that crossed the RVOT. Preoperative multidetector computed tomography is helpful in precise delineation of the coronary arteries.

TA Associated With IAA

Several studies demonstrated that patients with TA and IAA have high mortality and reoperation rate.[2,9,15-18] The Congenital Heart Surgeons Society study reported on 50 patients with TA-IAA operated between 1987 and 1997; 34 deaths occurred and the overall survival rate in patients with TA-IAA was 31% at 10 years.[4] Furthermore, at 5 years after TA-IAA repair, only 28% were alive without reoperation. Russell et al[2] suggested that IAA was the single greatest risk factor for mortality in patients with TA. The highest mortality rate in patients with TA-IAA was in those with concomitant TV insufficiency, and it approached 68%.[2,4] In contrast to these reports, our results with TA-IAA were favorable. The presence of an IAA was not a risk factor for mortality. We have previously reported our experience with TA-IAA, which described 2 early deaths in 16 patients.[8,19] In this study, we report an additional 3 patients with TA-IAA, 2 of whom have survived single-staged repair of the TA-IAA and were doing very well. The third patient initially underwent repair of the IAA, followed by TA repair 5 months later. This patient has undergone 3 RV-to-PA conduit replacements and has not needed any aortic arch reoperations and was well at 31 years after initial TA repair.

There is potential for recurrence of aortic arch obstruction in patients with IAA. Aortic arch reoperation rate in the Congenital Heart Surgeons Society

study was 13.2% (5/38). Brown et al[15] reported that 23.1% of patients required aortic arch reoperation after a mean of 29.1 months. We have previously reported a freedom from aortic arch reoperation of 57.1% at 15 years.[19] In this study, we observed further improvement of freedom from aortic arch reoperation to 68.8% at 20 years when compared with our earlier study.[19] Aortic arch repairs were done using the end-to-side technique in 79% (15/19) of patients, which in our hands, carried low mortality and aortic arch reoperation rates.[19,20] As previously described, we resect all ductal tissue and extensively mobilize the descending aorta to ensure a tension-free anastomosis.[21]

TV Insufficiency

TV insufficiency occurs in approximately 25% of patients.[2,22,23] Some suggested that TV insufficiency was well tolerated and not associated with mortality.[6,24] However, others believed that lack of TV competence was a risk factor for death and was one of the most important factors influencing early outcomes.[2,4,6,25-27]

Russell et al,[2] who reviewed 23 TV operations in 572 patients with TA who were operated between 2000 and 2009, concluded that despite the higher early mortality in concomitant TA and TV repair than in TA alone (30% vs 10%, respectively), failure to address significant TV insufficiency was associated with poor outcomes. Others[9,14] have reported that moderate-to-severe TV insufficiency was a risk factor for mortality. We identified TV insufficiency in 77 patients (59 mild and 18 moderate-to-severe), 18 of whom underwent concomitant TV repair during TA repair. There were 2 patients without TV insufficiency who underwent concomitant TV repair owing to significant TV stenosis. Neither TV insufficiency nor TV operation were risk for mortality.

Kaza et al[27] performed concomitant truncal valvuloplasty in all patients with preoperative moderate-to-severe TV insufficiency. They described 17 patients undergoing TV operation between 1995 and 2008 with no early deaths and 1 late death, and only 5 of 17 patients required TV reoperation.[27] At our institution, 18 patients had moderate-to-severe TV insufficiency. Before 2000, of 8 patients with moderate-to-severe TV insufficiency, 1 underwent TV repair and died (early); 7 patients did not undergo concomitant TV repair, 3 of whom subsequently required late TV repair or replacement with 1 late death. Of the remaining 4 patients, 2 died (1 early death and 1 late death) and 2 had trivial TV insufficiency at last follow-up. After 2000, 9 patients underwent concomitant TV surgery, with 2 deaths (1 early death and 1 late death), and 1 patient did not. Therefore, only 27.3% (3/18) of patients with initial moderate-to-severe TV insufficiency have survived without TV operation. Although no statistical analysis is feasible because of small numbers, we advocate TV surgery for TV insufficiency greater than a moderate central jet.

Overall, the long-term outcomes of TV repair or replacement have been good, with most patients having none or trivial TV insufficiency. However, concomitant TV repair was associated with a high reoperation rate, with 11 patients requiring TV reoperation.

LIMITATIONS

This study was limited by its retrospective nature. Perioperative techniques have varied during the study period. Some variables contained a relatively small number of patients, thus limiting multivariate analysis.

CONCLUSION

Following repair of TA, patients had good long-term functional status but had high reoperation rate. Repair of the TV and IAA was not a risk factor for mortality. A CAA, low body weight, previous surgical intervention, and need for postoperative ECMO were risk factors for early death. DiGeorge syndrome was associated with late death, most commonly from infection.

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CONGENITAL HEART

Surgical Intervention for Anomalous Origin of Left Coronary Artery From the Pulmonary Artery in Children: A Long-Term Follow-Up

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Background. Anomalous left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital heart defect with limited data on long-term outcomes after surgical intervention.

Methods. We conducted a retrospective review of all children (N = 42) who underwent surgical repair of ALCAPA between 1980 and 2014 at the Royal Children's Hospital, Melbourne.

Results. Twenty-nine (69% [29 of 42]) patients underwent coronary reimplantation, 12 (29% [12 of 42]) had intrapulmonary baffle (Takeuchi) repair, and 1 (2% [1 of 42]) patient had ligation of the anomalous coronary artery. Nine (21%, 9 of 42) patients had concomitant mitral valve (MV) repair at the time of ALCAPA repair. A left ventricular assist device (LVAD) was used in 36% (15 of 42) of patients. Early mortality was 2.4% (1 of 42 patients). Median follow-up was 14 years (mean, 13 years; range, 4 months–31 years). There were no late deaths. Survival was 98% at 20 years. Freedom from reoperation was 81%, 81%, and 76% at 5, 10, and 20 years after operation, respectively. Eight patients underwent late MV repair or replacement at a median of 3 years (mean, 8 years; range, 2 months–25 years) after operation. Freedom from late MV repair or replacement was 86% at 5 and 10 years and 81% at 20 years after operation. Eleven (26% [11 of 42]) patients had severe mitral regurgitation (MR) preoperatively. Of those 11 patients, 5 (45% [5 of 11]) had concomitant MV repair at the time of ALCAPA repair, 3 (27% [3 of 11]) had late MV repair or replacement, and the remaining 3 (27% [3 of 11]) patients had mild MR at last follow-up. Thirty-six (90% [36 of 41]) patients had normal left ventricular function and 4 (10% [4 of 41]) patients had mildly reduced left ventricular (LV) function at last follow-up.

Conclusions. ALCAPA can be operated on with good outcomes. Persistent MR and a moderate rate of late MV repair warrants close follow-up.

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Anomalous left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital anomaly, which if left unrepaired has a mortality rate up to 90% [1]. Left ventricular (LV) dysfunction and ischemic mitral regurgitation (MR) secondary to mitral annular dilatation and ischemic papillary muscle dysfunction contributes to the morbidity and mortality in this condition.

Several surgical techniques have been described for repair of ALCAPA, including ligation of the anomalous artery [2], bypass grafting [3], intrapulmonary artery baffle or Takeuchi repair [4], and coronary reimplantation to the aorta [5]. However, the decision to repair the mitral valve (MV) at the time of operation is controversial. After revascularization of the anterolateral wall of the left ventricle, the MV may regain reasonable function, despite severe preoperative MR.

Good early surgical outcomes of ALCAPA repair have been described [6–11]. We have previously reported on midterm outcomes of ALCAPA repair in a smaller group of patients [6]. There are few single-institution studies on the long-term outcomes of patients with ALCAPA, including outcomes related to the MV. Therefore we sought to review the surgical management of ALCAPA repair at our institution and to evaluate the associated MV disease, its management, and long-term outcomes.

Patients and Methods

Patients

The Human Research Ethics Committee at the Royal Children's Hospital approved the study. Between 1980 and 2014, 42 children underwent repair of ALCAPA

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Abbreviations and Acronyms

ALCAPA = anomalous left coronary artery from the pulmonary artery
ASD = atrial septal defect
CoA = coarctation of the aorta
CPB = cardiopulmonary bypass
LA = left atrial
LCA = left coronary artery
LV = left ventricular
LVAD = left ventricular assist device
LVEDD = left ventricular end-diastolic diameter
MPA = main pulmonary artery
MR = mitral regurgitation
MV = mitral valve
PA = pulmonary artery
PDA = patent ductus arteriosus

at the Royal Children's Hospital. Data were obtained retrospectively by review of medical records from initial admission until last cardiology follow-up.

Definitions

Early mortality was defined as death occurring within 30 days of operation or before hospital discharge. All other deaths were considered late. Severity of MR was graded using conventional guidelines [12].

Data Analysis

Data were analyzed using Stata, version 12 (StataCorp LP, College Station, TX). Descriptive statistics for continuous data are expressed as mean ± standard deviations (range), whereas skewed continuous data are expressed as median (range). Categorical data are summarized as frequencies and percentages. Kaplan-Meier actuarial survival curves were used to analyze and plot time-related end points. Statistical significance was set at $p < 0.05$.

Results

From February 1980 to March 2014, 42 children underwent repair of ALCAPA at the Royal Children's Hospital. Preoperative patient characteristics are summarized in Table 1. Median age at operation was 140 days (mean, 276 days; range, 49 days–5 years). There were 34 (81% [34 of 42]) patients less than 1 year of age. Median weight at operation was 5.7 kg (mean, 6.7 kg; range, 2.3 –23 kg).

Repair of ALCAPA was done by reimplantation of the anomalous artery in 29 (69% [29 of 42]) patients, an intrapulmonary baffle (Takeuchi repair) in 12 (29% [12 of 42]) patients (Fig 1), and ligation of an anomalous left circumflex artery arising from the pulmonary artery in 1 (2% [1 of 42]) patient.

Nine (21%, 9 of 42) patients had concomitant MV repair at the time of the initial operation. The median age of patients who underwent concomitant MV repair was 147 days (range, 74 days–1.8 years) compared with 141 days (range, 78 days–5 years) in those who did not undergo such repair. There was no significant difference in age between those who had concomitant MV repair and those who did not ($p = 0.87$). Mean cardiopulmonary bypass (CPB) time in patients who had concomitant MV repair was 184 ± 50 minutes compared with 137 ± 79 minutes in patients who did not have concomitant MV repairs ($p = 0.09$). Mean aortic cross-clamp time in patients who had concomitant MV repair was 112 ± 22 minutes compared with 70 ± 39 minutes in patients who did not have concomitant MV repair ($p = 0.006$). Of the concomitant MV repairs, 8 (89% [8 of 9]) were undertaken in patients who had reimplantation of the anomalous artery, and 1 (11% [1 of 9]) was undertaken in a patient who had a Takeuchi repair.

Additional concomitant repair occurred in 1 patient (2% [1 of 42]). This patient presented with incipient LV rupture through a transmural anterior infarction, which was resected and reconstructed [13]. At the completion of the operation, 15 patients (36% [15 of 42]) required a LV assist device (LVAD). This was a centrifugal pump with left atrial (LA) and aortic cannulation through a midline sternotomy and an open chest. Twelve of the 15 patients who required an LVAD were noted to have a significant rise in LA pressure and a reduction in mean arterial pressure after being weaned from CPB, which prompted the use of an LVAD. The remaining 3 patients received LVADs electively. There was no relationship between the use of LVADs and the time of aortic cross-clamping (LVAD, 95 ± 40 minutes versus no LVAD, 79 ± 45 minutes; $p = 0.35$). The LVAD was removed at a mean of 4 ± 2 days (range, 2–8 days) after the operation. One patient was placed on extracorporeal membrane

Table 1. Preoperative Patient Characteristics (n = 42)

Age at repair, mean, median (range)	276 d, 140 d (49 d–5 y)
Weight at repair, mean, median (range)	6.7 kg, 5.8 kg (2.3–23 kg)
Echocardiographic findings	
Ejection fraction	30.0% ± 15.4%
Fractional shortening	17.0% ± 10.0%
LVEDD	4.0 ± 0.6 cm
Overall LV function	
Normal	7% (3 of 42)
Reduced	31% (13 of 42)
Poor	36% (15 of 42)
Mitral valve regurgitation	
Mild	33% (14 of 42)
Moderate	40% (17 of 42)
Severe	26% (11 of 42)
Concomitant anomalies	7% (3 of 42)
ASD	2% (1 of 42)
CoA	2% (1 of 42)
PDA	2% (1 of 42)

ASD = atrial septal defect; CoA = coarctation of the aorta; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; PDA = patent ductus arteriosus.

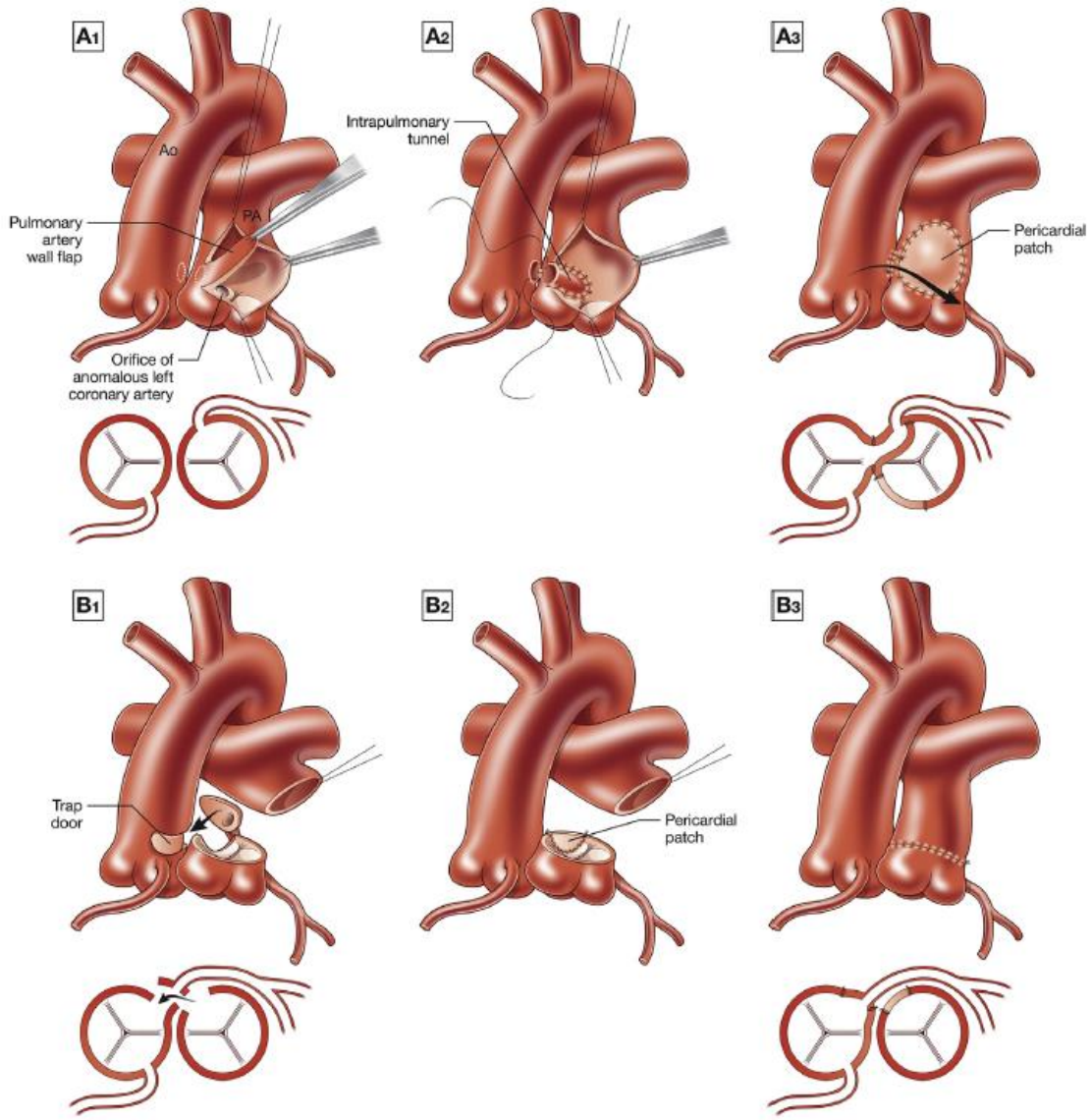

Fig 1. Repair of anomalous left coronary artery from pulmonary artery (PA). (A1–A3) Takeuchi repair. (A1) Opening of main pulmonary artery (MPA) with creation of flap of anterior PA wall. (A2) Creation of aortopulmonary window and baffling of anomalous coronary artery with flap of anterior PA wall. (A3) Pericardial patch reconstruction of MPA. (B1–B3) Reimplantation of anomalous coronary artery. (B1) Transection of MPA, removal of anomalous coronary ostium, and creation of trapdoor on aorta. (B2) Attachment of anomalous coronary artery to aorta and reconstruction of MPA defect with pericardial patch. (B3) Reanastomosis of MPA.

oxygenation 1 day after ALCAPA repair because of cardiac arrest and respiratory failure. She remained on extracorporeal membrane oxygenation for 1 day. She remains well at 8-year follow-up.

Mortality

Early mortality was 2.4% (1 of 42 patients). In 2008, an 11-month-old girl weighing 6.5 kg presented with congestive cardiac failure and was found to have ALCAPA with mild MR and severe LV dysfunction. She underwent repair of ALCAPA through reimplantation. LV function remained poor when she was weaned from CPB and she received an LVAD. Four days postoperatively she had a cerebral infarction secondary to thromboembolism in the LVAD pump and died.

There were no late deaths. Overall survival was 98% ± 2% (95% confidence interval [CI], 86–100) at 5, 10, and 20 years.

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Management of the Mitral Valve

Preoperatively, 13 (31% [13 of 42]) patients had mild MR, 18 (43% [18 of 42]) patients had moderate MR, and 11 (26% [11 of 42]) patients had severe MR. MV outcomes are shown in Figures 2A and 2B.

Concomitant MV repair was undertaken in 9 (21% [9 of 42]) patients—5 with severe MR and 4 with moderate MR. Six patients underwent suture annuloplasty, 2 patients underwent plication of part of the mitral valve, and 1 patient underwent ring annuloplasty. Two of these patients required additional MV repair at 70 days and 4.1 years, respectively. One patient has undergone 2 redo MV repairs because of persisting MR. Freedom from MV reoperation for those patients who underwent concomitant MV repair was 71% ± 18% (95% CI, 23–92) at 10 years (Fig 3).

An additional 6 patients, who did not have concomitant MV repair, underwent 7 late MV operations at a median of 3 years (range, 11 months–25 years) after initial ALCAPA repair because of persisting severe MR (n = 3) or MR worsening to a severe degree (n = 3) after ALCAPA repair. This consisted of MV repair in 4 patients and MV replacement in 2 patients. One patient has undergone 2 MV replacements at 1.5 years and 22 years after initial ALCAPA repair. Freedom from late MV repair or replacement in patients who did not undergo concomitant MV repair was 86% ± 6% (95% CI, 71–94) at 5 and 10 years and 81% ± 8% (95% CI, 67–91) at 20 years. Of the additional 6 patients who underwent late MV operation, the initial repair was reimplantation of the anomalous artery in 3 (50% [3 of 6]) patients, Takeuchi repair in 2 (33% [2 of 6]) patients, and ligation of the anomalous artery in 1 (17% [1 of 6]) patient.

Of the 11 patients with severe MR, 5 (45% [5 of 11]) underwent MV repair at the time of ALCAPA repair. In addition 2 (18% [2 of 11]) underwent late MV repair, and 1 (9% [1 of 11]) underwent late MV replacement. The remaining 3 (27% [3 of 11]) patients had mild MR at last follow-up. All patients with preoperative severe MR had normal LV function and either no MR (n = 2) or mild MR (n = 9) at last follow-up.

At most recent follow-up, 16 patients were free of MR and 24 patients had mild MR (Figs 2A, 2B).

Reoperation

Ten patients underwent a total of 11 reoperations at a mean of 9 years (range, 2 months–25 years) after operation. Freedom from *any* reoperation was 88% ± 7% (95% CI, 74–96) at 5 and 10 years and 76% ± 8% (95% CI, 60–88) at 20 years after operation. Reoperations included MV repair (n = 6), MV replacement (n = 2), and pericardial patch augmentation of the main PA because of stenosis (n = 1) in a patient who underwent a Takeuchi procedure.

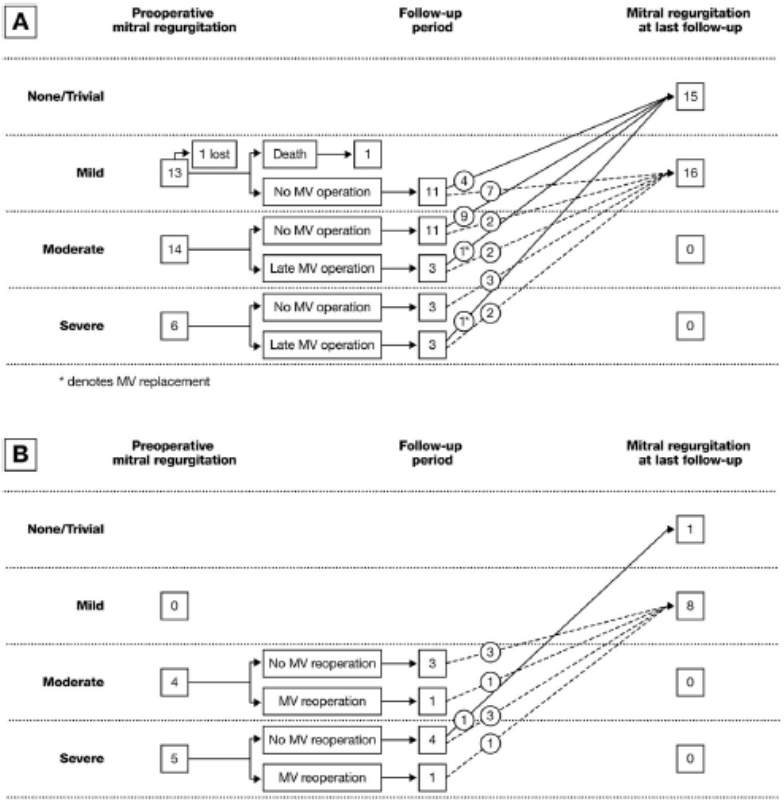

Fig 2. Outcomes of mitral valve (MV) (A) without and (B) with concomitant MV repair at anomalous left coronary artery from the pulmonary artery (ALCAPA) repair.

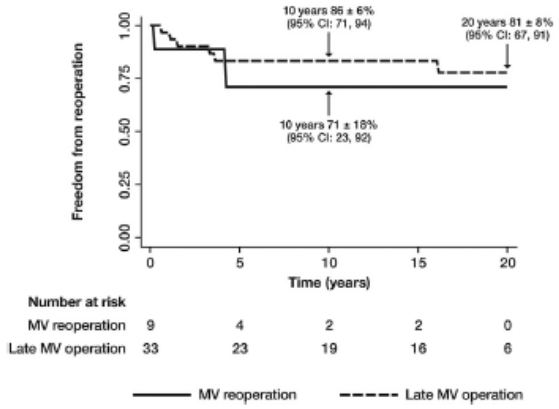

Fig 3. Freedom from mitral valve (MV) reoperation and late mitral valve operation. Freedom from MV reoperation in patients who underwent concomitant MV repair versus late MV operation in patients who did not undergo concomitant MV repair.

LV Function

Serial postoperative echocardiograms were available in 32 patients. In these patients, LV function—based on ejection fraction or qualitative assessment—normalized at a median time of 9.5 months (2.3–15.8 months). Echocardiographic reports were available for all 40 patients at last follow-up; LV function was qualitatively assessed as mildly reduced in a total of 4 patients (10% [4 of 40]), whereas all the remaining patients had normal LV function.

Patency of the Coronary Artery

Because all patients were asymptomatic, no routine coronary angiography was performed. All patients who had a Takeuchi repair (n = 12) were asymptomatic at a mean follow-up of 22 years. Two patients underwent coronary angiography at 10 and 23 years after operation, which demonstrated normal coronary arteries. Both of these patients had normal LV function, mild MR, and a negative stress test and were asymptomatic at the time of coronary angiography. Although 2 of these 12 patients required late MV repair (n = 1) or replacement (n = 1), they did not have any evidence of ischemia. After coronary reimplantation (n = 28), all patients were asymptomatic at a mean follow-up of 9 years. All 28 survivors are currently asymptomatic. One asymptomatic patient had coronary angiography at 1 year after operation, which demonstrated normal coronary arteries. Three patients had stress tests at 8, 9, and 15 years after operation, respectively, which were normal. Although 5 patients had late MV repair (n = 4) or replacement (n = 1), they did not have any evidence of ischemia. All 5 patients underwent echocardiography and electrocardiography before repair. All 5 patients had normal LV function and no regional wall motion abnormalities. None had any ischemic changes on electrocardiography. All patients had patency of the proximal LCA confirmed by echocardiography at the most recent follow-up.

Follow-Up

Follow-up was 100% complete for local patients. One international patient was lost to follow-up after returning overseas after the operation. Median follow-up was 14 years (mean, 13 years; range, 4 months–31 years). Thirty seven patients (93% [37 of 40]) were followed up within the past 5 years. Although 7% (3 of 40) did not have follow-up in the past 5 years, these patients had 7, 10, and 19 years of follow-up, respectively. Twenty-seven patients (68% [27 of 40]) had at least 10 years of follow-up, and 34 patients (85% [34 of 40]) had at least 5 years of follow-up.

Comment

This study demonstrates that surgical repair of ALCAPA can be achieved with good results. Earlier repairs at our institution were through an intrapulmonary baffle described by Takeuchi and associates [4], which was shown to produce no mortality. Despite the low mortality, some patients may experience supravalvular pulmonary stenosis, baffle obstruction, baffle leaks, and aortic regurgitation afterward [14–16]. One patient in this study who underwent a Takeuchi repair required reoperation 7.5 years later because of stenosis of the main PA. After a mean follow-up of 22 years in patients who underwent Takeuchi repairs, we have not encountered any baffle obstructions. All patients since 1995 have undergone reimplantation of the anomalous coronary artery to the aorta at our institution. After a mean follow-up of 9 years in patients who underwent reimplantation, we have not encountered stenosis of the implanted coronary artery.

Early mortality in patients with ALCAPA has been reported to be from 0% to 16% [6, 8–11, 14, 17–21]. Late mortality is rare and survival of 86% to 100% at 10 years has been reported [8, 9, 17, 19]. Mortality from previous studies is summarized in Table 2. An earlier report from our center demonstrated no early or late deaths [6]. We had only 1 early death in our cohort of 43 patients with a median age of 140 days with no late deaths and an overall survival of 98% at 20 years. Edwin and associates [22] reported 27 patients who underwent ALCAPA repair between 1994 and 2011, with a hospital mortality of 3.7% (1 of 27). Seven patients required an LVAD. They determined that a fractional shortening of less than 20% and a cross-clamp time of greater than 56 minutes predicted more than 80% LVAD use. They suggested that in patients with severe LV dysfunction preoperatively, high mortality may result without the use of an LVAD. In our experience, most patients (12 of 15) needed an LVAD because of difficulty weaning from CPB, with a subsequent rise in LA pressure and reduction in mean arterial pressure. In 3 patients, LVADs were used electively. Traditionally, our center has had a low threshold for the use of an LVAD after ALCAPA repair.

Whether to repair the MV at initial repair remains a contentious issue. Several studies reported that concomitant MV repair increases aortic cross-clamp time on an already ischemic myocardium. Although aortic cross-clamp time was significantly higher in patients who

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Long-term outcomes of complete vascular ring division in children: a 36-year experience from a single institution

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Abstract

OBJECTIVES: Complete vascular rings are rare and cause tracheoesophageal compression. Following surgical division, some patients have persisting tracheomalacia. We aim to assess the long-term outcomes of complete vascular ring division.

METHODS: All patients ($n = 132$) who underwent surgical division of a complete vascular ring between 1978 and 2014 were identified from the hospital database and retrospectively reviewed.

RESULTS: Complete vascular rings consisted of a double aortic arch ($n = 80$), right aortic arch with an aberrant subclavian artery and left ligamentum arteriosum ($n = 50$), right aortic arch with mirror image branching and left ligamentum arteriosum ($n = 1$), and a left aortic arch with right descending aorta and right ligamentum arteriosum ($n = 1$). Kommerell's diverticulum was identified in 10 patients. Preoperative tracheomalacia was identified via bronchoscopy in 25 patients. Concomitant tracheal reconstruction was not performed in any patient. Kommerell's diverticulum was resected in 1 patient. The hospital mortality rate was 1.5% (2/132). There were no late deaths. The overall survival rate was 98.3 ± 1.2% (95% CI: 93.4, 99.6) at 20 years. Postoperatively, persistent tracheal compression was reported in 3 patients, and tracheomalacia in 16 patients. The rate of freedom from reoperation was 88.6 ± 4.0% (95% CI: 77.9, 94.3) at 20 years. No patient required tracheal surgery during the follow-up period. Follow-up was 92% (121/132) complete, with a median follow-up of 11.4 years (range 44 days to 36 years). At the last follow-up, 7 patients had mild tracheomalacia.

CONCLUSIONS: Outcomes of division of a complete vascular ring are excellent. Tracheomalacia often improves following division of the vascular ring. Respiratory symptoms following complete vascular ring division are uncommon.

Keywords: Complete vascular ring • Surgery • Congenital heart disease

INTRODUCTION

A complete vascular ring is a rare congenital cardiovascular anomaly which encircles the trachea and oesophagus, compressing them. The two most common types of complete vascular rings are a double aortic arch, and a right aortic arch with aberrant left subclavian artery (SCA) and left ligamentum arteriosum, which together account for 85–95% of cases [1]. Due to compression of the trachea, there may be ongoing morbidity related to persisting tracheomalacia. We therefore aimed to assess the long-term outcomes of children who underwent division of complete vascular rings.

MATERIALS AND METHODS

Definitions

Early mortality, complication and reoperation were defined as those occurring within 30 days of surgery or prior to hospital discharge. All other deaths, complications and reoperations were considered late. Complete vascular rings are of three types: (i) double aortic arch, (ii) right aortic arch with left ligamentum arteriosum with or without aberrant left SCA and (iii) left aortic arch with right ligamentum arteriosum with or without aberrant right SCA. Tracheomalacia is defined as weakness of the trachea resulting in an airway that is more susceptible to collapse [2]. Severity of tracheomalacia is subjective, but has been described as mild if the obstruction during expiration is to one half of the lumen, moderate if it reaches three quarters of the lumen and severe if the posterior wall touches the anterior wall [3].

Patients

The institutional Human Research Ethics Committee at the Royal Children's Hospital (RCH) approved the present study. Between 1978 and 2014, 132 patients underwent complete vascular ring

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division at RCH. Vascular rings consisted of a double aortic arch ($n = 80$); right aortic arch with aberrant left SCA and left ligamentum arteriosum ($n = 50$); right aortic arch with mirror image branching and left ligamentum arteriosum ($n = 1$); and left aortic arch with right-sided descending aorta and right ligamentum arteriosum ($n = 1$). Kommerell's diverticulum was identified in 10 patients. Data were obtained by review of medical records from initial admission until the last follow-up. This included inpatient notes, surgical reports and outpatient letters.

Data analysis

Data was analysed using Stata version 12 (StataCorp LP, College Station, TX, USA). Descriptive statistics for continuous data are expressed as means ± standard deviations (range), whilst skewed continuous data are expressed as medians (interquartile range). Categorical data are summarized as frequencies and percentages. Risk factors for binary outcomes were determined by univariable and multivariable logistic regression analysis. Linear regression analysis was used for continuous variables where appropriate. Kaplan-Meier actuarial survival curves were used to analyse and plot time-related endpoints. Statistical significance was set at $P < 0.05$.

Table 1: Patient characteristics

Variable	Total ($n = 132$)
Median age at repair	1 year (range 5 days to 15.7 years)
Median weight at repair	8.7 kg (range 0.9–76 kg)
Type of complete vascular ring	
DAA	60.6% (80/132)
RAA and left ligamentum arteriosum	37.8% (50/132)
Kommerell's diverticulum	20% (10/50)
RAA with mirror-image branching, and left ligamentum arteriosum	0.8% (1/132)
LAA with right-sided descending aorta, and right ligamentum arteriosum	0.8% (1/132)
Concomitant cardiovascular anomalies	
Tetralogy of fallot	6.8% (9/132)
Atrial septal defect	4.5% (6/132)
Patent ductus arteriosus	3.0% (4/132)
Ventricular septal defect	3.0% (4/132)
Double-outlet right ventricle	1.5% (2/132)
Hypertrophic obstructive cardiomyopathy	1.5% (2/132)
Single coronary artery (right coronary artery from the left coronary artery)	0.8% (1/132)

DAA: double aortic arch; LAA: left aortic arch; RAA: right aortic arch.

RESULTS

Clinical presentation and diagnosis

Patient characteristics are outlined in Table 1. In this study, 123 patients underwent repair at less than 5 years of age, including 66 patients who were younger than 1 year. Only 5 patients who underwent repair were 10 years of age or older. Concomitant cardiovascular anomalies were present in 17.4% (23/132) of patients. All patients were symptomatic at presentation. Most patients (95%, 125/132) presented with respiratory symptoms due to compression of the trachea. Respiratory symptoms were stridor in 77.3% (102/132) of patients; cough in 35.6% (47/132) of patients; or recurrent respiratory tract infections in 19.7% (26/132) of patients. Dysphagia was an uncommon presentation, present in only 15.9% (21/132) of patients.

The trend of imaging modalities is depicted in Fig. 1. An echocardiogram was obtained in all patients. Early in the study period, the diagnosis was often made by a combination of echocardiography, cardiac catheterization and barium swallow test. Since the 1990s magnetic resonance imaging (MRI) and computed tomography (CT) became readily available, with CT being the preferred imaging modality as the anatomy can often be clearly delineated (Fig. 1). Thirty-eight patients underwent bronchoscopy prior to surgical intervention.

Operative management

Patients with a double aortic arch underwent repair at a younger age than those with a right aortic arch and left ligamentum (1.3 ± 1.6 years vs 2.6 ± 3.6 years, $P = 0.004$). Surgery was performed via a left thoracotomy ($n = 114$), median sternotomy ($n = 15$) or right thoracotomy ($n = 3$). The operative technique is outlined in Fig. 2. Concomitant repair of other cardiovascular

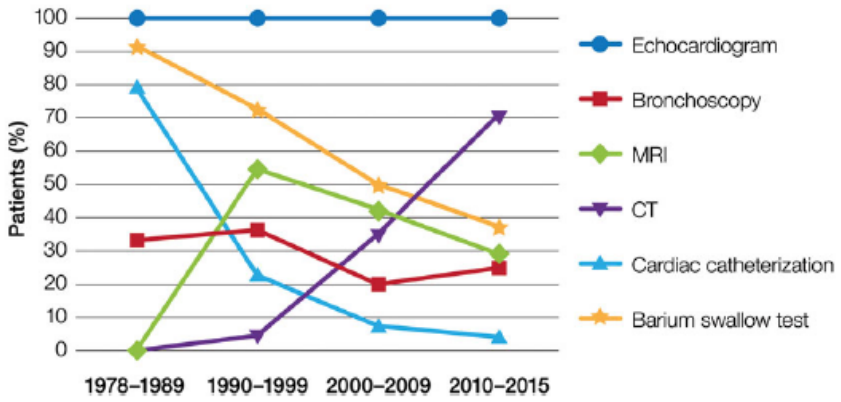

Figure 1: Frequency of imaging modalities over the 4 decades.

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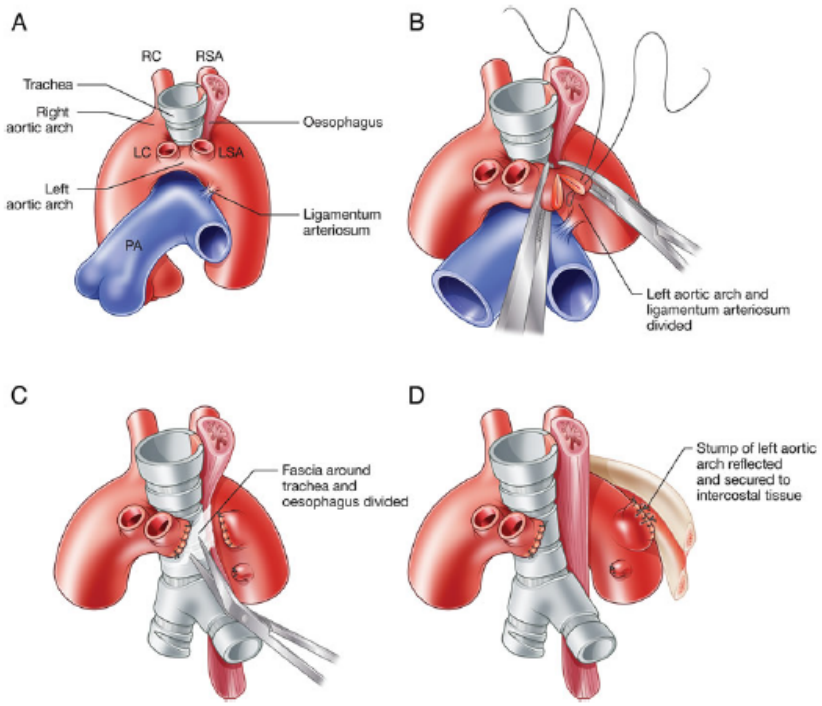

Figure 2: Double aortic arch repair. Double aortic arch (**A**). Repair of the double aortic arch is undertaken through division of the smaller arch and division of the ligamentum arteriosum (**B** and **C**). The distal remnant of the divided arch or diverticulum of Kommerell is oversutured. The oversutured stump or the base of the left subclavian artery is sutured to the chest wall (**D**).

anomalies was undertaken in 16 patients, in 14 of them with cardiopulmonary bypass.

In patients with a double aortic arch, the smaller of the two arches was divided—this was the left arch in 64 patients (80%, 64/80), and the right arch in 16 patients (20%, 16/80). Some patients had equal-sized aortic arches and the division of the arch was at the surgeon's discretion. Eight patients underwent arteriopexy following division of the arch. Following division, the innominate artery was suspended from the anterior chest wall in seven patients and the left SCA was suspended to the chest wall in one patient.

In patients with a right aortic arch and left ligamentum arteriosum, the ligamentum was divided, which relieved tracheoesophageal compression. Twenty patients underwent arteriopexy in which a suture was placed through the divided ligamentum arteriosum or adventitia of the divided arch and suspended from the vertebral column or chest wall (Fig. 2D). The aortic end of the divided ligamentum arteriosum was sutured to the vertebral column in 4 patients; the descending aorta was suspended from the chest wall in 4 patients; and the left SCA was suspended from the posterior chest wall in 12 patients, including 8 patients with Kommerell's diverticulum. Of the 10 patients with Kommerell's diverticulum, only 1 patient—the oldest patient in this series (15.7 years)—underwent resection of the diverticulum, and reimplantation of the left SCA onto the descending aorta with a 10 mm Gore-Tex tube. This patient is currently well after 2 years of follow-up. We have not encountered any recurrent tracheal or oesophageal compression in patients with Kommerell's diverticulum. Once the smaller or rudimentary arch is divided, the remnant of the aortic arch that comes from the distal arch or Kommerell's diverticulum is sutured over. Thus, no diverticulum, either that of Kommerell or of divided aortic arch, persists. Arteriopexy (Fig. 2D) of the oversutured diverticulum or the left SCA, can provide sufficient space in the chest to avoid compression.

One patient with a left aortic arch, right-sided descending aorta and right ligamentum arteriosum underwent repair via a right thoracotomy with division of the ligamentum and suspension of the descending aorta to the posterior chest wall. One patient with the right aortic arch with mirror image branching and left ligamentum arteriosum underwent repair via a left thoracotomy with division of the left ligamentum and suspension of the descending aorta to the posterior chest wall.

Mortality and morbidity

Postoperative complications are summarized in Table 2. The hospital mortality rate was 1.5% (2/132). Two patients with Noonan's syndrome died in 1987 and 2009 of progressive hypertrophic cardiomyopathy. Of these two early deaths, one patient had a double aortic arch, while the other patient had a right aortic arch and left ligamentum. There were no late deaths. The overall survival rate was 98.3 ± 1.2% (95% CI: 93.4, 99.6) at 20 years. There were no identifiable risk factors for mortality on multivariable analysis.

Management of tracheomalacia

Tracheomalacia was identified in 25 patients preoperatively via bronchoscopy. There was no concomitant tracheal reconstruction during complete vascular ring division in any patient. Postoperatively, tracheomalacia was identified via bronchoscopy in

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Table 2: Frequency of postoperative morbidity

	DAA ($n = 80$)	RAA and left ligamentum ($n = 50$)	Other vascular rings ($n = 2$)	Total ($n = 132$)
Persistent tracheomalacia	12.5% (10/80)	10% (5/50)	50% (1/2)	12.1% (16/132)
Respiratory infection	7.5% (6/80)	6% (3/50)	0%	6.8% (9/132)
Chylothorax	3.8% (3/80)	8% (4/50)	0%	5.3% (7/132)
Recurrent laryngeal nerve palsy	6.3% (5/80)	2% (1/50)	0%	4.5% (6/132)
Horner's syndrome	2.5% (2/80)	2% (1/50)	0%	2.3% (3/132)
Persistent tracheal compression	2.5% (2/80)	2% (1/50)	0%	2.3% (3/132)
Pneumothorax	2.5% (2/80)	0%	0%	1.5% (2/132)
Pleural effusion	1.3% (1/80)	0%	0%	0.8% (1/132)

DAA: double aortic arch; RAA: right aortic arch.

16 patients, which included 10 patients who had preoperative tracheomalacia, and 6 patients with newly identified tracheomalacia after surgery. A single patient was unable to be extubated due to severe tracheomalacia and underwent a tracheostomy for long-term continuous positive airway pressure which was removed 14 months later. The patient is currently well with only mild tracheomalacia after 4 years of follow-up.

A total of seven patients had persisting tracheomalacia at the last follow-up. Of patients with preoperative tracheomalacia, 5 patients had ongoing tracheomalacia at the last follow-up, while 2 patients had intermittent wheeze, and 18 patients were asymptomatic. Two patients with newly identified postoperative tracheomalacia had persisting tracheomalacia at the last follow-up. There were no tracheal reconstructions during the follow-up period.

Following division of complete vascular rings, persistent tracheal compression from external (extra-tracheal) vascular structures occurred in two patients, while one patient had a discrete, short-segment tracheal stenosis. The first patient who underwent double aortic arch division had ongoing compression from residual ductal tissue which was subsequently resected. The second patient with a right aortic arch and left ligamentum had ongoing compression from the aortic arch. The left SCA was suspended to the posterior chest wall. This patient did not have Kommerell's diverticulum. The third patient had a short-segment tracheal stenosis identified on bronchogram and the patient was asymptomatic, therefore no clinical intervention was undertaken. These three patients did not have evidence of tracheomalacia, and are currently asymptomatic at 1, 36 and 13 years of follow-up, respectively.

Reoperation

Nine patients underwent reoperations. Three patients required reoperation due to their vascular ring. Two patients required reoperation after identification of ongoing tracheal compression as described above. One patient was unable to be extubated and required a tracheostomy. The rate of freedom from reoperation due to the vascular ring was 96.9 ± 1.8% (95% CI: 90.1, 99.0). All other reoperations were due to concomitant cardiovascular anomalies, namely a ventricular septal defect repair ($n = 3$), right ventricular outflow tract resection ($n = 2$), branch pulmonary artery reconstruction ($n = 1$), Blalock–Taussig shunt division ($n = 1$), right ventricle to pulmonary artery conduit insertion ($n = 1$) and subaortic stenosis resection ($n = 1$). The rate of freedom from any reoperation was 88.6 ± 4.0 (95% CI: 77.9, 94.3) at 20 years.

Long-term outcomes

Follow-up was 92% (121/132) complete. The median follow-up time was 11.4 years (mean 11.2 years, range 44 days to 36 years). There was no persistent tracheal compression in children with Kommerell's diverticulum. At the last follow-up, 17 patients had mild respiratory symptoms, attributed to mild asthma in 10 patients and mild tracheomalacia in 7 patients.

DISCUSSION

Division of a double aortic arch and other forms of complete vascular rings were described in the mid-1940s by Gross [4, 5]. There have been several retrospective studies [1, 6–13] analysing the outcomes of division of complete vascular rings. However, only a few of them reported a long-term follow-up [6–9]. Surgical division of complete vascular rings is performed safely with excellent results [1, 6–13]. In our study, there were no late deaths and only 2 early deaths due to progressive hypertrophic cardiomyopathy in patients with Noonan's syndrome. This is similar to other centres who reported mortality rates in the range of 0–5% [1, 6–13].

In our experience, tracheomalacia often improves. We have not performed any tracheal reconstruction in patients with complete vascular rings. Of the 38 patients who underwent preoperative bronchoscopy, tracheomalacia was found in 25 patients and was confirmed to have resolved via bronchoscopy in 10 patients, while an additional 10 patients were asymptomatic and thus were not investigated. New mild tracheomalacia was identified in 2 patients at the last follow-up, and both have intermittent stridor with exercise. It is likely that patients with new postoperative tracheomalacia had preoperative tracheomalacia; however, these two patients did not have preoperative bronchoscopy. It is not common practice to perform bronchoscopy preoperatively or postoperatively in patients with complete vascular rings at our institution. We do not believe bronchoscopy is essential in the initial diagnostic workup of these patients as none of our patients have undergone tracheal surgery, and we have found that following division of the vascular ring, respiratory symptoms are often alleviated. Bronchoscopy may be useful in the postoperative period to assess for tracheomalacia in patients with ongoing respiratory symptoms. As most patients are asymptomatic following surgery, they therefore do not require respiratory investigation. Patients with ongoing respiratory symptoms can often be managed conservatively with regular follow-up.

CONGENITAL

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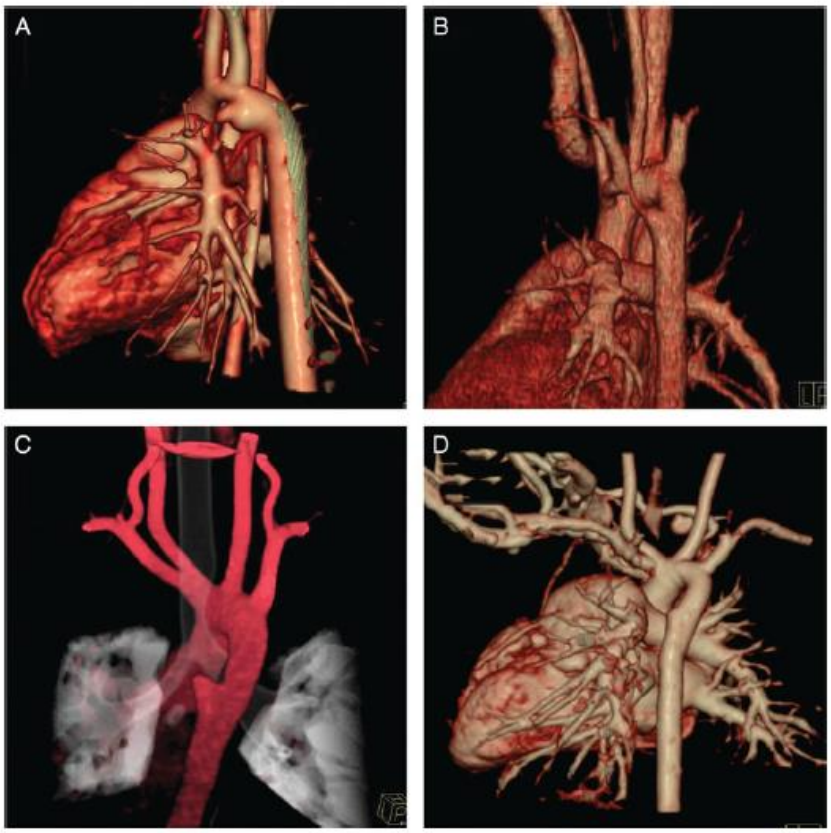

Figure 3: Spectrum of complete vascular ring anomalies on computed tomography. (**A**) Double aortic arch with two patent arches. (**B**) Double aortic arch with severely hypoplastic, yet patent, left aortic arch. (**C**) Double aortic arch with an atretic left aortic arch—this anomaly may be misinterpreted as a right aortic arch with left ligamentum arteriosum. (**D**) Right aortic arch with an aberrant left subclavian artery and left ligamentum arteriosum.

It is uncommon to have consistency in preoperative imaging over a large study period. Although many patients undergo a number of imaging modalities, CT is the imaging modality of choice at the Royal Children's Hospital. The CT scan provides a clear delineation of the aortic arch and adjacent anatomy (Fig. 3), and can be achieved relatively rapidly in 10–15 s, compared to 30–45 min for a sedated MRI [6]. It is important to keep in mind that patients with complete vascular rings have a spectrum of vascular anomalies. In most patients with double aortic arch, both arches are clearly seen with (Fig. 3A) or without (Fig. 3B) site of insertion of the ligamentum arteriosum. Obliterated aortic arch (Fig. 3C) or ligamentum arteriosum (Fig. 3D) may not be seen on CT scan and these patients may be misinterpreted by radiologists as not having a complete vascular ring. In the latter, the diagnosis of a complete vascular ring is made clinically and confirmed intraoperatively. Ligamentum arteriosum on the opposite side of the remaining arch must always be divided. It is prudent for all patients to undergo an echocardiogram to assess for intracardiac anomalies. The use of barium swallow and cardiac catheterization has decreased over time, and are now seldom performed. This trend in imaging is consistent with other studies [6, 9].

Kommerell's diverticulum was first described in 1936 by Burckhard F. Kommerell, who reported a patient with a left aortic arch and aberrant origin of the right SCA from the descending thoracic aorta [14, 15]. It has also been suggested that patients with a Kommerell's diverticulum should undergo primary resection during complete vascular ring division to avoid later compression of the trachea [6, 16, 17]. Backer and colleagues [6, 10] report on 18 patients on whom they have reoperated to resect the Kommerell's diverticulum and reimplanted the left SCA onto the left carotid artery; as well as on 20 patients who underwent resection during primary operation for their vascular ring [16]. They reported that histological evaluation of the resected portion of artery revealed medial necrosis, which places the patient at risk for later aneurysm formation [16], and advocated resection of the diverticulum, stating that this prevented the need for late reoperation in this subgroup of patients due to recurrent tracheal compression.

We do not commonly resect Kommerell's diverticulum. If, intraoperatively, there appears to be ongoing compression of the trachea or oesophagus following division of the ligamentum, arteriopexy of the left SCA or the remnant of the divided arch to the chest wall effectively relieves residual compression. To date, we have not encountered recurrence of symptoms or aneurysmal formation of the diverticulum or the remnant of the divided arch.

Limitations

This study is subject to the usual limitations of a retrospective study. Perioperative techniques have varied during the study

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period. Statistical analysis of risk factors was limited due to a relatively small number of patients and outcomes.

CONCLUSIONS

Long-term outcomes of division of a complete vascular ring are excellent. Tracheomalacia often improves following division of the vascular ring. Respiratory symptoms following complete vascular ring division are uncommon.

Funding

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Conflict of interest: none declared.

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A.4: Brizard CP et al. J Thorac Cardiovasc Surg 2017;154:256-265.

Long-term results of anatomic correction for congenitally corrected transposition of the great arteries: A 19-year experience

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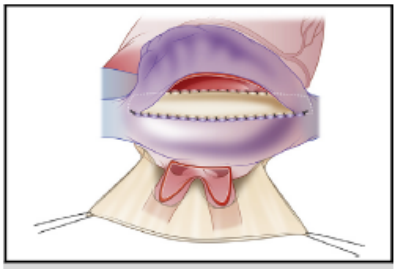
ABSTRACT

Objective: The surgical indication, timing, strategy, and surgical technique for anatomic correction of congenitally corrected transposition of the great arteries are challenging. We evaluated the long-term results at The Royal Children's Hospital Melbourne.

Methods: Review of 32 successive anatomic corrections between 1996 and 2015.

Results: Twenty-one double-switch (66%), 6 Senning/Bex-Nikaidoh (19%), and 5 Senning/Rastelli (16%) procedures were performed (median age, 1.9 years). Median follow-up was 5.4 years with 4 deaths and 1 heart transplant. Cumulative incidence of late reoperation was 8%, 29%, and 59% at 1, 5, and 10 years, respectively. Twenty-six patients had full follow-up with native hearts. Nineteen had normal left ventricle (LV) function. Late LV dysfunction, mostly mild, was not related to needing a pacemaker ($P = .4$) or a pulmonary artery band (PAB) ($P = .08$). Previous PAB was linked to the need for aortic valve surgery or neoaortic regurgitation moderate or greater ($P = .03$). Six required Senning revision. The introduction of the Shumacker modification of the Senning has generated stable pulmonary venous pathways. Six patients developed postoperative iatrogenic atrioventricular block dependent on a permanent pacemaker.

Conclusions: Anatomic correction is a surgical challenge. It provides excellent functional outcomes in survivors with a significant need for reoperation and a definite risk of death or transplantation. Normal LV function should be expected in most patients. LV dysfunction was not linked to PAB or pacemaker requirement but surgery without LV training had better long-term LV function. The Shumacker modification provided stable venous pathways. Iatrogenic atrioventricular block remains a challenge. (J Thorac Cardiovasc Surg 2017;154:256-65)



Senning modification according to Shumacker creating large compliance venous chambers.

Central Message

Anatomic correction for congenitally corrected transposition of the great arteries is a complex surgery. It provides excellent functional outcomes in survivors.

Perspective

Understanding the long-term results of anatomic correction for congenitally corrected transposition of the great arteries allows for improvement in the consideration of timing, strategy, and technical details of the surgery in these patients. This will subsequently improve patient outcomes in our center and others.

See Editorial Commentary page 266.

Symptoms or evidence of declining cardiac function in patients with congenitally corrected transposition of the great arteries (ccTGA) require surgical management to control the evolution of cardiac failure. The results of physiologic correction maintaining a systemic right ventricle (RV) have been poor,[1-3] whereas anatomic correction surgery restores the morphologic left ventricle (LV) and mitral valve (MV) into their systemic role.[4] The literature

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Scanning this QR code will take you to the supplemental tables, figures, and video for this article.

Abbreviations and Acronyms

AR = aortic regurgitation
ccTGA = congenitally corrected transposition of the great arteries
CHB = complete heart block
LV = left ventricle
LVOT = left ventricular outflow tract
MR = mitral regurgitation
MV = mitral valve
neo-AV = neoaortic valve
PAB = pulmonary artery band
PPM = permanent pacemaker
RCH = Royal Children's Hospital
RV = right ventricle
TR = tricuspid regurgitation
TV = tricuspid valve
VSD = ventricular septal defect

surrounding this procedure is expanding. The procedure combines the correction of the atrioventricular discordance using an atrial switch (Senning procedure at The Royal Children's Hospital [RCH]), and simultaneously the correction of ventriculoarterial discordance. Thus, the combined techniques are the Senning-arterial switch or double-switch, Senning-Rastelli procedure, and Senning-Bex/Nikaidoh procedure.

This study aimed to contribute to the body of knowledge and to further refine the surgical indication, timing, and pitfalls of anatomic correction of ccTGA by reviewing our experience during the past 19 years.

METHODS

Study Population

This study was reviewed and approved by the RCH Human Research Ethics Committee (reference No. 34184A). The need for patient consent was waived due to the retrospective nature of the study.

ccTGA was defined as patients with discordant atrioventricular and ventriculoarterial connections. Morphologic diagnoses of patients were established by 2-dimensional echocardiography and confirmed at surgery. The hospital database was screened to identify patients with a diagnosis of ccTGA or synonymous terms. Of 84 children known to RCH with this diagnosis up to August 2015, 32 patients had undergone 1 of 3 anatomic correction procedures from 1996 onward at RCH and were included in this study (Figure E1). Twenty-seven patients with ccTGA had their decisive surgery during the same time span. There were 16 Fontan procedures for unbalanced ventricles, 7 Fontan procedures for unsuitable anatomy for repair, and 4 physiologic repairs.

Follow-up

Preoperative, operative, and follow-up data on the patients were collected from hospital databases and from referring cardiologists between March and November 2015. One international patient was lost to follow-up.

An objective review of incomplete echocardiographic reports was obtained from a cardiologist at RCH. The severity of valvular regurgitation was graded from 0 (none), 1 (trivial), 2 (mild), 3 (moderate), to 4 (severe).[5] Subjective evaluation of LV function was utilized when no objective measure was recorded. For those studies where an objective measure of ejection fraction was available, we used the correlation of normal function for ejection fraction > 51%, mild dysfunction 41% to 50%, moderate dysfunction 31% to 40%, and severe dysfunction ≤ 30%.

Statistical Analysis

All data were exported to and analyzed using IBM SPSS Statistics version 22.0 (IBM-SPSS Inc, Armonk, NY) and R version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported as median and range and/or interquartile range (IQR). Categorical variables were reported as counts and associated percentages. Analyses between categorical variables employed 2-sided Pearson χ^2 tests. Competing risks survival methods were used to describe the cumulative incidence of the event of late reintervention and reoperation with death and heart transplantation as the competing risks. Kaplan-Meier curves were used to describe freedom from death or heart transplantation following anatomic correction. Cox proportional hazards models and likelihood ratio tests were used to assess the association of prior pulmonary artery band with the event of aortic valve surgery or neoaortic valve (neo-AV) regurgitation moderate or greater, and the effect of age at surgery (in years), permanent pacemaker insertion (time-varying covariate), and prior pulmonary artery band (PAB) with the event of reduced LV function at follow-up postanatomic correction. Event rates at 1, 5, and 10 years were reported with corresponding 95% confidence intervals (CIs). No multivariate analysis was performed due to the small numbers of events.

Definitions

Early death, reintervention, or reoperation was defined as occurring before hospital discharge or within 30 days of surgery. Late death, reintervention, or reoperation was defined as occurring after discharge and more than 30 days after surgery.

Permanent pacemaker (PPM) placement is the first instance of PPM placement. PPM revision is a change in pacemaker leads or generator box at any time after initial PPM placement.

RESULTS

Morphologic Data

There were 18 male patients (56%). Characteristics of the patients are detailed in Table 1. Twenty-nine patients (91%) had situs solitus, 2 (6%) patients had situs inversus, and 1 had left isomerism (3%). This latter patient was kept in the series because he underwent an anatomic correction procedure. Coronary anatomy was confirmed as 1LADCX2R in 19 (59%) patients.

A ventricular septal defect (VSD) was present in 25 patients (78%); 13 patients had associated pulmonary or subpulmonary stenosis, and 12 patients had no pulmonary circulation protection. Eight (25%) patients had features of Ebstein's anomaly of the tricuspid valve (TV).

Nine patients (28%) had a conduction anomaly before corrective surgery. One had acquired complete heart block (CHB) following a palliative procedure performed outside the RCH (LV outflow tract [LVOT] resection), 3 had complete heart block, 4 had second-degree heart block, and 1 had first-degree heart block.

Preoperatively, 31 (97%) patients had normal LV function and 27 (84%) had normal RV function. Seven (22%) patients had moderate or greater tricuspid regurgitation (TR). No

TABLE 1. Patient characteristics stratified by type of anatomic correction

Characteristic	Double switch (n = 21) (%)	Senning-Rastelli (n = 5) (%)	Senning-Bex/Nikaidoh (n = 6) (%)
Demographic			
Sex			
Male	11 (52)	2 (40)	5 (83)
Female	10 (48)	3 (60)	1 (17)
Congenital cardiac anomalies			
VSD	14 (67)	5 (100)	6 (100)
IVS	7 (33)	0 (0)	0 (0)
PS	3 (14)	1 (20)	6 (100)
Pulmonary atresia	0 (0)	4 (80)	0 (0)
Ebsteinoid features of TV	8 (38)	0 (0)	0 (0)
Congenital heart block	8 (38)	0 (0)	0 (0)
CoA	2 (10)	0 (0)	0 (0)
Hypoplastic aortic arch	1 (5)	0 (0)	0 (0)
Situs			
Solitus	21 (100)	4 (80)	4 (67)
Inversus	0 (0)	1 (20)	1 (17)
Isomerism	0 (0)	0 (0)	1 (17)

Values are presented as n (%). *VSD*, Ventricular septal defect; *IVS*, intact ventricular septum; *PS*, pulmonary stenosis; *TV*, tricuspid valve; *CoA*, coarctation of the aorta.

patients had greater than mild aortic regurgitation (AR), mitral regurgitation (MR), or pulmonary regurgitation.

Twelve patients (all double-switch with requirement for LV retraining) underwent a cardiac catheterization procedure before corrective surgery. The preoperative LV/RV pressure was close to 0.7 or above in all patients but 1 patient (0.56). Six patients also underwent preoperative cardiac magnetic resonance imaging. All had an indexed LV mass below the normal lower limit of 63 g/m^2 (mean, 41.67 $\pm$ 11.55 g/m^2).

Procedures Before Anatomic Correction

Twenty (63%) patients underwent surgical procedures before anatomic correction. They are included in Table 2. Median age at first palliation was 0.12 years (range, 0.01-11.12 years).

Twelve patients (38%) (all double-switch) received a PAB. Median age at placement of first PAB was 0.23 years (range, 0.01-11.1 years), and the median time from first PAB placement to anatomic correction surgery was 1.5 years (range, 0.04-4.2 years). The purpose of the band was LV retraining (10 patients) or control of pulmonary blood flow (2 patients). Three patients required PAB tightening at a subsequent procedure.

Pacemakers were placed in 5 (16%) patients before anatomic correction. Four were placed for the patients with CHB (3 congenital and 1 iatrogenic during palliation), and 1 was placed for a patient with symptomatic second-degree heart block.

Anatomic Correction

Primary correction was achieved in 12 patients (38%). Median age at anatomic correction was 1.9 years (range, 0.1-13.5 years; IQR, 0.8-5.1), and median weight was 11.1 kg (range, 3.8-57.7 kg; IQR, 7.4-20.1). Twenty-one patients (66%) underwent the double-switch procedure, 5 patients (16%) underwent Senning-Rastelli procedure, and 6 patients (19%) underwent Senning-Bex/Nikaidoh procedure. Of 21 patients who underwent the double-switch, 14 had a VSD, and 7 had an intact ventricular septum. All 5 patients who underwent the Senning-Rastelli procedure had VSD and pulmonary stenosis; all had an earlier palliation with Blalock-Taussig shunt placement. All 6 Senning-Bex/Nikaidoh patients had a VSD and pulmonary stenosis; 3 were shunted before. Indications for surgery have been stratified by surgery type in Table 2.

Eight patients received a sutureless Senning modification of the Shumacker technique (2 double-switch, 2 Senning-Rastelli, and 3 Senning-Bex/Nikaidoh)[6] (Figure 1 and Video 1). The Lecompte maneuver was used in 16 patients (15 double-switch and 1 Senning-Bex/Nikaidoh). The median cardiopulmonary bypass and aortic crossclamp times were 333 minutes (range, 184-558 minutes; IQR, 280-431) and 210 minutes (range, 113-378 minutes; IQR, 185-283), respectively.

Table E1 details concomitant procedures during the anatomical correction. Twenty-four of 25 patients with VSD (96%) had a VSD closure. Two pacemakers were placed (6%) for preoperative second-degree atrioventricular block. Pulmonary artery repair or reconstruction was performed in 4 (13%) patients. There were 4 instances of intraoperative valve repair (1, 2, and 1 instances of TV, MV, and pulmonary valve repair, respectively). Two Senning-Bex/Nikaidoh patients had straddling MV requiring reimplantation of part or whole of 1 papillary muscle into the LV and 2 Senning-Bex/Nikaidoh patients had double translocation (ie, translocation of the pulmonary root).

TABLE 2. Indication for corrective procedure and previous palliations

Corrective procedure	Previous palliations	Indication	Notes
Double-switch	PAB, PM	Severe TR at early age	–
	–	Severe TR at early age	–
	–	Elective at 2-3 mo (w/o PAB)	–
	PAB (shunt control), PM	Symptomatic	–
	–	Severe TR at early age, LV untrained	LVAD postoperative
	–	Elective at 2-3 mo (w/o PAB)	ECMO postoperative
	–	Elective at 2-3 mo (w/o PAB)	–
	–	Elective, LV 60% systemic	LVAD postoperative
	PAB	LV trained	–
	PAB (shunt control), PDA lig	Elective	–
	PAB, aortic arch repair, PDA lig	LV trained	–
	PAB	LV trained	–
	BT shunt	Elective	–
	PAB, coarctation repair	LV trained	–
	PAB, PM	LV incompletely trained	LVAD postoperative
	–	Elective	–
	PAB, PM	LV trained	–
	–	Severe TR	–
	PAB	LV trained	–
	PAB, PDA lig, LVOT resection, PM	LV trained, poor RV and LV function	–
	PAB	LV trained	LVAD postoperative
Senning-Rastelli	BT shunt, PDA lig, LPA patch	Symptomatic	–
	BT shunt	Elective	–
	BT shunt, PDA lig, LPA patch	Elective	–
	BT shunt	Elective	–
	BT shunt ×2	Symptomatic	–
Senning-Bex/Nikaidoh	BT shunt	Elective	–
	-	Symptomatic	–
	BT shunt	Elective (previous palliations)	–
	–	Symptomatic	–
	–	Symptomatic	–
	–	Elective	–

PAB, Pulmonary artery band; *PM*, pacemaker; *TR*, tricuspid regurgitation; *w/o*, without; *LV*, left ventricle; *LVAD*, left ventricular assist device; *ECMO*, extracorporeal membrane oxygenation; *PDA lig*, patent ductus arteriosus ligation; *BT*, Blalock-Taussig; *LVOT*, left ventricular outflow tract; *RV*, right ventricle; *LPA*, left pulmonary artery.

Two double-switch patients required neo-aortic mechanical valve replacement. One neo-AV had been damaged at the time of initial palliation (LVOT resection). For the other patient, the neoaortic root was extremely distended and a transoesophageal echocardiogram at the end of the operation demonstrated significant AR. The valve was not salvageable and required immediate replacement.

There was no operative mortality. During the early postoperative period, 4 (13%) double-switch patients required a left ventricular assist device. This was indicated for completion of LV training in 3 patients. One patient (3%) required extracorporeal membrane oxygenation for impossibility to wean bypass. The chest was left open in 12 patients (38%). Two patients (6%) had cardiac tamponade, 7 patients (22%) had drainage of pleural effusion, and 4 (13%) had chylothorax managed conservatively. One emergency mediastinal exploration for bleeding was performed.

Median intensive care unit stay was 5.3 days (range, 1.6-36.5 days; IQR, 2-8.8), and median intermittent positive-pressure ventilation time was 79 hours (range, 4-778 hours; IQR, 32.5-176.2). Median hospital stay length was 16 days (range, 5-121 days; IQR, 9-22.5).

Early Reoperation

Ten patients required cardiac-related early reoperation. Seven were pacemaker placements due to development of iatrogenic CHB (5 dual-chamber pacemakers, 1 cardiac resynchronization therapy, and 1 ventricular pacemaker backup not used because the child regained normal sinus rhythm) across 3 double-switch, 2 Senning-Bex/Nikaidoh, and 2 Senning-Rastelli procedures with no differences across the 3 surgery types. There was 1 pacemaker revision and 1 Senning revision. One patient required MV repair, and 1 patient required aortic valve repair secondary to moderate AR.

Late Reinterventions and Reoperations

Ten patients had late reoperations after anatomic correction (Table 3). Eleven PPM revisions occurred across 7 of these patients. If PPM revisions are excluded, overall 7

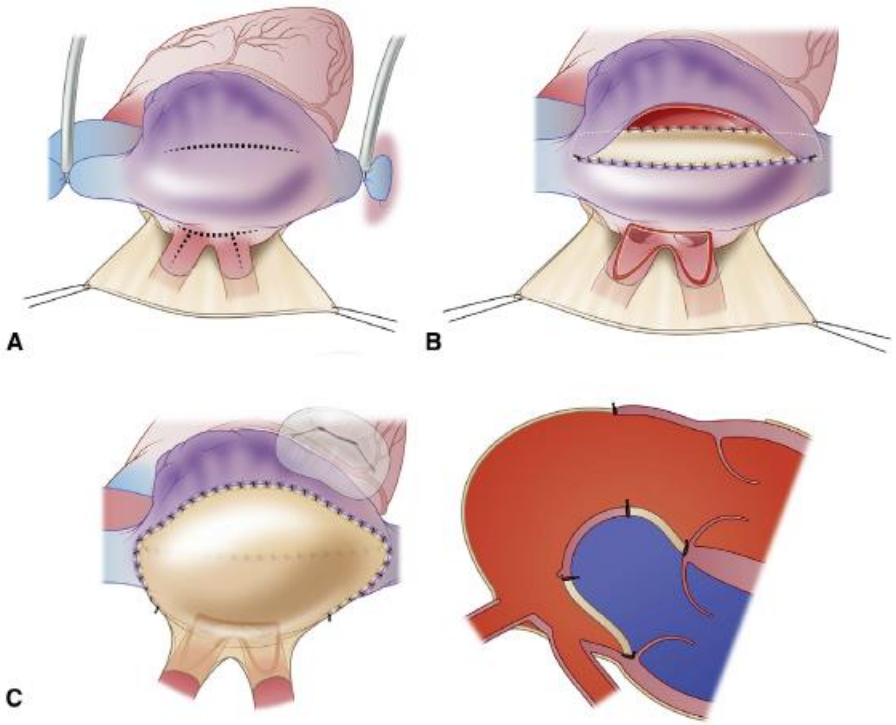
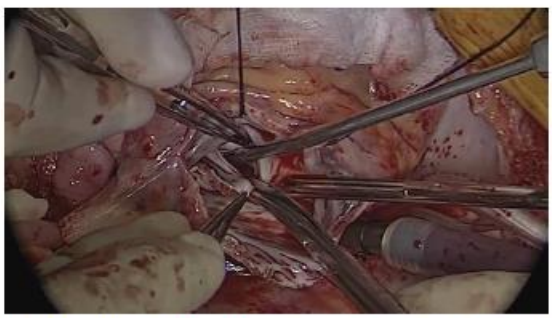


FIGURE 1. Senning modification according to the Shumacker modification (Illustrated by Bill Reid). A, Atrial incisions. Horizontal on the right atrium, at the level of the superior edge of the superior and inferior vena cava. On the left atrium, horizontal immediately below the interatrial groove with minimal dissection of the latter; two perpendicular incisions on the superior aspect of the right pulmonary veins and excision of the edges to create a large orifice, larger than the required mitral valve size for the body surface area. B, Augmentation of the systemic venous channel with a long patch. C, *Left*, Rotation of the rightward aspect of the pericardium creates the inferior aspect of the pulmonary venous channel. The inferior aspect is totally sutureless. *Right*, Schematic horizontal cut demonstrating the enlarged compared with a classic Senning.

of 10 patients required other late reoperations (5 were double-switch patients and 2 underwent Senning-Bex/Nikaidoh procedure). There were 5 Senning revisions, 1 pacemaker for spontaneous development of CHB 9.1 years after anatomic correction, and 1 patient who required a Berlin heart and subsequent heart transplant 7 months after anatomic correction.



VIDEO 1. Modified Shumacker technique for Senning procedure. This video, with voiceover from the primary author, demonstrates the modified Shumacker technique for the Senning procedure utilized during an anatomic correction procedure at The Royal Children's Hospital Melbourne, Australia. Video available at: http://www.jtcvsonline.org/article/S0022-5223(17)30588-3/addons.

Cumulative incidence of late reoperation (excluding PPM revision) was 8% (95% confidence interval [CI], 0%-18%), 29% (95% CI, 8%-49%), and 39% (95% CI, 12%-65%) at 1, 5, and 10 years, respectively (Figure 2).

Further expression of these figures as event-free survival was 82% (95% CI, 69%-98%), 61% (95% CI, 44%-86%), and 51% (95% CI, 31%-84%) at 1, 5, and 10 years, respectively (Figure 2). No late reinterventions or reoperations were associated with the Senning-Rastelli repair.

Follow-up

One international patient had no follow-up. Concurrent follow-up data were complete for 27 surviving patients with 156.3 patient-years for 31 patients and a median of 5.4 years for those surviving (range, 0.1-17.9 years).

There were 4 deaths: 1 early (Senning-Rastelli) and 3 late (3 double-switch). Kaplan-Meier analysis based on these patients yields a risk of death of 15% (95% CI, 0%-27%). The early death occurred in hospital, 33 days

TABLE 3. Late reinterventions or reoperations associated with each patient

Anatomic correction type	Reoperation or reintervention 1	Time since anatomic correction (y)	Reoperation or reintervention 2	Time since anatomic correction (y)	Further reinterventions or reoperations	Time since anatomic correction (y)
DS	Senning revision, PA aneurysm repair, PPM revision	0.4	–	–	–	–
DS	LVAD (Berlin heart)	0.6	Heart transplant	0.6	–	–
DS	PPM revision	0.9	Senning revision	2.1	PPM revision	2.2, 8.5, 13
DS	PPM revision	2.6	–	–	–	–
DS	PPM revision	4.9	PPM revision	9.5	–	–
DS	Senning revision; PPM revision	4.9	–	–	–	–
DS	PPM revision	8.2	–	–	–	–
DS	PPM placement	9.1	–	–	–	–
SBN	Senning revision, PPM revision	1.8	–	–	–	–
SBN	Senning revision	3.4	–	–	–	–

DS, Double switch (Senning + arterial switch operation); *PA*, pulmonary artery; *PPM*, permanent pacemaker; *LVAD*, left ventricular assist device; *SBN*, Senning-Bex/Nikaidoh.

following anatomic correction and was attributed to neurologic complications. The late deaths occurred 61, 103, and 587 days following anatomic correction. The first patient (double-switch with VSD closure, LVOT resection and TV/MV repair) presented with congestive heart failure with severe neoaortic root dilation and AR with functional MR. The condition rapidly progressed to multiple cardiac arrests. The second patient (double-switch with VSD closure and preoperative PAB) developed progressive congestive cardiac failure. At autopsy the deterioration was attributed to obstructed pulmonary venous drainage in an area that was patent at corrective surgery. The third (double-switch with VSD closure, preoperative PAB, and pacemaker for congenital CHB) developed progressive systemic pulmonary hypertension several months after revision of the pulmonary venous baffle of the Senning despite no obstruction recurrence. The patient died of dominant right heart failure.

One double-switch patient with VSD closure had an aortic arch repair and PAB as a premature neonate. The double-switch was technically difficult and required 2 intraoperative revisions and extracorporeal membrane oxygenation to leave the operating room. A PPM was inserted for acquired CHB. Early reoperation was required for baffle dehiscence and MV repair for MR. The child deteriorated over 6 months and was subsequently listed for transplant; long-term LVAD support was required. At last follow-up 1.4 years following orthotopic transplant, the patient was described as active without limitations.

In 26 surviving patients with native hearts, LV and RV function was normal in 19 and 24 patients, respectively. Seven patients had LV dysfunction: mild in 5, moderate in 1, and severe in 1 patient (Table 4). Longitudinal observations for these 7 patients have been demonstrated in Figure E2. The risk of LV dysfunction at follow-up was not linked to receiving a pacemaker at any stage (hazard ratio, 2.1; 95% CI, 0.35-12.4; $P = .4$). Previous PAB for retraining was not related to late LV dysfunction (hazard ratio, 4.4; 95% CI, 0.8-25; $P = .08$).

Freedom from death, heart transplantation, and reduced LV function moderate or greater was 81% (95% CI, 68%-98%), 77% (95% CI, 62%-95%), and 77% (95% CI, 62%-95%) for all patients at 1, 5, and 10 years, respectively (Figure E3, *A*). If separated into groups, these figures translated to 79% (95% CI, 62%-100%), 73% (95% CI, 55%-96%), and 73% (95% CI, 55%-96%) for double switch patients alone at 1, 5, and 10 years, respectively; and 91% (95% CI, 75%-100%) for Senning-Rastelli or Senning/Bex-Nikaidoh patients at 1, 5, and 10 years (Figure E3, *B*).

Two patients (1 double-switch, 1 Senning-Rastelli) had a change from no AR preoperatively to moderate or greater at late follow-up. Longitudinal observations for these 2 patients have been demonstrated in Figure E2, *B*. Previous PAB was correlated with the need for aortic valve surgery or with having neo-AV regurgitation moderate or greater (hazard ratio, 8.5; 95% CI, 0.95-76; $P = .03$). TR improved or remained stable in all but 1 patient. Nine patients had mild MR, and 3 had moderate MR. Two patients had aortic root dilatation, which was moderate in a Senning-Rastelli patient and severe in a double-switch patient.

Senning pulmonary venous baffles were mildly obstructed in 2 patients (1 of these patients had required an early Senning revision), but no patients with the Shumacker Senning modification had obstruction or required revision. No Senning-Rastelli patients had obstructed conduits.

DISCUSSION

Anatomic correction is accepted as a surgical option for the management of patients with ccTGA to treat or prevent the failure of the systemic RV. Outcomes are encouraging but morbidity and mortality are attached to this approach.[7] To further legitimize this approach, we seek to characterize the morbidity and mode of failure after anatomic correction to reduce morbidity and improve results. A work in

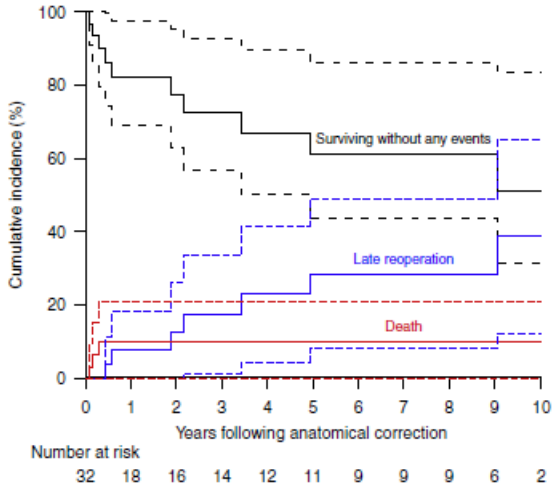


FIGURE 2. Competing risk plot for late reoperation and event-free survival following anatomic correction. The cumulative incidence of late reoperation (excluding PPM revision) was 8% (95% confidence interval [CI], 0%-18%), 29% (95% CI, 8%-49%), and 39% (95% CI, 12%-65%) at 1, 5, and 10 years, respectively. Further expression of these figures as event-free survival was 82% (95% CI, 69%-98%), 61% (95% CI, 44%-86%), and 51% (95% CI, 31%-84%) at 1, 5, and 10 years, respectively. The risk of death was 10% (95% CI, 0%-21%) at 1, 5, and 10 years. The patient with transplantation was included in Figure 2 as part of the late reoperation category. Note that the dotted lines on each figure indicate the 95% CI for each solid line category.

Time	Surviving without any event (*black*)	Late reoperation (*blue*)	Death (*red*)
1 y	82% (69%-98%)	8% (0%-18%)	10% (0%-21%)
5 y	61% (44%-86%)	29% (8%-49%)	10% (0%-21%)
10 y	51% (31%-84%)	39% (12%-65%)	10% (0%-21%)

progress, this complex surgery requires continuous feedback to refine the timing, the surgical strategy, and the technical details.

The long-term survival and functional benefits after anatomic correction have been demonstrated in patients with severe preoperative TR or RV failure.[8] This study confirms the improvement of RV and TV function following anatomic correction for ccTGA. Of the 26 surviving patients with follow-up data available and native hearts in situ, all but 1 have stable or improved TR when compared with their preoperative status at last follow-up, and RV function was normal in most patients.

Freedom from late reintervention and reoperation after anatomic correction has been investigated previously. Hraska and colleagues[9] had the same procedure groups as used in this current series, with event-free survival rates of 95%, 57%, and 57% at 1, 5, and 10 years, respectively.

With regard to atrial repair, reintervention rate for Senning revision was reported as 11% (of 113 patients) in 1 study,[7] but lower in another.[10] In our series, 6 patients required a Senning revision in the early or late postoperative period for pulmonary venous channel obstruction, of which 1 died during the late reoperation period from pulmonary hypertension without reobstruction. The Senning technique we use has evolved over the duration of the series. One goal is to remove the potential for stenosis of the superior vena cava often seen in classical Senning procedures and to increase the size of the atrial compliance chambers.[11] Therefore, we have always used a patch to augment the systemic venous channel and augmented the outer part of the pulmonary venous channel. In this series we successively used patches of treated autologous pericardium, polytetrafluoroethylene 0.6 mm, then autologous pediculated pericardium at that site. The last modification is itself a modification of the Shumacker technique[6] where the pericardium is left in situ and a sutureless technique is used for the junction with the pulmonary veins incision. No patients who received this modification of the Shumacker technique during their Senning-developed stenosis. However, our follow-up time of these patients is short. Our first patient to undergo this modification was in early 2012 and our median follow-up time is only 0.59 years (range, 0.10-3.4 years).

With the double-switch, there is risk for neoaortic root enlargement and AR.[12] Of the patients who received the double-switch procedure, 1 has severe aortic root dilatation at recent follow-up. Another required atrioventricular repair during the early postoperative period for moderate AR. The PAB has also been discussed as a contributor to postoperative AR.[9,10] Tightness of the band,[10] or the proximity to the cusps,[9] could be promoting factors. We found that having a PAB correlated with need for aortic valve surgery or with AR moderate or greater at follow-up. Two patients with severe subpulmonary stenosis should be outlined: the first had ccTGA with VSD and a pulmonary valve suitable for a double-switch after resection of the stenosis. After a simple postoperative course, he developed severe AR within weeks and died in hospital while being listed for semielective aortic valve replacement. The second patient had the same anatomy. He also had a very suitable valve after resection of the stenosis but, at surgery, we found the pulmonary sinuses and the valve so thin and weakened by the protection provided by the stenosis that we elected to do a Bex-Nikaidoh procedure instead, with pulmonary translocation. Retrospectively, we should have used the same approach for the first patient.

With the Bex/Nikaidoh procedure, 6 Senning-Bex/Nikaidoh repairs were performed with no deaths. Two developed iatrogenic CHB. Complete follow-up for this group was available, with a median of 2.1 years (range, 0.1-8.5 years) of follow-up. We found that a straddling MV did not constitute a contraindication for the Senning-Bex/Nikaidoh. Two patients from the Senning-Bex/Nikaidoh group required a late Senning revision using the Shumacker modification. One was required due to stenosis

TABLE 4. Patients with left ventricular (LV) dysfunction at follow-up

Letter reference in Figure E2	Previous procedures	Age at procedure (y) surgery type, and year	LV pressure at correction	Ventricular function at follow-up	Pacing mode and indication	Comments
A	BT shunt ×2	13 y SR 2002	Systemic	SF 32% EF 52%	VVI back-up (not used)	–
B	1 sub-pulmonary resection, DDD pacing 1998 2 PAB training 2002	12 y DS 2006 + aortic valve replacement + PPM upgrade	110%	EF 15%-20%	DDD biventricular iatrogenic	Stable severe LV dysfunction since before surgery
C	1 neonatal PAB (for protection)	1-y DS 1996	Systemic	EF 42%	DDD iatrogenic	Low normal LV function
D	1 PAB 2006 2 PAB tightening 2007	14-y DS 2009 + aortic valve replacement	Systemic	EF 50% SF 26%	None	Ventricular function improved after upgrade of aortic valve to 23 mm
E	1 neonatal VVI pacing 2 PAB training, DDD PPM 2004	4-y DS 2005 + LVAD (2 d)	56%	EF 54%	DDD biventricular congenital	Upgrade to biventricular pacing improved function
F	1 PAB 2013 2 PAB tightening 2013	13-y DS 2015 + DDD	90%	SF 25%	DDD congenital	Ventricular function declined over time
G	–	0.4-y DS 2008 + sub-pulmonary resection + LVAD (3 d) + DDD	60%	EF 50% SF 31%	DDD congenital	Improved function with new leads 2013

LV, Left ventricle; *BT*, Blalock-Taussig; *SR*, Senning-Rastelli; *SF*, shortening fraction; *EF*, ejection fraction; *VVI*, ventricular pacemaker; *DDD*, dual-chamber pacemaker; *PAB*, pulmonary artery band; *DS*, double switch; *PPM*, permanent pacemaker; *LVAD*, left ventricular assist device.

of the pulmonary venous pathway. The other was mild and performed electively in conjunction with a pacemaker replacement. In both, no recurrent narrowing was noted at follow-up. Experience with the Senning-Bex/Nikaidoh procedure is otherwise limited in the previous literature. Hu and colleagues[13] had 4 patients with ccTGA and atrial situs solitus undergo the Senning-Bex/Nikaidoh procedure; there were no deaths, but 1 patient required extracorporeal membrane oxygenation. Hraska and colleagues[9] had 1 patient with ccTGA with atrial situs inversus and an inlet VSD. We find that the added complexity of the Senning-Bex/Nikaidoh over the Senning-Rastelli is justified because the LVOT is perfectly aligned, and any VSD is accessible and easily closed from the RV aspect. Moreover, because the best candidates have mild valvular pulmonary stenosis and a decent pulmonary orifice, a double translocation can be done and should prevent a need for reoperation. The Bex-Nikaidoh operation in ccTGA and situs solitus does not mean an obligatory heart block. We have been extremely careful to excise the pulmonary valve with as little LVOT muscle as possible.

There have also been concerns about deterioration in LV function following anatomic correction for ccTGA.[7,9,12,14] In our series, there were 7 patients with reduced LV function: 5 had mild and stable dysfunction, 1 had moderate dysfunction, and 1 had severe dysfunction at last follow-up. Across these 7 patients, 6 had a double-switch, and 1 had a Senning-Rastelli procedure. The patient with severe dysfunction is the 1 who had subpulmonary resection in another hospital. He underwent LV retraining in our unit despite severe biventricular failure. He had an even pressure ratio before the double-switch but poor function bilaterally. This was considered a palliative procedure to delay transplantation. After 10 years, the patient is not listed for transplantation. For patients with full follow-up and native hearts in situ, we could not demonstrate that PAB for LV retraining or having a pacemaker was related to late LV dysfunction. However, there was often a combination of the 2; that is, patients with LV dysfunction who had a previous PAB and/or have a pacemaker in situ. We could not perform a multivariable analysis because of the small sample size. Review of our data revealed significant differences among patients in the pace of the training, the level of LV pressure reached before correction, and the age at first PAB. Quinn and colleagues[15] observed that early results of the double-switch procedure in patients whose morphologic LV required training compared favorably with those of patients whose morphologic LV required no training. However, an increased risk of deterioration of morphologic LV function over time was observed in patients whose morphologic LV required training. This was found by other authors[7,14] and more specifically in

double-switch patients, as in this present series (although we found that the LV dysfunction was stable over time).

The natural incidence of complete heart block in ccTGA is approximately 1% to 2% per 100 patient-years.[16] The management of pacing is an integral part of management of ccTGA. Summarized details of pacing systems are provided in Table E2. Seven patients had a pacemaker for conduction anomalies before or during the anatomic correction (of the 7, 1 was for iatrogenic CHB from a procedure before anatomic correction, 3 were for congenital CHB, and the remainder for second-degree block). Eight patients required a pacemaker for CHB after anatomic correction: during the early reoperation period, 6 were for iatrogenic CHB and 1 had a ventricular pacemaker backup not used after recovery of normal sinus rhythm, whereas during the late reoperation period, 1 spontaneously developed CHB. Current knowledge of the conduction anatomy does not always prevent such events.[8,9,17] In situs solitus, although there is often suspicion of an anterior node,[18] we have worked with the assumption of a normal posterior node in the presence of septal alignment (due to a small or atretic pulmonary trunk) as advocated by Hosseinpour and Ho.[19] At our institution we have not made a practice of electrophysiology study to delineate the course of the conduction system before surgery. We are concerned that catheter manipulation could damage the vulnerable conduction system and would not necessarily allow atrioventricular block to be avoided at surgery. For all our patients with VSD we have used the technique advocated by De Leval and colleagues,[20] with suturing on the RV side of the septum. As our management strategies have evolved, we have paid more attention to pacing lead position. We now use a biventricular pacing system (cardiac resynchronization therapy) every time a pacemaker is needed. In that configuration, the LV electrode is at the base between the left anterior descending and circumflex arteries, and the RV electrode is at the apex. With simple DDD pacemakers, the location of the ventricular electrode is paramount and should be at the LV apex. In 2 patients, moderately depressed LV function had improved secondarily to near normal (ejection fraction of 54% and 50%, respectively) with the repositioning of the ventricular lead to the LV apex or introduction of biventricular pacing (Table 4). The conduction system in ccTGA is already vulnerable and the risk and management of iatrogenic CHB remains a significant challenge.

This series spans 19 years. It encompasses the introduction of several significant innovations in our speciality. The blood cardioplegia is the most important and has made this surgery achievable without the pressure of time. The range of complexity could be expanded to include MV surgery, aortic translocation, Senning modification, complex coronary translocation, and so on. The developing complexity is not a goal per se, but corresponds to a quest to achieve biventricular physiology whenever balanced ventricles are present. The theoretically significant physiologic superiority above a Fontan physiology can only be translated in our patients' quality of life and exercise ability if mortality is low, if the need for reoperation is limited and predictable, and if complications limiting the quality of the result are absent. The duration of this series, together with the literature available, has allowed us to identify 4 main categories of complication leading to reintervention and/or death: the neo-AV regurgitation, the pulmonary venous pathway of the Senning, the LV dysfunction, and the iatrogenic atrioventricular block. We believe that we are now in control of the pulmonary venous pathway with the Shumacker modification. With regard to damage to the neo-AV by PAB, we orient our strategy toward early repair and avoiding PAB for shunt control. Similarly, we consider and have done neonatal/early infancy repairs for neonates or young infants with an intact ventricular septum and severe TR. Lastly, we believe that LV retraining should be initiated very early in life, with minimal gradient, to allow patients to progressively grow into their band. The LV dysfunction encountered in our series is mild, responded to repositioning of the pacing electrodes when this problem was identified, and is otherwise stable over time. Exclusively a double-switch issue, we are convinced that it is a training issue and not an intraoperative technical problem. The iatrogenic atrioventricular block seems to remain the last, inescapable challenge.

Limitations

This was a retrospective study spanning a long time frame. The learning curve and evolution of the strategy and the surgery (ie, introduction of aortic translocation or the Senning modification) together with the amalgamation of 3 different procedures make the series inhomogeneous. The statistical analysis is not strongly powered and does not allow us to draw strong definite inferences.

CONCLUSIONS

The anatomic correction in this series provided excellent functional outcomes with strictly normal LV function demonstrated in three-quarters of the survivors and mild dysfunction in most of the other quarter. Continuous technical improvement and understanding the causes of less-than-perfect result should reduce the significant need for reoperations and the risk of death or transplantation. Four issues have been identified at follow-up:

1. The status of the aortic valve. The PAB can damage the future aortic valve in patients who receive an arterial switch.
2. LV function can be abnormal in double-switch patients who need retraining. We suspect that PAB may provide inadequate LV training in older patients or when done too fast. Future strategies should avoid leading to that

situation; the double-switch may be safer in infancy than later in life with PAB training. When required, the LV training should be initiated early in life and the patient should grow into a loose band.

3. The secondary stenosis of the lower aspect of the pulmonary venous pathway of the Senning has been responsible for half of the deaths and of almost all the reoperations not related to a pacemaker. The inception of the Shumacker modification of the Senning has provided stable venous pathways.
4. The risk of iatrogenic CHB remains a significant challenge. Meticulous attention to LV pacing lead position is required with growing interest for biventricular pacing.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: congenitally corrected transposition (ccTGA), arterial switch operation, Senning procedure, aortic translocation

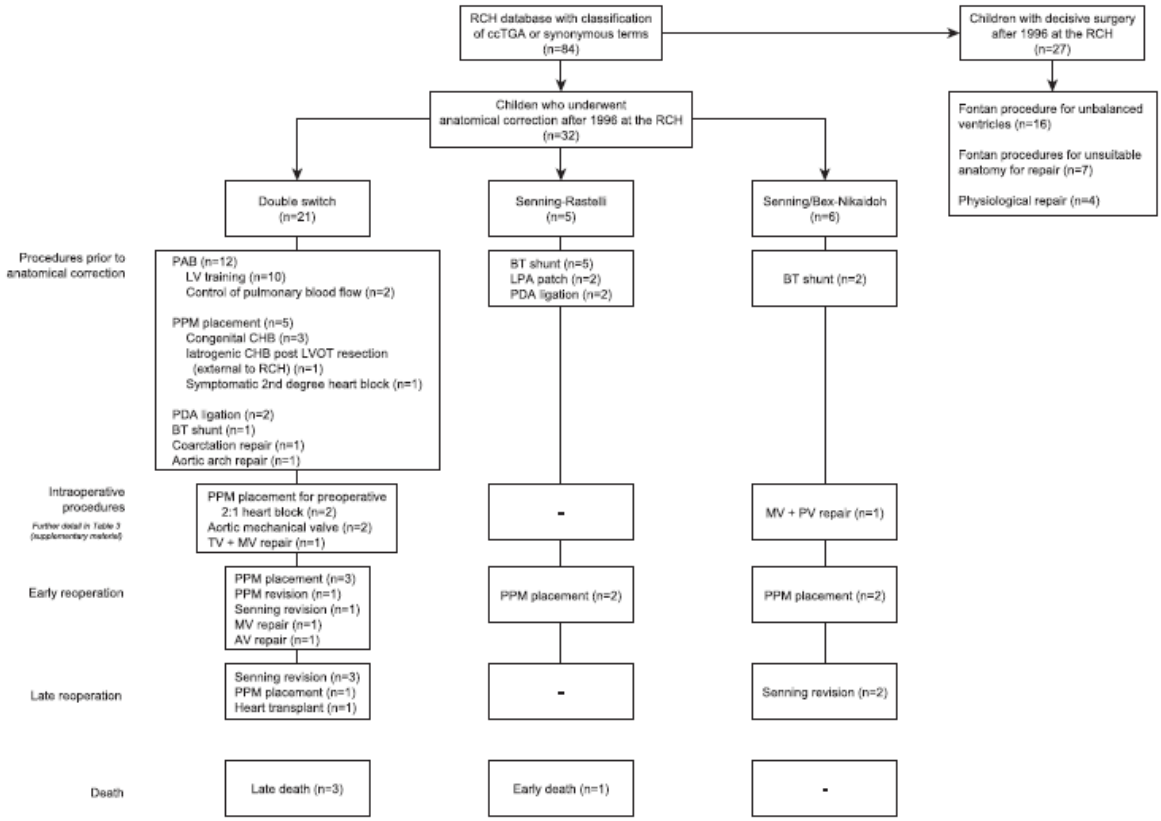
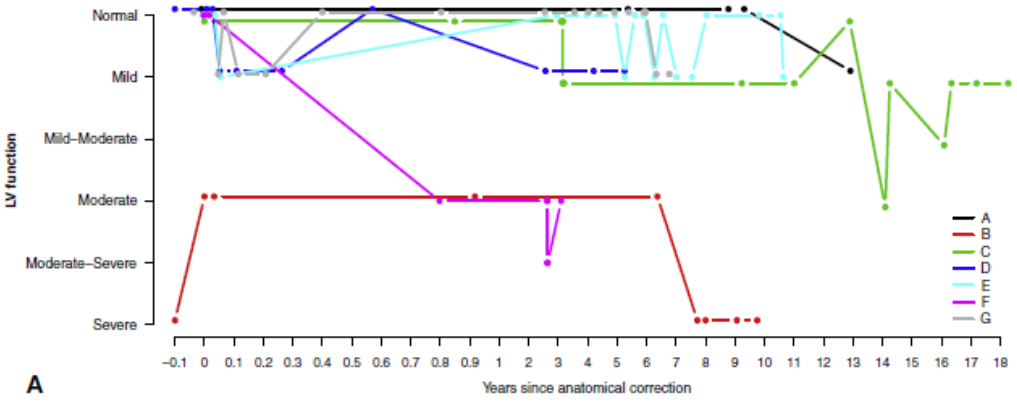


FIGURE E1. Block flowchart diagram of patients and procedures. This figure depicts the 32 patients of the study, separated into anatomic correction groups, and lists the procedures and interventions taken at various stages before and following anatomic correction. The number of deaths from each group is listed at the bottom of the diagram. *RCH*, Royal Children's Hospital Melbourne; *ccTGA*, congenitally corrected transposition of the great arteries; *PAB*, pulmonary artery band; *LV*, left ventricle; *PPM*, permanent pacemaker; *CHB*, complete heart block; *LVOT*, left ventricular outflow tract; *PDA*, patent ductus arteriosus; *BT*, Blalock-Taussig; *LPA*, left pulmonary artery; *TV*, tricuspid valve; *MV*, mitral valve; *PV*, pulmonary valve; *AV*, aortic valve.



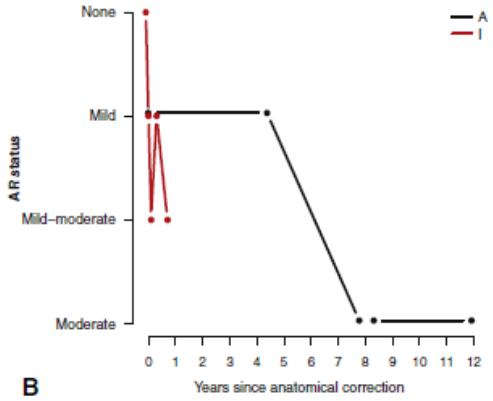


FIGURE E2. Longitudinal observation of postoperative left ventricle (*LV*) function and aortic regurgitation. A, Longitudinal observations for postoperative LV function for children (n = 7) noted to have mild or greater LV dysfunction at latest follow-up, with grading of LV function provided at various time points throughout their preceding follow-up. Letters in panel A correlate with those indicated in Table 4. B, Longitudinal observations for postoperative aortic regurgitation (*AR*) for children (n = 2) noted to have moderate or greater AR at latest follow-up, with grading of AR provided at various time points throughout their preceding follow-up.

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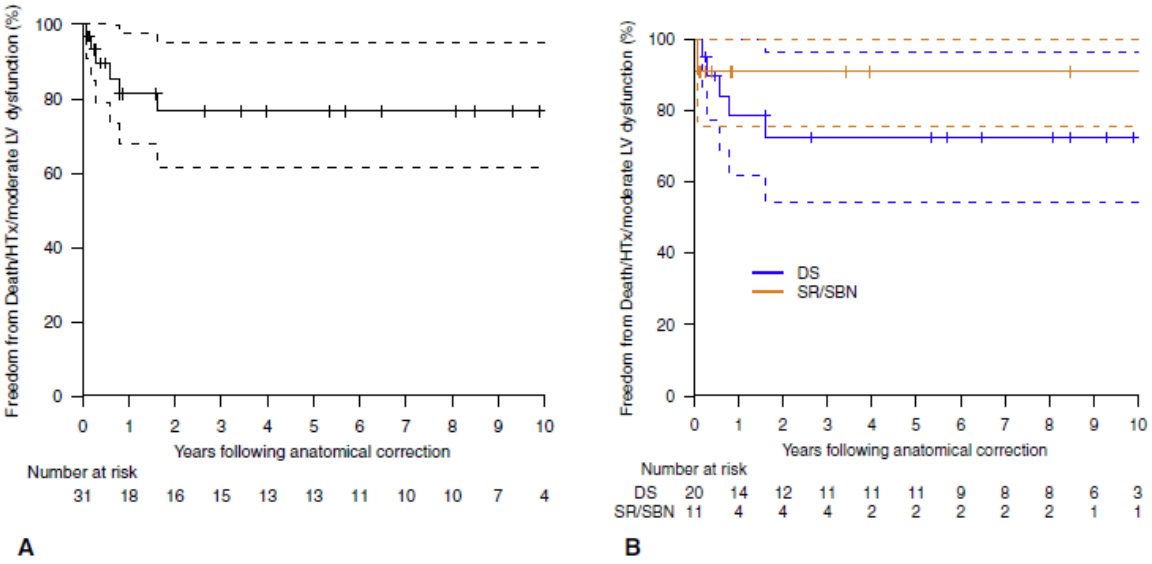

FIGURE E3. Freedom from death, heart transplantation, and moderate or greater left ventricle (*LV*) function. A, Freedom from death, heart transplantation, and moderate or greater LV function was 81% (95% confidence interval [CI], 68%-98%), 77% (95% CI, 62%-95%), and 77% (95% CI, 62%-95%) for all patients at 1, 5, and 10 years, respectively. B, If separated into groups, these freedom figures translated to 79% (95% CI, 62%-100%), 73% (95% CI, 55%-96%), and 73% (95% CI, 55%-96%) for double switch patients alone at 1, 5, and 10 years, respectively; and 91% (95% CI, 75%-100%) for Senning-Rastelli (*SR*) or Senning/Bex-Nikaidoh (*SBN*) patients at 1, 5, and 10 years. The dotted lines on each figure indicate the 95% CI for each solid line category. The above figures exclude a child who already had severe LV function before anatomic correction. *HTx*, Heart transplantation.

Time	All patients	DS (*blue*)	SR/SBN (*orange*)
1 y	81% (68%-98%)	79% (62%-100%)	91% (75%-100%)
5 y	77% (62%-95%)	73% (55%-96%)	91% (75%-100%)
10 y	77% (62%-95%)	73% (55%-96%)	91% (75%-100%)

TABLE E1. Concomitant procedures at anatomic correction

Concomitant procedure	No. of patients
Ventricular septal defect closure	24
Pulmonary artery repair or reconstruction	5
Pacemaker placement	2
Neoaortic valve replacement	2
Mitral valve repair	2
Subpulmonary stenosis resection	2
Pulmonary translocation (Senning-Bex/Nikaidoh patients)	2
Tricuspid valve repair	1
Pulmonary valve repair	1
Patent ductus arteriosus ligation	1
Left coronary augmentation (segment of innominate artery)	1
Coarctation repair	1

TABLE E2. Details of children with pacemakers in situ

Time of placement	Operation type	No. of systems	Years paced (to follow-up or death)	Most recent pacemaker mode	Notes
Before anatomic correction	DS	4	14	CRT	Congenital CHB
	DS	5	18	CRT	Iatrogenic CHB from LVOT resection before anatomic correction
	DS	2	1.8	DDD	Congenital CHB; deceased
	DS	1	6.9	DDD	Congenital CHB
	DS	2	8.5	DDD	2nd degree atrioventricular block
At time of anatomic correction	DS	1	0.8	DDD	Preoperative 2nd degree atrioventricular block
	DS	2	6.5	DDD	Preoperative 2nd degree atrioventricular block
Early reoperation period	SBN	1	0.07	CRT	Iatrogenic CHB
	SR	1	0.07	DDD	Iatrogenic CHB; deceased
	DS	1	0.13	DDD	Iatrogenic CHB; deceased
	DS	1	1.9	DDD	Iatrogenic CHB; heart transplant
	SBN	2	3.9	DDD	Iatrogenic CHB
	SR	1	12	VVI	Back-up system placed, not used
	DS	2	18	DDD	Iatrogenic CHB
Late reoperation period	DS	1	2.8	DDD	Spontaneous CHB

DS, Double switch; *CRT*, cardiac resynchronization therapy; *CHB*, complete heart block; *LVOT*, left ventricular outflow tract; *DDD*, dual-chamber pacemaker; *SBN*, Senning-Bex/Nikaidoh; *SR*, Senning-Rastelli; *VVI*, ventricular pacemaker.

A.5. Konstantinov IE et al. J Thorac Cardiovasc Surg 2017;154:953-954.

ACQ

From cellular senescence to regeneration: A quest for the holy grail for the next generation of surgeons?

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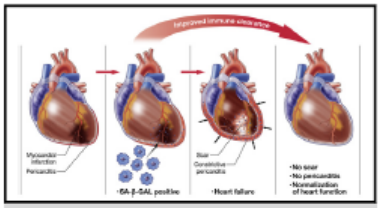

Accumulation of senescent, senescence-associated β-galactosidase–positive, cells appears to play a key role in the initiation of regeneration processes. Improving immune clearance of senescent cells may result in regeneration of the damaged tissue.

Central Message

Accumulation of senescent cells appears to play a key role in the initiation of regeneration process. Improving immune clearance of senescent cells may result in regeneration of the damaged tissue.

See Article page 966.

In 2006, Harriet, 1 of 3 tortoises believed to be taken from the Galapagos Islands by Charles Darwin on his historic 1835 voyage aboard the HMS Beagle, died of heart failure in an Australian zoo. She was 176 years old. Although this fascinating fact may have passed unnoticed by most cardiothoracic surgeons, it may have a subtle yet direct relevance to the broader aspects of tissue regeneration. In 1961, Leonard Hayflick and Paul Moorhead discovered that human embryonic-derived cells could divide only a limited number of times and stopped dividing after an average of 50 cycles.[1] In comparison, cells from the Galapagos tortoise divided approximately 110 times, whereas mouse cells divided about 15 times. This phenomenon is known today as the Hayflick limit, or replicative senescence.

The potential clinical significance of such cellular senescence is exemplified in a thorough and insightful study published in this issue of the *Journal* by Han and colleagues.[2] The authors report that pericardial interstitial cells (PICs) taken from patients with constrictive pericarditis underwent complete division arrest at approximately 14 passages, whereas PICs from patients without pericarditis reached arrest at approximately 25 passages. Senescent cells produced more collagen, attracted more white blood cells, and deposited more calcium. The PICs from patients with pericarditis exhibited senescent changes, including telomere shortening and increased senescence-associated β-galactosidase (SA-β-gal) activity, a classical marker of cellular senescence. Furthermore, expression of genes involved in extracellular matrix deposition, calcium accumulation, and inflammatory cell recruitment were up-regulated in senescent cells, whereas genes of matrix-degrading enzymes were down-regulated. The authors suggest that cellular senescence may contribute to pericardial structural remodeling in idiopathic and post-surgical constrictive pericarditis.

What is the broader relevance of cellular senescence to our routine surgical practice? This question brings us back to yet another fascinating example of evolution in action. Salamanders have a remarkable ability to regenerate damaged complex structures, such as parts of their hearts, brains, eyes, and even amputated limbs. Incredibly, they can do this over and over again, regardless of their age. It was recently demonstrated that salamanders have a superbly efficient mechanism of eliminating senescent cells via macrophage-dependent immune clearance[3] (Figure 1, *A*). Interestingly, senescent cells are strongly induced during the initial stage of regeneration, but then are completely cleared by the time the damaged organ is regenerated. This phenomenon of induction and clearance of senescent cells appears to be central to the regeneration process.[3] Furthermore, this process may also play an important role in embryonic tissue development in mammals.[4,5] Most remarkably, it appears that the mammalian myocardium continues to retain this regenerative capacity even during postnatal development, at least in the neonatal period.[6,7] Accumulation of senescent cells in mammals appears to be linked to the age-related decline in regenerative capability[8] and may lead to a number of age-related disorders,[9] of which constrictive pericarditis may be just one example.

Clearly, the biological significance of cellular senescence goes far beyond constrictive pericarditis. Efficient elimination of senescent cells in humans (Figure 1, *B*) may become a promising therapeutic strategy not only in patients with constrictive pericarditis, but also in those with evolving myocardial infarction or with any damage to an organ

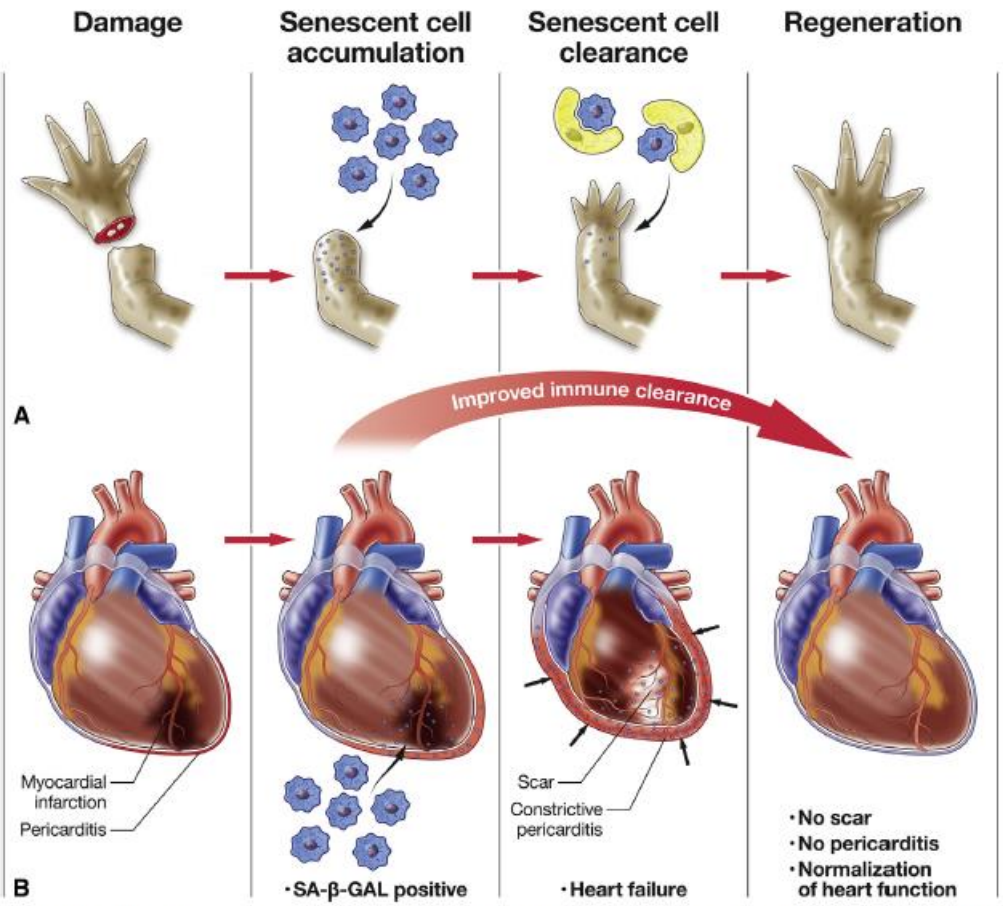

FIGURE 1. Accumulation of senescent, senescence-associated β-galactosidase–positive, cells appears to play a key role in the initiation of regeneration process. A, In salamanders, senescent cells are efficiently eliminated via macrophage-dependent immune clearance, with complete regeneration of the damaged limb or organ. B, In humans, accumulation of senescent cells after myocardial infarction or pericarditis may result in scar formation and constrictive pericarditis. Improving the immune clearance of senescent cells may result in regeneration of the damaged tissue. *SA-β-GAL*, Senescence-associated β-galactosidase.

with impaired regenerative potential. Could constrictive pericarditis be reversed by effective elimination of senescent cells? Could myocardial function be improved by inducing cellular regeneration after myocardial infarction? Could hypoplastic myocardium be regenerated in congenital heart disease? Will advances in cellular biology revolutionize the surgical management of cardiovascular disorders, or will such interventions remain an elusive holy grail? Time will tell. Whatever the case may be, solid knowledge of cellular biology will be indispensable for the next generation of academic surgeons.

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ORIGINAL ARTICLE: EDUCATION

Early Mentoring of Medical Students and Junior Doctors on a Path to Academic Cardiothoracic Surgery

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Background. In 2005 the Department of Cardiothoracic Surgery at The Royal Children's Hospital started an early academic mentoring program for medical students and junior doctors with the aim of fostering an interest in academic surgery.

Methods. Between 2005 and 2015, 37 medical students and junior doctors participated in research in the Department of Cardiothoracic Surgery at The Royal Children's Hospital. Each was given an initial project on which to obtain ethics approval, perform a literature review, data collection, statistical analysis, and prepare a manuscript for publication. A search of the names of these former students and doctors was conducted on PubMed to identify publications.

Results. A total of 113 journal articles were published in peer-reviewed journals with an average impact factor of 4.1 (range, 1.1 to 19.9). Thirty (30 of 37, 81%) published at least one article. A mean of 4.3 journal articles was published per student or junior doctor (range, 0 to 29). Eleven (11 of 37, 30%) received scholarships for their research. Nine (9 of 37, 24%) have completed or are enrolled in higher research degrees with a cardiothoracic surgery focus. Of these 9, 2 have completed doctoral degrees while in cardiothoracic surgery training. Five will complete their cardiothoracic surgery training with a doctoral degree and the other 2 are pursuing training in cardiology.

Conclusions. A successful early academic mentoring program in a busy cardiothoracic surgery unit is feasible. Mentoring of motivated individuals in academic surgery benefits not only their medical career, but also helps maintain high academic output of the unit.

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Fostering an academic interest in young doctors undergoing cardiothoracic training has long been seen as an important part of the cardiothoracic specialty. With overall interest and numbers of cardiothoracic training program applicants declining, especially in the United States [1–5], involving medical students and junior doctors through the medium of research may help to identify and support excellent candidates [6]. In addition, as modern surgery evolves, it becomes even more relevant to develop research skills to interpret evidence around new technology and innovation. Most importantly, developing surgeons capable of sustained high-quality academic excellence is vital to ensure the bright future of our specialty. With this in mind, surgeons at the Department of Cardiothoracic Surgery at The Royal Children's Hospital in Melbourne, Australia, started an early academic mentoring program for medical students and junior doctors with the aim of fostering an interest in academic surgery.

Material and Methods

Between 2005 and 2015, 37 medical students and junior doctors participated in a structured research program (Fig 1) of the Department of Cardiothoracic Surgery at The Royal Children's Hospital. In Australia, the pathway to become a cardiothoracic surgeon typically involves 6 to 7 years of study in university to obtain a medical degree, followed by 1 year of internship. After 1 to 3 years after graduation from medical school, one typically applies to the Royal Australasian College of Surgeons (RACS) for specialist training in cardiothoracic surgery. Therefore, most trainees are in their late twenties by the time they start specialist training. The length of the RACS cardiothoracic surgery training program is 6 years (Fig 2A).

The medical students of the University of Melbourne came for full-time research placement for 1 year from the advanced medical science program. From 2014, the program was transformed into the scholarly selective program of 6 months of full-time research preceded by 6 months of part-time research (Fig 2B). Seventeen students (46%, 17 of

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Fig 1. Algorithm for academic cardiothoracic surgeon pathway. (PhD = doctor of philosophy.)

EDUCATION

37) were female, and 32 (32 of 37, 86%) began as medical students completing research terms as part of their medical degree. After completion of either program, the student was further selected by surgeons for doctoral candidature (Fig 2B), mentored beyond graduation from medical school, and prepared for entry into cardiothoracic surgery training. Junior doctors were those who graduated from medical school, but had not yet obtained specialist qualifications.

Each medical student or junior doctor was given an initial project on which to obtain ethics approval, perform a literature review, data collection, statistical analysis, and prepare a manuscript for publication. These projects were retrospective outcomes-based reviews of patients with a particular congenital heart disease. Students were posted full time to the unit with opportunity for dedicated daily meetings with surgical supervisors and clinical observation in and outside the operating theater. Medical students also received a weekly 1 hour of formal teaching by a consultant cardiothoracic surgeon on the entire curriculum of congenital cardiothoracic surgery. Junior doctors in the research program were working full time and typically met with surgical supervisors on a weekly basis. At these meetings with supervisors, the participants were educated in the collection of data, creation of a database, and statistical analysis. In addition to support from their supervisor, participants also had access to support from statisticians through the Clinical Epidemiology and Biostatistics Unit of the Murdoch Children's Research Institute. A search of the names of these former students and doctors was conducted on PubMed to identify publications.

Results

Journal Publications

A total of 113 journal articles were published in peer-reviewed journals with an average impact factor of 4.1

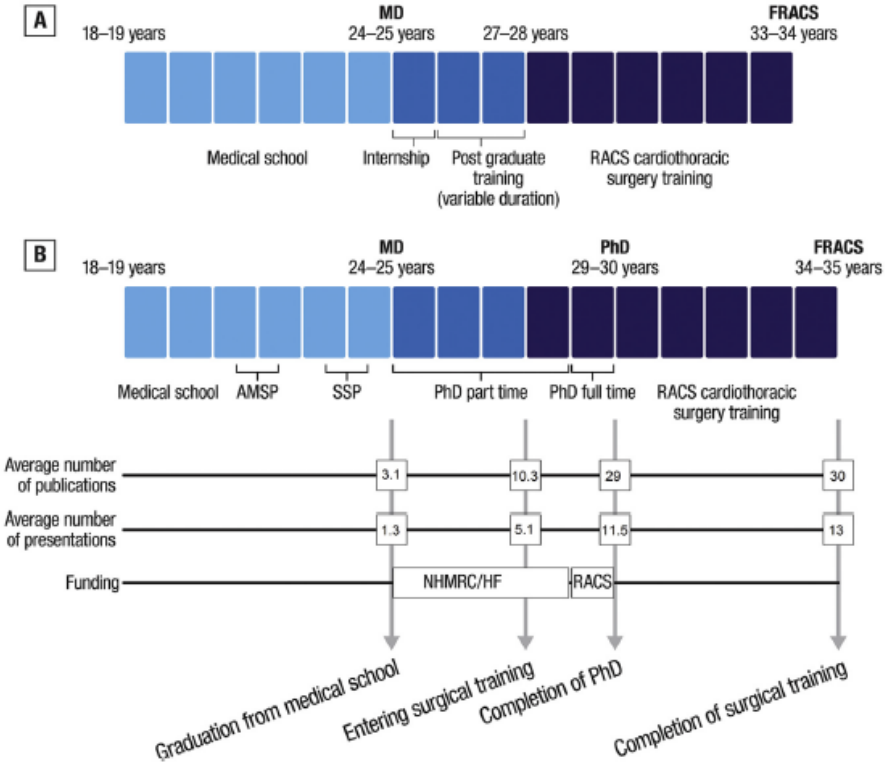

Fig 2. (A) Pathway of cardiothoracic surgical training in Australia. (B) Pathway of academic cardiothoracic surgical training in Australia with a doctoral component developed at The Royal Children's Hospital. (AMSP = Advanced Medical Science Program; FRACS = Fellow of Royal Australasian College of Surgeons; HF = Heart Foundation of Australia; MD = medical doctor; NHMRC = National Health and Medical Research Council; PhD = doctor of philosophy; RACS = Royal Australasian College of Surgeons; SSP = Scholarly Selective Program.)

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Table 1. Doctoral Students' Achievements

PhD Student	No. Publications	No. Presentations	Funding	Training	PhD Degree Complete
1	15	6	NHMRC, HF	Current CTS trainee	In progress
2	16	5	NHMRC, HF	Current CTS trainee	In progress
3	17	8	NHMRC	Pursuing CTS training	In progress
4	39	17	NHMRC, HF, RACS	Current CTS trainee	Finished
5	14	6	NHMRC, HF, RACS	Current CTS trainee	In progress
6	5	0	NHMRC	Pursuing Cardiology training	In progress
7	29	6	HF, RACS	Current CTS trainee	Finished
8	5	3	HF	Pursuing CTS training	In progress
9	14	12	NHMRC, HF	Pursuing Cardiology training	In progress

CTS = cardiothoracic surgery; HF = Heart Foundation of Australia; NHMRC = National Health and Medical Research Council; No. = number; PhD = doctor of philosophy; RACS = Royal Australasian College of Surgeons.

(range, 1.1 to 19.9). The journal most commonly published in was *The Annals of Thoracic Surgery* (Table 1). There were a mean 4.3 journal articles published per student or junior doctor (range, 0 to 29). Thirty (30 of 37, 81%) published at least one article. A student or junior doctor was first author in 80 (80 of 113, 71%) of the journal articles. Of the 113 articles, 96 (85%) were retrospective outcomes studies, 13 (12%) were editorial comments, 3 (3%) were case reports, and one was a review article.

Scholarships

Eleven students or junior doctors (11 of 37, 30%) received scholarships for their research, including National Health and Medical Council Research scholarships (n = 7), Heart Foundation of Australia scholarships (n = 8), and RACS scholarships (n = 3).

Table 2. Number of Publications per Journal

Journal	No. Publications
The Annals of Thoracic Surgery	30
Journal of Thoracic and Cardiovascular Surgery	29
European Journal of Cardiothoracic Surgery	14
Heart Lung and Circulation	8
Interactive Cardiovascular and Thoracic Surgery	7
Seminars in Thoracic and Cardiovascular Surgery	5
International Journal of Cardiology	3
Journal of American College of Cardiology	3
Australia New Zealand Journal of Surgery	3
World Journal of Paediatric Congenital Heart Surgery	3
Circulation	2
Journal of the American Heart Association	2
Heart	2
Internal Medicine Journal	1
Expert Review of Medical Devices	1
Journal of Thoracic Disease	1

No. = number.

Higher Research Degrees

Nine students (9 of 37, 24%) have completed or are enrolled in higher research degrees with a cardiothoracic surgery focus. Of these 9, 2 have completed doctoral degrees while in cardiothoracic surgery training. Five will complete their cardiothoracic surgery training with a doctoral degree, and the remaining 2 are pursuing their training in cardiology (Table 2).

Presentations

Students enrolled in the early mentoring program presented their research at scientific meetings, including the American Association for Thoracic Surgery (n = 10), American Heart Association (n = 5), European Association of Cardiothoracic Surgery (n = 6), The Society for Thoracic Surgery (n = 6), and national Australian (n = 23) annual meetings. The latter included annual meetings of the Cardiac Society of Australia and New Zealand (ANZ), the ANZ Society of Cardiac and Thoracic Surgeons, and RACS.

Comment

The results of an early academic mentoring program at The Royal Children's Hospital in Melbourne, Australia, indicate the overwhelming success of engaging and mentoring motivated students early in their medical careers. It is our belief that such a program helps identify students and doctors with an interest in cardiothoracic surgery and aids in attracting the best candidates to our specialty.

The early mentoring is crucial to the future of our specialty, particularly as it appears that declining interest in surgery may lead to a shortage in cardiothoracic surgeons [7]. Loss of interest in cardiothoracic training may relate to concerns around lifestyle, the length of training, and the current job market [8]. Exposure to positive role models early on can only be beneficial to improving perceptions of cardiothoracic training [9]. Indeed, the inspirational value of direct contact with academic cardiothoracic surgeons for motivated individuals early in their careers cannot be overemphasized. The mentorship of senior surgeons involved in these research orientated

programs encourages enthusiastic candidates to consider becoming academic cardiothoracic surgeons. This interest is fostered not only through research conducted, but also through involvement and exposure to other departmental activities. A similar, successful program run by the Johns Hopkins Hospital cardiothoracic team has yielded encouraging results [6].

Aside from attracting potential cardiothoracic surgeons, our program was successful in building research skills early on in the careers of the program participants. This is important regardless of whether the student or junior doctor decides to pursue a career in cardiothoracic surgery or another specialty.

The results of our early academic mentoring program show that medical students and junior doctors in our unit produced a significant number of publications. It is also clear from our experience that such a high level of departmental research output would not have been possible without the contribution of the students and junior doctors. An improvement in departmental research output has previously been shown by others with clinical fellowship programs [10]. However, owing to the heavy load of clinical responsibilities, clinical research can only be efficiently conducted by prepared individuals who have already mastered basic methods of clinical research. Therefore, the involvement of medical students and junior doctors is beneficial not only to the individual medical trainees, but also to the department, and most importantly, the specialty as a whole. Most importantly, such an early mentoring model develops an academic surgeon capable of obtaining competitive research funding at the national level, producing high-quality sustained research, and, above all, the early mentoring enables capable students to become future leaders of the specialty.

In conclusion, a successful early academic mentoring program in a busy cardiothoracic surgery unit is feasible. Mentoring of motivated individuals in academic surgery not only benefits their medical career, but also helps maintain the high-quality academic output of the unit.

EDUCATION

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EDITORIAL COMMENTARY

Translocation of intramural coronary artery in the arterial switch operation: Divide and conquer?

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Tyson A. Fricke, MBBS, BMedSci, and Igor E. Konstantinov, MD, PhD, FRACS

Central Message

Transfer of the IMCA in the ASO can be challenging. However, excellent results can be achieved with reproducible techniques of coronary translocation.

See Article page e127.

Today, the operative mortality of the arterial switch operation (ASO) is expected to be less than 2% for children born with transposition of the great arteries and an intact interventricular septum.[1] A single coronary artery is no longer a risk factor for death in most large-volume institutions.[1,2] In contrast, an intramural coronary artery (IMCA) has been reported to increase operative mortality

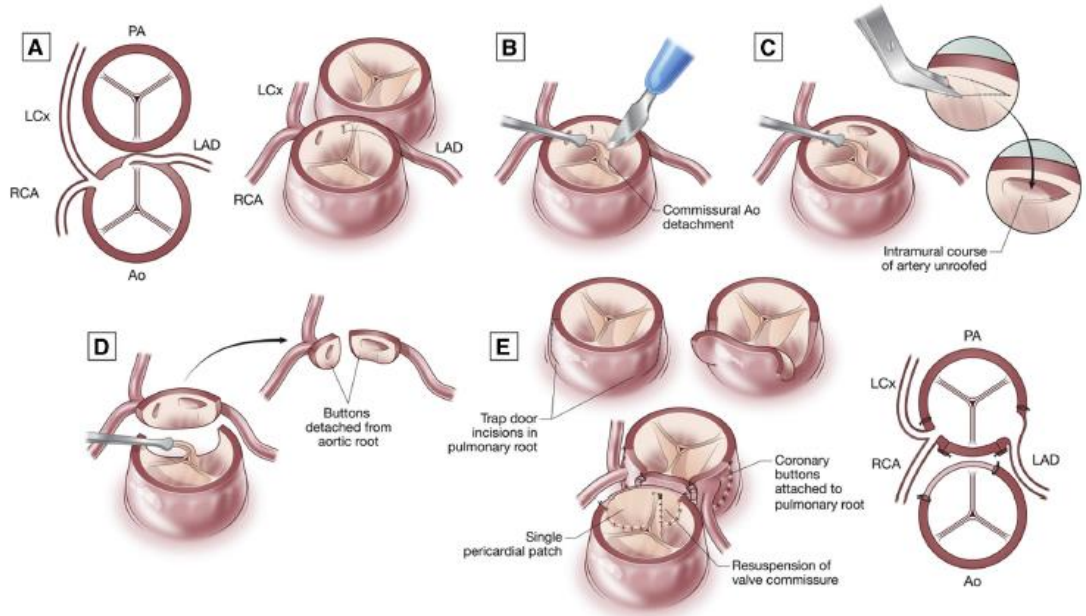

FIGURE 1. Surgical technique of Shaher 2a IMCA transfer. After identification of the intramural segment (A), detachment of the posterior commissure of the aortic (neopulmonary) valve is performed (B). The IMCA is unroofed (C). The coronary arteries are detached and transferred as 2 separate buttons using the trapdoor technique, the pulmonary artery is reconstructed with a single autologous pericardial patch, and the posterior neopulmonary valve commissure is reattached to the patch (D and E). *RCA*, Right coronary artery; *LCx*, left circumflex coronary artery; *PA*, pulmonary artery; *LAD*, left anterior descending artery; *Ao*, aorta.

to more than 20%.[3] In the current issue of the *Journal*, Ko and colleagues[4] describe a technique for coronary translocation in a patient with an IMCA undergoing the ASO. They have previously applied this aortic sinus pouch technique for a patient with a single coronary artery undergoing the ASO.[5] Such implantation of a single coronary button is an interesting approach to deal with an IMCA. In fact, the initial approach to IMCA transfer used by Roger Mee in the 1980s at the Royal Children's Hospital in Melbourne was also a single button transfer of both coronary arteries.[6] Subsequently, a trapdoor technique for coronary translocation during the ASO, which was originally described by Brawn and Mee,[7] has been modified for translocating IMCA by the Royal Children's Hospital team.[6] Our technique involves detaching the posterior commissure of the neopulmonary valve if the coronaries arise in close proximity and unroofing the IMCA if the ostium is stenotic. The excised coronary button is then transferred to a medially based trapdoor (Figure 1). We have previously reported outcomes on 28 patients with IMCA operated with this technique with no deaths.[8] The first 3 patients in our experience had coronary translocation as a single button facilitated by a pericardial hood. After a mean follow-up of 26.3 years (median, 26.6 years; range, 25.3-26.9 years), these 3 patients are alive and well. The subsequent 25 children with IMCA underwent ASO with individual translocation of both coronary arteries using the trapdoor technique.[8] The latter 25 patients are all alive without the need for coronary reintervention after a mean 16.5 years (median, 17.7 years; range, 5.5-25.3 years). Thus, IMCA has not been a risk factor for mortality at our institution.[1]

The patient described by Ko and colleagues[4] had Shaher 2a coronary anatomy, with the left anterior descending coming from sinus 1 and the circumflex coronary artery and the right coronary coming from sinus 2. Of the 28 patients with IMCAs described in our recent article, 2 patients had this specific anatomy.[8] Both patients underwent unroofing of the IMCA, division into 2 buttons, and a standard coronary translocation using our trapdoor technique. These patients are alive and asymptomatic 22 and 23 years after ASO.

It appears that the technique of Ko and colleagues[4] is an elegant approach and might become a useful addition to the armamentarium of the congenital cardiac surgeon, provided that this technique results in good long-term outcomes. Time will tell.

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Impact of truncal valve surgery on the outcomes of the truncus arteriosus repair

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Abstract

OBJECTIVES: Preoperative moderate or greater truncal valve (TV) insufficiency is one of the most important factors influencing mortality in children with truncus arteriosus. We therefore sought to determine the impact of TV insufficiency and concomitant TV surgery on children who underwent truncus arteriosus repair at a single institution.

METHODS: We reviewed 180 patients who underwent truncus arteriosus repair between 1979 and 2016. Preoperative echocardiography demonstrated TV insufficiency in 80 patients (mild: 33.9%, 61/180; moderate: 9.4%, 17/180 and severe: 1.1%, 2/180).

RESULTS: Twenty-one patients had concomitant TV surgery with an early mortality of 19% (4/21) and overall survival of 70.8 ± 10.1% at 25 years. There were 60 neonates, 11 of whom had concomitant TV surgery with an early mortality of 27% (3/11) and overall survival of 62.3 ± 15.0% at 20 years. Concomitant TV repair ($P = 0.5$) was not a risk factor for death. TV reoperation was common in those who had concomitant TV surgery, with freedom from reoperation of 19.2 ± 14.9% at 20 years. In the remaining 159 patients, 14 required subsequent TV surgery, and the freedom from TV surgery was 84.0 ± 4.6% at 20 years. At a median follow-up of 18.5 years, TV insufficiency was none or trivial in 79.6% (109/137) and mild or less in 98.5% (135/137) of patients.

CONCLUSIONS: Most patients with mild TV insufficiency are free from TV surgery up to 25 years. The durability of TV repair is poor. Most patients with moderate or greater TV insufficiency and a quadricuspid TV will require TV surgery.

Keywords: Truncal valve • Truncus arteriosus • Surgery

INTRODUCTION

Truncus arteriosus (TA) accounts for 0.7–3% of congenital cardiac defects [1, 2]. Our recent review of 171 patients with TA managed at The Royal Children's Hospital described good short- and long-term outcomes following complete repair [3].

The impact of truncal valve (TV) insufficiency and concomitant TV surgery on the outcomes of TA repair are not well defined. Preoperative mild TV insufficiency is often well tolerated; however, moderate or greater TV insufficiency has been reported as one of the most important factors influencing mortality [4–8]. Concomitant TV surgery in patients with moderate or greater TV insufficiency may be beneficial in reducing mortality and later TV surgery. We therefore sought to determine the impact of TV insufficiency and concomitant TV surgery on children who underwent TA repair at a single institution.

PATIENTS AND METHODS

Patients

Between 1979 and 2016, 180 consecutive patients underwent repair of TA (Fig. 1). Data were obtained by review of medical records from initial admission until the last cardiology follow-up. Overall follow-up was 98.6% (137/139) complete for survivors with a median follow-up of 18.5 years (mean 17.3 years; range 1–35 years). Two patients were lost to any follow-up. Patients who underwent concomitant TV surgery had a median follow-up

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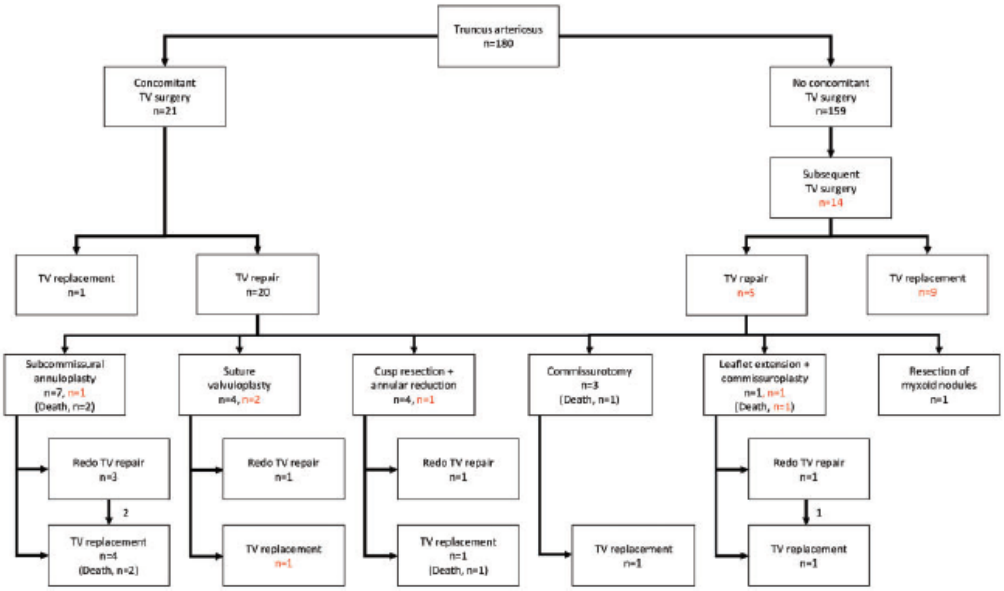

Figure 1: Flow chart of outcomes following TV surgery. Values in red indicate subsequent TV surgery. TV: truncal valve.

of 14.6 years (mean 13 years, range 1–24 years). At the last follow-up, all patients were in New York Heart Association Class I/II.

Definitions

Early mortality and reoperation were defined as those occurring within 30 days of surgery or prior to hospital discharge. All other deaths and reoperations were considered late. Subsequent TV surgery was defined as the first TV surgery done after the initial TA repair. The presence of TV insufficiency was evaluated by pre-operative transthoracic echocardiography (TTE) and colour Doppler imaging using standard echocardiographic criteria [9–12], including M-mode assessment of left ventricular function, Doppler assessment of pressure half-time (mild >500 ms; moderate = 500–200 ms; severe <200 ms), diastolic flow reversal in the descending aorta (mild = brief, early diastolic reversal; moderate = intermediate; severe = holodiastolic flow reversal), colour-flow regurgitant jet size (mild = small central jet <25% LVOT; moderate = intermediate jet greater than mild but no signs of severe; severe = large central jet >65% LVOT) and measurements of the truncal regurgitant jet width:annulus ratio (mild <25; moderate = 25–64; severe ≥65). TV insufficiency was graded qualitatively from none/trivial to severe. Generally, TV surgery was performed at TA repair when preoperative TV insufficiency was graded as moderate or greater. More modest degrees of TV insufficiency were repaired only when intraoperative decision-making dictated that TV repair was necessary.

Data analysis

Data were analysed using STATA version 12 (StataCorp LP, College Station, TX, USA). Descriptive statistics for continuous data are expressed as means ± standard deviations (range), while skewed continuous data are expressed as medians (interquartile range). Categorical data are summarized as frequencies and percentages. Univariate and multivariate logistic regression and Cox proportional hazard modelling were used to determine the risk factors for mortality and reoperation. The Kaplan–Meier actuarial survival (±standard error) was used to analyse and plot time-related endpoints. Statistical significance was set at P-value <0.05.

RESULTS

Patient characteristics are summarized in Table 1. Overall median age at TA repair was 52 days (mean 144 days; range 1 day–8.7 years), and the median weight was 3.5 kg (mean 4.1 kg; range 1.2–23 kg). Preoperative TTE determined TV insufficiency in 80 patients (Table 1). Twenty-two patients had an associated interrupted aortic arch (IAA), of whom 21 had mild or less TV insufficiency and 1 had moderate TV insufficiency.

Mild or less truncal valve insufficiency

A total of 161 patients had mild or less TV insufficiency on preoperative TTE. Nine of these patients underwent concomitant TV surgery. Two patients with no TV insufficiency underwent commissurotomy due to TV stenosis. Four patients who were deemed to have mild TV insufficiency on preoperative TTE were in fact found to have at least 'moderate' TV insufficiency on intraoperative echocardiography and underwent concomitant TV surgery. One patient had a TV with a flail leaflet and was repaired despite mild TV insufficiency. One patient underwent commissurotomy to facilitate unroofing of an intramural coronary artery. One patient underwent resection of large myxoid nodules from the free edge of the cusps. There was 1 early death in this patient cohort, described below. There were no late deaths. There have been 3 TV reoperations (redo TV repair, $n = 1$; TV replacement, $n = 2$) in this patient cohort. Long-term TV status is good with all patients ($n = 8$) having mild or less TV insufficiency.

There were 152 patients with mild or less TV insufficiency who did not undergo concomitant TV surgery. Early mortality in this patient cohort was 11.2% (17/152) and long-term survival at

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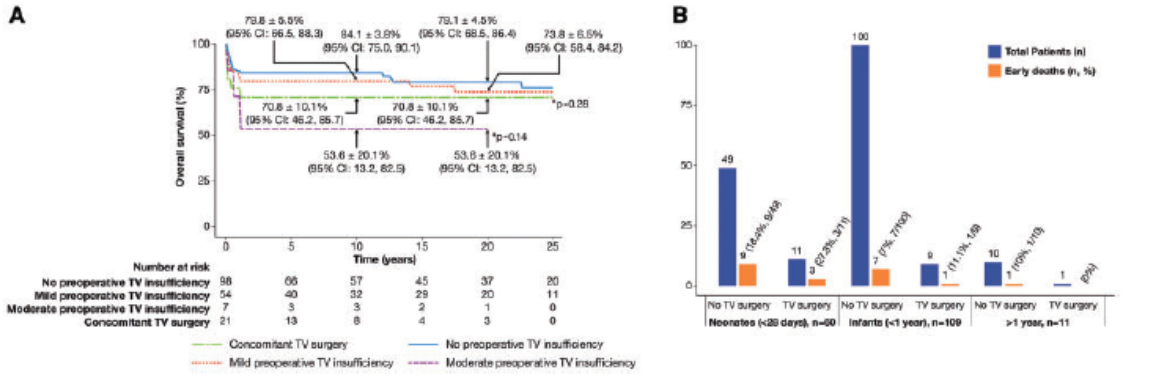

Figure 2: Mortality in patients with TV insufficiency and concomitant TV surgery. (**A**) Kaplan–Meier overall survival of TV insufficiency and concomitant TV surgery. *Log-rank mild or less TV insufficiency versus concomitant TV repair. #Log-rank mild or less TV insufficiency versus moderate TV insufficiency. (**B**) Early mortality in neonates, infants and children >1 year. CI: confidence interval; TV: truncal valve.

worsening TV insufficiency at 6 days, 8 months and 13.3 years, respectively. The remaining 2 patients have not undergone any TV surgery, both of whom had a tricuspid TV and had mild TV insufficiency at the last follow-up. There was no statistical difference between patients with moderate TV insufficiency who did not undergo concomitant TV surgery and those with mild or less TV insufficiency ($P = 0.14$) (Fig. 2A).

Concomitant truncal valve surgery

Twenty-one patients underwent 'concomitant' TV surgery at TA repair. The TV was bicuspid in 2, tricuspid in 7 and quadricuspid in 12 patients. Seven patients (mild, $n = 3$; moderate, $n = 3$; severe, $n = 1$) underwent subcommissural annuloplasty (Fig. 3). Four patients (mild, $n = 1$; moderate, $n = 3$) underwent suture valvuloplasty (Fig. 4). Four patients (mild, $n = 1$; moderate, $n = 2$; severe, $n = 1$) underwent TV cusp resection and annular reduction (Fig. 5). Three patients underwent commissurotomy (none, $n = 2$; mild, $n = 1$). One patient with moderate TV insufficiency underwent TV cusp elongation with glutaraldehyde-treated autologous pericardium and commissuroplasty. One patient with mild TV insufficiency underwent resection of large myxoid nodules from the free edge of the cusps. One patient with moderate TV insufficiency required TV replacement with a 10-mm aortic homograft. No patient with a concomitant IAA underwent TV surgery.

There were 4 early deaths in children who underwent concomitant TV surgery. The first death occurred in 1981 in a 1.7-kg, 1-day-old girl with moderate TV stenosis who underwent TV commissurotomy. She had cardiac arrest on postoperative day (POD) 7 and died. The second death occurred in 2001 in a 3.3-kg, 55-day-old girl with moderate TV insufficiency who underwent subcommissural annuloplasty. She had severe tracheobronchomalacia and an acute myocardial infarction and died on POD 1. The third death occurred in 2005 in a 3-kg, 7-day-old girl with severe TV insufficiency and Scimitar syndrome who underwent subcommissural annuloplasty and right pneumonectomy due to pulmonary haemorrhage. She emergently underwent TV replacement on POD 0 due to severe TV insufficiency and was placed on extracorporeal membrane oxygenation (ECMO). Unfortunately, she could not be weaned off ECMO and later died on POD 12. The fourth death occurred in 2010 in a 3.3-kg, 21-day-old boy with moderate TV insufficiency who required preoperative ECMO for 3 days due to severe respiratory distress, sepsis and cardiac arrest. He underwent subcommissural annuloplasty and remained on ECMO. He could not be weaned off ECMO and treatment was withdrawn on POD 17. There was no statistical difference in early deaths between patients who underwent concomitant TV surgery and those who did not [19% (4/21) vs 11% (17/159); $P = 0.26$]. There were 2 late deaths. Overall survival in patients who had concomitant TV surgery was 70.8 ± 10.1% (95% CI 46.2–85.7) at 20 years (Fig. 2A) and was not statistically different from patients with mild or less TV insufficiency ($P = 0.28$). Furthermore, concomitant TV surgery ($P = 0.50$), moderate or greater TV insufficiency ($P = 0.34$) or a quadricuspid TV ($P = 0.51$) were not identified as risk factors for mortality on univariable analysis. Most concomitant TV surgery was performed in the last 2 decades; therefore, the era of surgery did not impact TV surgical outcomes.

Truncal valve reoperation

Reoperation on the TV (including following concomitant TV surgery, $n = 13$ and subsequent TV surgery, $n = 14$) occurred in 27 patients. Concomitant TV surgery ($P = 0.001$, hazard ratio 7.9, 95% CI 3.4–18.5) and a quadricuspid TV ($P = 0.04$; hazard ratio 2.4, 95% CI 1.1–5.4) were risk factors on Cox regression for late operation on the TV.

TV reoperation was common in patients who had concomitant TV surgery. Thirteen patients underwent TV reoperation at a median time of 2.4 years (1.0–5.2 years). Freedom from TV reoperation was 19.2 ± 14.9% (95% CI 1.6–51.9) at 20 years (Fig. 6). The type of TV repair was not associated with reoperation rate. One patient who underwent commissurotomy due to TV stenosis required TV replacement at 8.5 years due to the TV being dysplastic and becoming moderately insufficient. Currently, only 2 patients had concomitant TV surgery and did not require TV reoperation. Both patients have mild TV insufficiency.

There were 159 patients (Fig. 1) who did not undergo concomitant TV surgery, 14 of whom required subsequent TV surgery (TV repair, $n = 5$ and TV replacement, $n = 9$) at a median time of 7.9 years (3.9–12.6 years) for persisting or worsening TV insufficiency. Freedom from subsequent TV operation was 84.0 ± 4.6% (95% CI 72.5–91.0) at 20 years. Surgical technique is summarized in Fig. 1. Seven of the 14 (50%) patients who underwent

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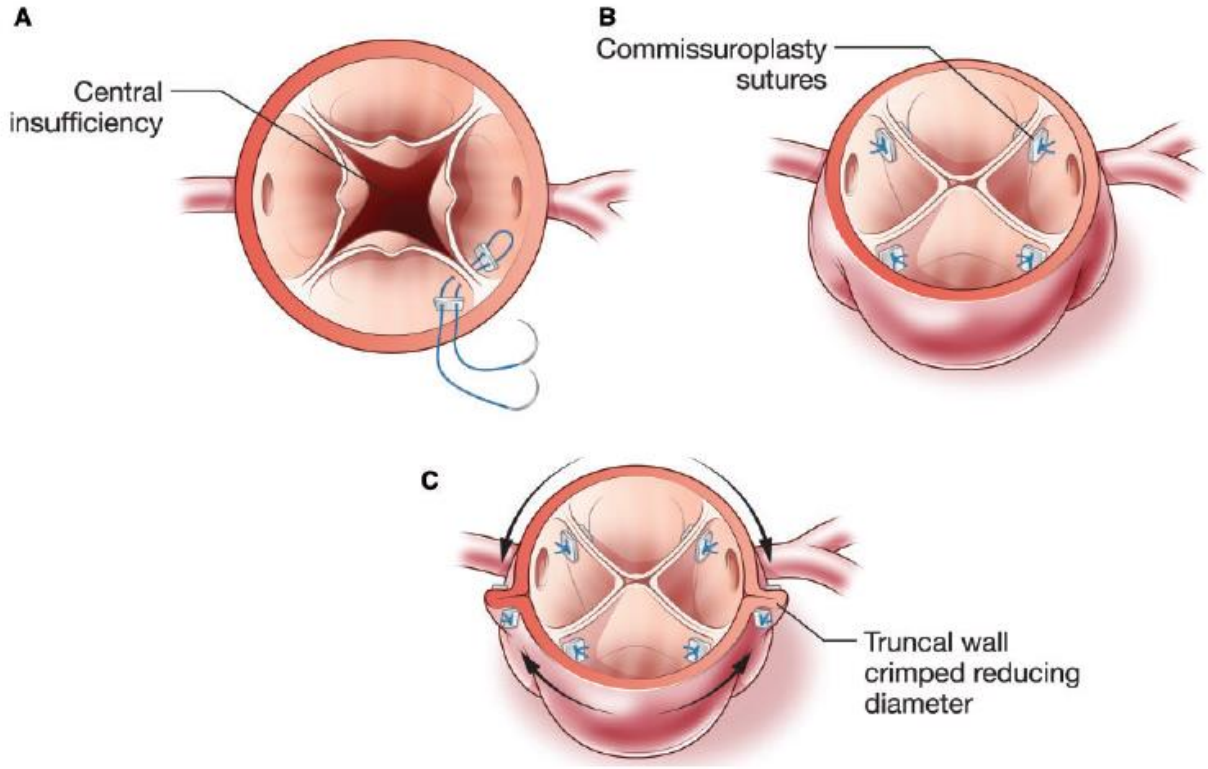

Figure 3: Subcommissural annuloplasty. Placement of 5-0 Ti-Cron (Medtronic, Minneapolis, MN, USA) sutures pledgeted with autologous pericardium to the subcommissural region of the truncal valve. This aims to improve central coaptation in patients with a large truncal valve annulus and relatively normal leaflets. If the sinotubular junction and annulus were dilated, they were also plicated with a full-thickness pledgeted suture.

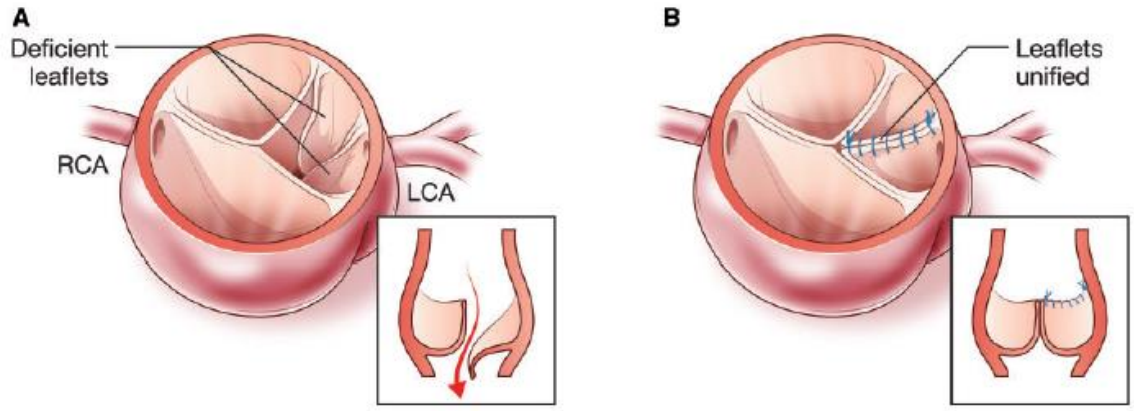

Figure 4: Suture valvuloplasty. Suture of a single prolapsing leaflet to the adjacent TV leaflet for support. LCA: left coronary artery; RCA: right coronary artery; TV: truncal valve.

subsequent TV surgery had a quadricuspid TV. Two patients required subsequent TV surgery (TV repair, $n = 1$ and TV replacement, $n = 1$) during their 'initial' hospital stay for TA repair. There was 1 late death in the 14 patients who underwent subsequent TV surgery. Of the 13 surviving patients, 10 have undergone TV replacement and 3 have mild or less TV insufficiency. There were 2 patients with concomitant IAA who required subsequent TV replacement—both patients are well 10 and 26 years, respectively. The need for aortic arch surgery did not impact on the progression of TV insufficiency.

Neonates

There were 60 neonates, of whom 33 had TV insufficiency. There were 24 neonates (40%, 24/60) operated between 1979 and 1999 and 36 neonates (60%, 36/60) between 2000 and 2016. Thirty neonates underwent TA repair in the last 10 years. Eighteen of the 60 (30%) neonates had concomitant IAA repair. There was a significantly ($P = 0.02$) higher proportion of early deaths among neonates (20%, 12/60) compared to older patients (7.5%, 9/120). However, neonatal surgery was not identified as a risk factor on

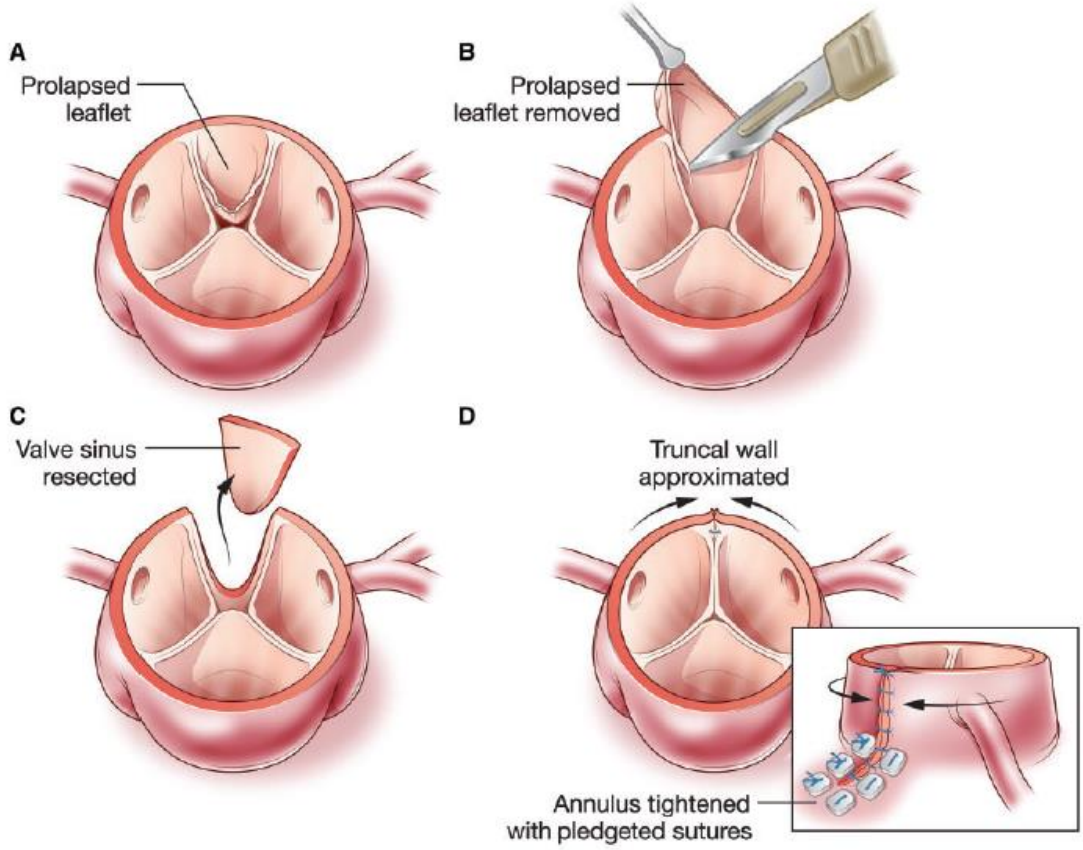

Figure 5: Cusp resection and annular reduction. First described by Imamura *et al.* [13] with tricuspidisation of a quadricuspid truncal valve. The smallest/incompetent leaflet is excised, along with the corresponding segment of the annulus. The remaining annular edges are sutured together to approximate the size of the ascending aorta.

univariable analysis for overall mortality ($P = 0.38$). Overall survival in neonates was 72.8 ± 5.8% (95% CI 59.4–82.3) at 20 years. Eleven neonates underwent concomitant TV surgery. Two neonates had severe TV insufficiency (quadricuspid TV, $n = 2$), 5 had moderate TV insufficiency (quadricuspid TV, $n = 3$; tricuspid TV, $n = 2$), 3 had mild TV insufficiency (quadricuspid TV, $n = 1$; tricuspid TV, $n = 2$) and 1 had no TV insufficiency (tricuspid TV, $n = 1$) but severe stenosis. Early mortality was 27% (3/11) (Fig. 2B), and overall survival was 62.3 ± 15.0% (95% CI 27.8–84.0) at 20 years. Neonatal TV surgery was not identified as a risk factor for mortality on univariable analysis ($P = 0.41$).

Of the 11 neonates who underwent concomitant TV surgery, 6 required TV reoperation (redo TV repair, $n = 1$; TV replacement, $n = 5$) at a median time of 250 days. Freedom from TV reoperation in neonates was 53.0 ± 17.6% (95% CI 17.0–79.7) at 1 year and 39.8 ± 17.5% (95% CI 9.5–69.6) at 10 years. In older patients ($n = 10$), the median time to TV reoperation was 5.7 years and freedom from reoperation was 100% at 1 year and 37.5 ± 17.1% (95% CI 8.7–67.4) at 10 years. There are 7 surviving neonates who underwent concomitant TV surgery, 4 of whom required TV replacement. The remaining 3 patients are free from reoperation, with mild or less TV insufficiency at the last follow-up. In the 37 surviving neonates who did not require concomitant TV surgery, 5 neonates required subsequent TV surgery at a median time of 6.5 years and 32 have mild or less TV insufficiency at the last follow-up.

DISCUSSION

TV insufficiency has been reported in approximately 25% of TA patients [7, 14]. There is no uniform approach in managing TV insufficiency, and its long-term impact is not well understood. It has been reported that patients with moderate or greater TV insufficiency have worse early outcomes [4–8, 15–21]. Our data show that there was no statistically significant difference between mortality and the degree of TV insufficiency, likely due to a small number of deaths. Russell *et al.* [7] reported the outcomes of 23 patients who had concomitant TV repair in a multi-institution review of 572 patients operated between 2000 and 2009. They reported a higher early mortality in patients who underwent concomitant TV repair (26%, 6/23) than those who underwent TA repair alone (10%, 53/545) [7]. Our study did not demonstrate a statistically significant difference in mortality in children undergoing concomitant TV surgery and those who did not.

Our data suggest that mild or less TV insufficiency is well tolerated and does not require intervention with a long-term freedom from TV surgery of 83.9% at 20 years. Patients with mild or less TV insufficiency in our cohort underwent concomitant TV surgery often to facilitate other procedures (e.g. unroofing of an intramural coronary artery) or due to TV stenosis. Conversely, most would agree that severe TV insufficiency must be addressed at the primary operation. Two patients in our cohort who had

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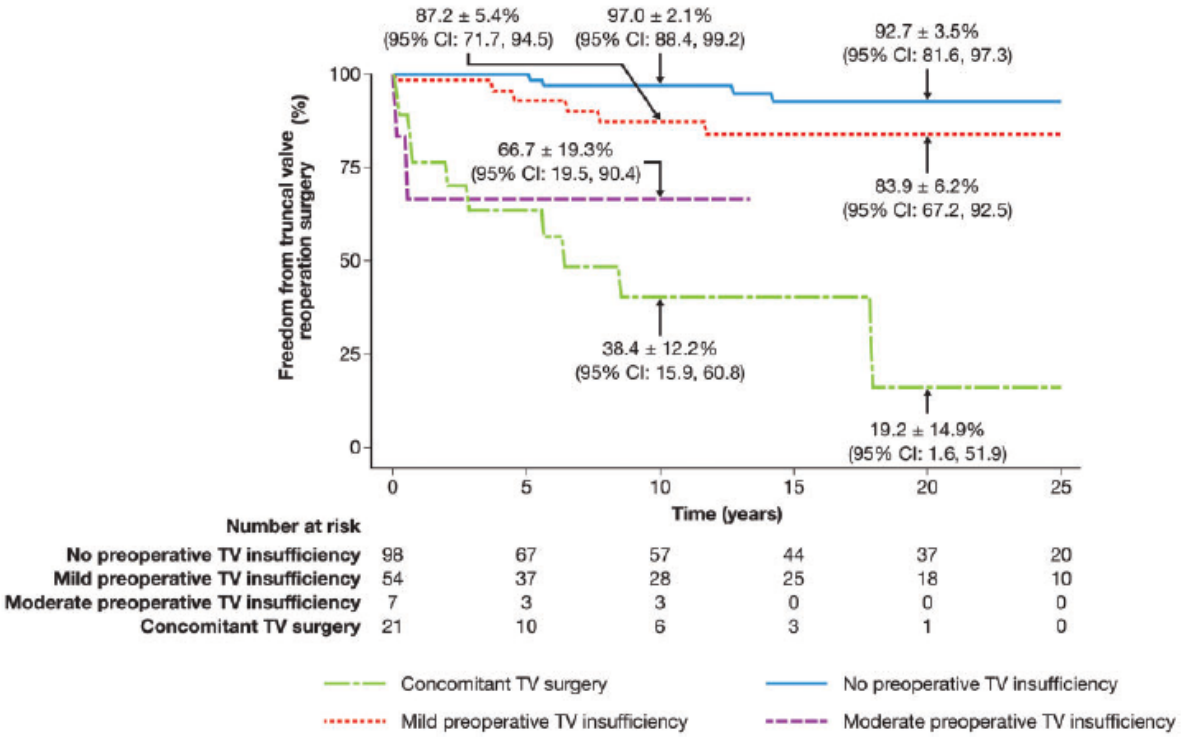

Figure 6: Freedom from TV reoperation surgery. Freedom from TV reoperation and subsequent TV surgery. TV: truncal valve.

Table 2: Outcomes of concomitant TV surgery

Study	Study period	Patients		Concomitant TV surgery		Concomitant TV repair, % (*n*/*N*)	Concomitant TV replacement, % (*n*/*N*)	Early mortality (overall), % (*n*/*N*)	Early mortality (neonates), % (*n*/*N*)	TV reoperation	Median follow-up (years)
		Total	Neonates	Total	Neonates						
Konstantinov *et al.* [4]	1987–1997	50	50	5	5	60 (3/5)	40 (2/5)	80 (4/5)	80 (4/5)	None	2.4
Henaine *et al.* [22]	1986–2003	153	134	9	NR	67 (6/9)	33 (3/9)	44 (4/9)	NR	2× TV replacements	8.1
Kaza *et al.* [8]	1995–2008	17	NR	14	NR	100 (14/14)	0	0	NR	5× redo TV repairs	2
Russell *et al.* [7]	2000–2009	572	NR	23	NR	96 (22/23)	4 (1/23)	26 (6/23)	NR	1× TV replacement 1× redo TV repair	NR
Russell *et al.* [23]	1979–2011	16	5	5	5	100 (5/5)	0	40 (2/5)	40 (2/5)	1× TV replacement	5.5
Myers *et al.* [21]	1997–2012	36	13	11	NR	100 (11/11)	0	27 (3/11)	3 deaths	7× redo TV repairs	3.2
Royal Children's Hospital	1979–2016	180	60	21	11	95 (20/21)	5 (1/21)	19 (4/21)	27 (3/11)	6× redo TV repairs 5× TV replacements	18

NR: not reported; TV: truncal valve.

severe TV insufficiency underwent TV surgery. Both were neonates and died. Contention arises in patients with moderate TV insufficiency. The decision to perform concomitant TV surgery in these patients is difficult. Obviously, concomitant TV surgery is more challenging and has been associated with higher mortality (Table 2), likely due to concomitant TV surgery often being required in younger and critically ill patients. This was not demonstrated in the current study—concomitant TV surgery was not associated with mortality. Our current approach is to repair the TV in children with moderate TV insufficiency, if possible. As shown in this study, most patients (76%, 13/17) with moderate TV insufficiency have required TV surgery at some point. This included 10 patients who underwent concomitant TV surgery and 3 who required subsequent TV surgery. Others [8, 22] have reported that moderate TV insufficiency is a risk factor for subsequent TV surgery if not addressed at TA repair.

Interestingly, most patients in our cohort who required TV surgery had a quadricuspid TV (concomitant, 57%, 12/21; subsequent, 50%, 7/14). Similarly, Russell *et al.* [23] reported that most patients who underwent TV surgery had a quadricuspid TV. In our cohort, most patients (79%, 15/19) with moderate or greater TV insufficiency had a quadricuspid TV; of whom, 11 have undergone TV surgery (concomitant, $n = 9$; subsequent, $n = 2$). In contrast, the remaining 39 patients with a quadricuspid TV and mild

or less TV insufficiency, only 2 required TV surgery. Based on this observation, we believe children with a moderate or greater TV insufficiency and a quadricuspid TV should undergo concomitant TV surgery.

Unfortunately, proportion of neonates is seldom reported; thus, the true impact of neonatal repair is not always feasible (Table 2). Clearly, concomitant TV repair in neonates would be the most challenging. One-third (60/180) of our patient cohort were neonates. This subgroup of patients had a significantly higher early mortality of 20% (12/60) compared to 7.5% (9/120) in older patients. As expected, children with more advanced degree of TV insufficiency required TV surgery earlier (Table 1). The timing of surgery is dictated by signs of heart failure. Over the study period, we tend to operate more during the neonatal period. Eleven neonates underwent concomitant TV surgery, with an early mortality of 27% (3/11), compared to 10% (1/10) in older patients (Fig. 2B). Similarly, Russell *et al.* [23] reported 5 neonates who underwent concomitant TV repair between 1979 and 2012 with an early mortality of 40% (2/5). This illustrates that management of neonates becomes much more complicated when concomitant TV surgery is required as they are often in a critical condition. Despite the challenges presented with neonatal TV surgery, neonates with moderate or greater TV insufficiency often present with overt signs of heart failure and we believe that there is no choice but to operate on the TV.

Although concomitant TV repair could be lifesaving, it has limited durability. Of our 20 patients who underwent concomitant TV 'repair', 12 required TV reoperation. Six neonates required TV reoperation with freedom from TV reoperation of 53% at 1 year and 40% at 10 years. Myers *et al.* [21] reported that 69% (9/13) of neonates who had TV repair required TV reoperation with freedom from TV reoperation of 23% at 10 years. Additionally, Kaza *et al.* [8] reported 29% (5/14) of patients who concomitant TV repair required TV reoperation with a freedom from TV reoperation of 50% at 7 years. Similar to others, we employed several surgical techniques for TV repair. Unfortunately, due to heterogeneity in TV morphology and surgical techniques, it is difficult to determine a specific surgical approach that offers the most durability. Rather than attempting to come up with the standardized technique of repair, one must individualize repair for each patient.

Limitations

This study is subject to the usual limitations of a retrospective study. Perioperative techniques may have changed over time. Due to heterogeneity in TV morphology, several surgical techniques were applied. Although all patients with moderate or greater insufficiency have undergone TV surgery since 2000, some patients with moderate insufficiency did not undergo concomitant TV surgery prior to 2000. Some variables contained a relatively small number of patients, thus limiting the multivariate analysis.

CONCLUSION

Most patients with mild TV insufficiency are free from TV surgery up to 25 years. The durability of TV repair is poor. Most patients with moderate or greater TV insufficiency and a quadricuspid TV will require TV surgery.

Conflict of interest: none declared.

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EDITORIAL COMMENTARY

CONG

Dead-space or dead-end: Can prolonged mechanical ventilation be predicted in all children after unifocalization?

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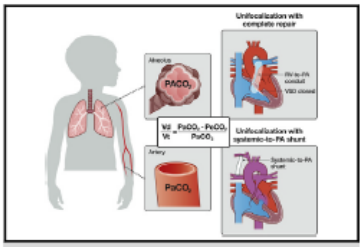

Bohr's formula might miscalculate dead-space ventilation fraction in patients with right-to-left shunting.

Central Message

Dead-space ventilation fraction might predict prolonged ventilation after unifocalization in pulmonary atresia, although this might not be applicable to patients with right-to-left shunting.

See Article page 1181.

An interesting study by Koth and colleagues[1] investigating the association between increased dead-space ventilation fraction (Vd/Vt) and prolonged mechanical ventilation in children undergoing surgery for tetralogy of Fallot, pulmonary atresia, and major aortopulmonary collaterals is published in this issue of *The Journal of Thoracic and Cardiovascular Surgery*. The study included 266 children who underwent unifocalization with complete repair and those who underwent unifocalization to a central shunt. The group has previously published the selection algorithm to determine if complete repair or shunting should be performed after unifocalization.[2] Complete repair with ventricular septal defect (VSD) closure was performed if pulmonary artery pressure remained <25 mm Hg at full flow via a separate perfusion circuit while still on full cardiopulmonary bypass, a right ventricle/left ventricle pressure ratio <0.5 can be expected after VSD closure.[2] If these criteria were not met the patients were shunted after unifocalization. Koth and colleagues concluded that an "elevated postoperative Vd/Vt is associated with prolonged ventilation in patients with tetralogy of Fallot/pulmonary atresia/major aortopulmonary collaterals after unifocalization."[1] To fully understand the study and its implications, one must delve into the basic science on which the current study is based.

In physiology, dead-space refers to the part of the tidal volume of air that does not take part in gas exchange in the lungs. Either this is because air remains in the airways where gas exchange does not occur or air reaches alveoli in lungs that are not adequately perfused. It was Danish physician Christian Bohr (1855-1911) who first described the equation of dead-space relative to tidal volume in 1891.[3] Bohr proposed that the difference between mean alveolar ($PACO_2$) and mixed expired ($PeCO_2$) partial pressures of CO_2 can be used to determine the proportion of the dead space. The equation was modified by Enghoff[4] in 1938 by substituting $PACO_2$, which was estimated using volumetric capnography in the Bohr equation, for arterial blood partial pressure of CO_2 ($PaCO_2$), from arterial blood gas sampling, to produce the formula applied by the authors:

$$\frac{Vd}{Vt} = \frac{PaCO_2 - PeCO_2}{PaCO_2}$$

When high concentrations of CO_2 from the venous blood reach the arterial side through intracardiac right-to-left shunting, $PaCO_2$ increases above $PACO_2$ level.[5] This would make $PaCO_2$ inappropriate for calculation of dead space volume in children with intracardiac right-to-left blood shunting. Such intracardiac right-to-left shunting occurs in all patients with pulmonary atresia, who could not achieve complete repair with VSD closure, but instead had systemic-to-pulmonary shunt after unifocalization (Figure 1). Furthermore, even corrections of Enghoff's dead space formula for shunt effects still overestimate Bohr's dead space.[5] The authors acknowledged this fact as a limitation of their study. Thus, it is not surprising that the group of patients with elevated Vd/Vt had a higher proportion of patients with postoperative shunt physiology (28% vs 14%; $P = .001$) compared with those with normal Vd/Vt.

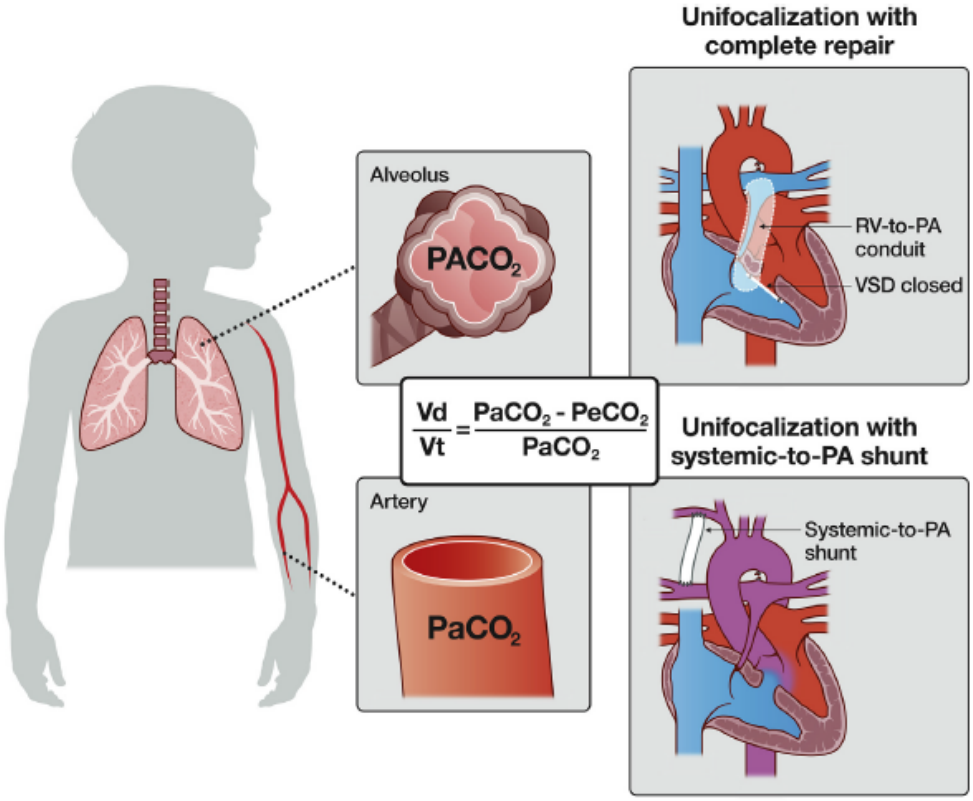

FIGURE 1. Enghoff's modification of Bohr's formula replaced alveolar partial CO_2 pressure (*$PACO_2$*) by arterial partial CO_2 pressure (*$PaCO_2$*) to calculate ratio between dead-space volume (*Vd*) and tidal volume (*Vt*). Although this formula is appropriate for patients who underwent unifocalization with complete repair, it might yield the wrong dead-space ventilation fraction (*Vd/Vt*) in those who underwent unifocalization without complete repair and were left with the right-to-left intracardiac shunt. Vd/Vt might predict prolonged ventilation after unifocalization in pulmonary atresia, although this might not be applicable to patients with right-to-left shunting. *RV*, Right ventricle; *PA*, pulmonary artery; *VSD*, ventricular septal defect.

In the analysis of all patients who had unifocalization, including both subgroups of patients (ie, complete repair and palliation with shunting), they showed that patients with an increased Vd/Vt were at a higher risk of prolonged ventilation compared with those with a normal Vd/Vt. An elevated Vd/Vt was not a risk factor for prolonged ventilation in multivariable analysis in either subgroup alone.

Although the results of this study should be interpreted with caution, this study is an important step forward. Identifying a noninvasive tool to reliably predict the risk for prolonged mechanical ventilation after unifocalization would be of great benefit to clinicians.

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ADULT

Commentary: A paradox of remote ischemic preconditioning: Remote understanding, remote relevance, and remote future?

Check for updates

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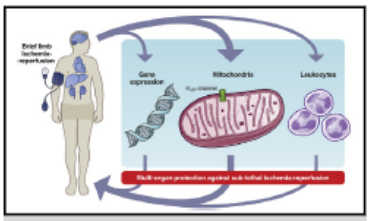

Limb ischemia-reperfusion induces changes that may result in multiorgan protection.

Central Message

Remote ischemic preconditioning may provide neuroprotection after heart surgery. The clinical relevance of such protection is yet to be demonstrated.

See Article page 1466.

Since its first description by Przyklenk and colleagues in 1993,[1] there has been an explosion of studies on the mechanism and clinical translation of remote ischemic preconditioning (RIPC). The simplicity, low cost, and safety of the clinical induction of RIPC make it an extremely attractive concept for researchers and clinicians alike. Paradoxically, despite feverish research over the past 2 decades, our understanding of RIPC remains as remote as ever. It is clear that RIPC profoundly modifies the genome and proteome[2-4] and that RIPC-induced protection can be blocked by sulfonylureas at the level of adenosine triphosphate-sensitive potassium channels in mitochondria (Figure 1).[5] It appears that combined with the direct effect at the level of mitochondria, genomic and proteomic changes result in decreased activation of leukocytes[3] and, perhaps, an overall decrease in inflammatory response to ischemia-reperfusion injury (IRI). Here the knowledge of the mechanism ends and a shadowy penumbra of unanswered questions begins. The lack of understanding of the mechanism of RIPC has not deterred the extensive research into its clinical translation.[6-8] Although the first clinical application in humans appeared promising,[8,9] multiple subsequent trials have failed to demonstrate any clinically significant benefit. Thus, the recent clinical research has only added to the confusion. Indeed, should RIPC confer clinically relevant multiorgan protection, the application of RIPC could be immense and applicable to any branch of medicine where IRI occurs, including transplantation, stroke, coronary angioplasty, and cardiac surgery.

Why is the powerful protective effect of RIPC against sublethal IRI—that has been so convincingly demonstrated in a great number of experimental studies—so hard to reproduce in clinical practice? It should be kept in mind that to have protection against sublethal IRI, one must, at minimum, have a sublethal IRI. Whereas in experimental animals, such sublethal IRI is consistently induced in a standardized fashion, we all try our very best to avoid sublethal IRI in our patients. Is inflammatory response to cardiopulmonary bypass in clinical practice comparable to sublethal IRI in experimental animals? Only those patients with sublethal IRI would be expected to benefit from the RIPC protection, and it is not possible to reproduce the same degree of sublethal IRI across all patients. Instead, mild IRI or hypoxia occurs in routine clinical practice in most of our patients. To solve a problem, one must have a problem. Could the RIPC protocol provide protection in the absence of meaningful IRI? Could this explain why the clinical application of RIPC to date has provided ambiguous results?

Gasparovic and colleagues[10] present a study on the effect of RIPC on inducing neuroprotection in patients undergoing coronary artery bypass grafting. They randomized 77 patients undergoing coronary artery bypass grafting to either a RIPC protocol or a sham procedure. Structural and functional connectivity magnetic resonance imaging as well as neurocognitive testing was performed postoperatively. Although the study was underpowered for the primary end point, elegant magnetic resonance imaging scans were used to calculate the pooled volume of ischemic lesions and to assess brain functional connectivity. They found that an almost equal number of patients in each group

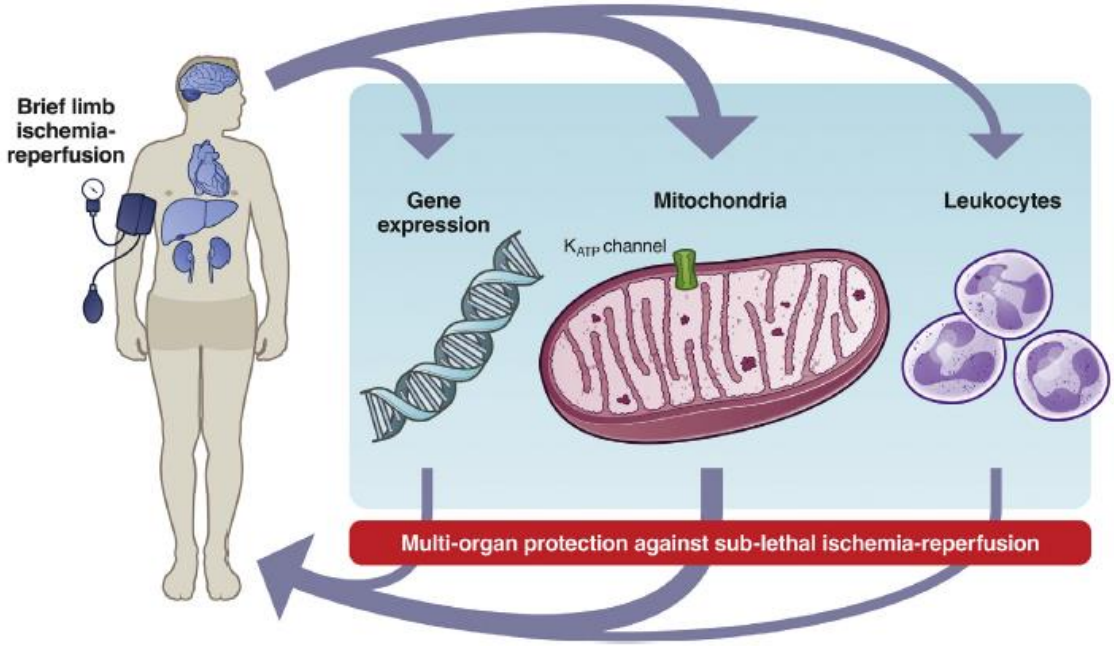

FIGURE 1. Overview of the remote ischemic preconditioning. Brief intermittent limb ischemia-reperfusion induces changes at the molecular, organoid, and cellular levels that collectively may result in multiorgan protection against subsequent sublethal ischemia reperfusion. K_{atp}, Adenosine triphosphate-dependent potassium channel.

had new ischemic brain lesions (27% in the RIPC group vs 24% in the control group). Yet, the RIPC group had a lower pooled volume of ischemic lesions. There was no statistically significant difference in postoperative neurocognition between the groups. If there is no difference in neurocognition, then one might ask about the clinical relevance of their results. Considering that 2 recent large clinical trials failed to show any clinically relevant benefit of the RIPC protocol,[6,7] what is the future of RIPC? Should it be abandoned? The concept of RIPC looks too attractive to dismiss. With the recent rapid progress in so-called omics technology and inducible pluripotent human stem cells modeling, it may be possible to dissect the mechanisms of RIPC in the not-too remote future.

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A.11. Fricke TA et al. J Thorac Cardiovasc Surg 2019;157:997-998.

COMMENTARY

ADULT

Alternative splicing in heart surgery: Lost in translation?

Check for updates

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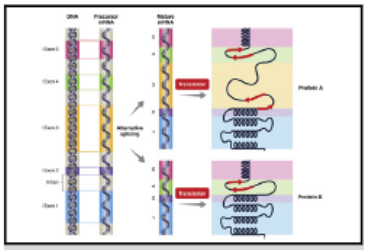

A phenomenon of alternative splicing occurs when 1 or more exons are not translated.

Central Message

Cold-inducible RNA-binding protein may be protective against cardiopulmonary bypass-induced brain injury.

See Article page 986.

Relentless pressure of survival has shaped molecular evolution in the most unusual ways. Among the stunning examples of such molecular evolution is the ability of some animals to withstand the rigors of winter. With no escape from the cold, some animals fall into hibernation. These animals have developed an amazing ability to survive winter by slowing their metabolism and saving vital energy. An astute mind cannot help but wonder if such a remarkable adaptation could be utilized for the benefit of patients undergoing heart surgery.

It appears that the decrease in body temperature that occurs in a hibernating animal or in a patient undergoing heart surgery with hypothermia induces rapid production of cold-inducible RNA-binding protein (CIRP).[1] CIRP is an evolutionarily conserved RNA-binding protein that is ubiquitously expressed in both animals and humans.[2] It has a number of roles and is upregulated in hypothermia, hypoxia, and inflammation.[3] The expression of CIRP peaks during temperatures of 28°C to 34°C and may have a neuroprotective effect in cold temperatures.[2] It appears that temperature-regulated alternative splicing may result in translation of different proteins in normothermia and hypothermia. Through alternative splicing, a rapid increase in CIRP levels is produced during hypothermia compared with normothermia where a dominant-negative protein overrides the functional form of CIRP.[1] Alternative splicing is nature's way by which 2 or more distinct proteins can be translated from a single gene (Figure 1). Can protection be lost in translation or gained? Alternative splicing may become a valuable, innate switch readily available for clinical use in surgery in the era of personalized genomic medicine. However, such clinical translation has to be used with caution until the end effects of the CIRP are fully elucidated. This is particularly important because other studies have highlighted CIRP's potent proinflammatory effects. In a murine model of liver ischemia-reperfusion, it was demonstrated that anti-CIRP treatment reduced the severity of ischemia-reperfusion injury.[4] Similarly, anti-CIRP treatment reduced the severity of renal ischemia-reperfusion injury in yet another murine model.[5] In humans, increased levels of CIRP were found in patients admitted to an intensive care unit with hemorrhagic shock[6] and have been found to be a prognostic indicator of poor outcome in patients with sepsis.[7] Further research has demonstrated that in sepsis, CIRP caused the release of proinflammatory cytokines from macrophages[6] and activated splenic T cells.[8]

Liu and colleagues[9] offer an insightful and thought-provoking article on the effect of CIRP on cardiopulmonary bypass (CPB)-induced brain injury. The authors divided 15 rats into 3 groups (ie, sham group, CPB group, and CPB group without CIRP expression). Rats were placed on CPB (or in the case of the sham group, cannulated without institution of CPB), cooled to 32°C, and arrested for 30 minutes before reperfusion. They found that in rats genetically engineered to not express CIRP there was more histologic evidence of disruption of the blood-brain barrier as well as a more severe injury to hippocampal neurons. This led to the conclusion that CIRP was protective against CPB-induced brain injury by reducing the breakdown of the blood-brain barrier. This is an exciting study because deeper insight into manipulation of alternative splicing may provide clinicians with a subtle, yet powerful, means of natural protection during the metabolic stress of surgery. Will this study translate into clinical practice? Time will tell.

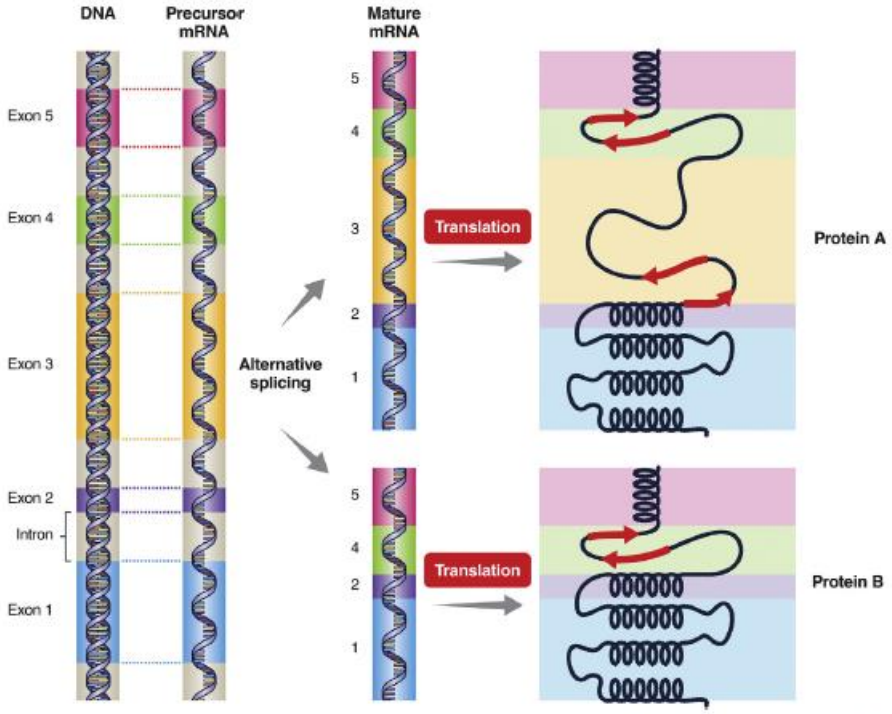

FIGURE 1. A phenomenon of alternative splicing occurs when 1 or more exons are not translated. This results in production of different proteins from the same gene. *mRNA*, Messenger RNA.

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A.12. Fricke TA, Konstantinov IE. Ann Thorac Surg 2019;107:302-310.

Arterial Switch Operation: Operative Approach and Outcomes

Check for updates

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The arterial switch operation has excellent early outcomes. Although the majority of patients are growing into healthy adults, a small subset require reoperation for pulmonary stenosis as well as neoaortic root dilatation and neoaortic valve regurgitation, especially as follow-up increases. Challenging subgroups include patients with anomalous coronary anatomy, concomitant aortic arch obstruction, Taussig-Bing anomaly, ventricular septal defect, and low operative weight, and patients with an intact interventricular septum who present late.

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REVIEW

The arterial switch operation (ASO) is one of the greatest achievements of pediatric cardiac surgery. Various palliative operations, including the atrial switches, were used to correct transposition of great arteries (TGA) before the first successful ASO by Adib Jatene on May 8, 1975, in São Paulo [1, 2]. Despite initial success, surgeons were hesitant to perform the ASO instead of the well-established and much safer atrial switch procedure [1]. In the 1980s, operative mortality for the ASO was as high as 30% to 60% and it was not until the 1990s that a low operative mortality was accomplished across most high volume institutions [3, 4]. A dramatic decrease in operative mortality was achieved in Melbourne by the Royal Children's Hospital team headed by Roger Mee [5]. The novel technique of medially hinged trapdoors for coronary translocation (Fig 1) was introduced in Melbourne and simplified the ASO. Indeed, the operative mortality was decreased at the Royal Children's Hospital to only 1.6% (2 of 129) for children with TGA who underwent the ASO from 1983 to 1989 [6].

Methods

A structured review of literature was performed using PubMed and MEDLINE databases. The search strategy involved combinations of the terms *arterial switch operation*, *transposition of the great arteries*, *aortic arch obstruction*, *Taussig-Bing anomaly*, and *outcomes*. The last search was conducted in December 2017.

Current Outcomes of the ASO

MORTALITY. Early mortality after the ASO in the modern era is reported between 1% and 3% [6–8]. Mortality is higher in more complex forms of transposition including Taussig-Bing anomaly (TBA) and TGA with aortic arch obstruction (AAO), such as coarctation of aorta (COA) or interrupted aortic arch (IAA) [9–11]. We have previously reported an operative mortality of 2.8% in 618 children with TGA, who underwent ASO from 1983 to 2009 at the Royal Children's Hospital, with an operative mortality higher for those with a ventricular septal defect (VSD) compared to those with an intact interventricular septum (IVS) (3.8% versus 1.8%) [6]. Long-term survival for our patients was 96% at 20 years postoperatively, similar to that reported by others [8, 12]. While not often the focus of ASO studies, postoperative morbidity has been shown to be significantly higher in more complex anatomy requiring the ASO with respect to longer duration of ventilation and postexubation hospital stay [13].

REOPERATION. Most reoperations after the ASO occur after the first postoperative year. Freedom from reoperation has been reported in a range of 79% to 97% at 10 years [12, 14–18], 76% to 87% at 15 years [14, 15, 18, 19], and 86% at 25 years (Table 1) [12].

The most common cause of late reoperation is pulmonary stenosis (PS) [12, 15, 17, 19–25]. The majority of the stenoses occur at the suture line in the neopulmonary artery and proximal pulmonary artery branches [12, 17, 26, 27]. The precise reason for PS post-ASO is unclear, but may be related to inadequate growth of the pericardium used to reconstruct the pulmonary artery, narrowing at the suture line or flattening of the pulmonary artery due to the neoaortic root pushing it anteriorly [26]. After a mean follow-up of 10.6 years, 2.6% of 618 patients operated at our institution required reoperation and another 2.6% required catheter reintervention for PS [6].

Reoperation for neoaortic root dilatation (neo-ARD) and neoaortic valve regurgitation (neo-AR) remains low in young adult survivors. The exact mechanism of neo-ARD is unknown, but it has been postulated that dedifferentiation of smooth muscle cells in the wall of the neoaortic root, ultimately promoting dilatation, may be a contributing factor [28]. Neo-ARD can be seen in up to 50% of ASO survivors by 10 to 15 years of age [29, 30].

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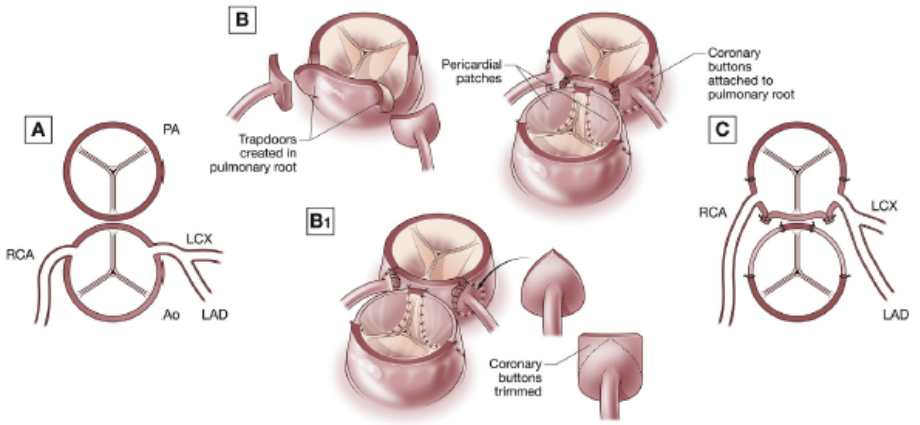

Fig 1. Trapdoor technique for arterial switch operation. (A) Following identification of coronary anatomy, (B) medially based trapdoors are made in the native pulmonary (neoaortic) root. To avoid further enlargement of the neoaortic root, (B1) the coronary buttons are trimmed and (C) coronary transfer is completed in standard fashion. (Ao = aorta; LAD = left anterior descending; LCX = left circumflex artery; PA = pulmonary artery; RCA = right coronary artery.)

Likewise, the mechanism of neo-AR is also unclear and is likely to be multifactorial. It has been suggested that neo-AR in ASO survivors may be the result of altered geometry of the neoaortic root or turbulence caused by the differences in size between the neoaortic root and the distal aorta, both of which have the potential to inhibit coaptation of the valvular leaflets [31, 32].

Aortic root and aortic valve surgery after ASO occurs in approximately 2% of patients at 10 years [6, 19, 33]. Of 720 patients who underwent ASO at the Royal Children's Hospital from 1983 to 2009, only 15 (2.1%) underwent surgery on the neoaortic root or neoaortic valve after ASO at a mean 8.8 years [34]. Freedom from neoaortic root or valve surgery in our institution was 95% at 20 years. Neo-ARD and neo-AR can be progressive, and a number of adult ASO survivors may require neoaortic root replacement in the coming years. In keeping with this, more reports of neoaortic root or valve replacement in patients in the second decade of follow-up have appeared in the literature as follow-up of ASO patients increases [8, 12, 14, 35]. This was evident in the study of Koolbergen and colleagues [35]. In their cohort of 391 ASO patients, freedom from neoaortic root reoperation was 99.3%, 97.3%, and 95% at 5, 15, and 20 years respectively.

Long-Term Cognitive Outcomes and Quality of Life After ASO

Data on cognitive outcomes and quality of life in adult survivors after the ASO are scarce. More focus is likely to be placed on this area as larger numbers of ASO survivors reach adulthood, the majority with very good cardiovascular function. We have investigated quality of life using the 36-Item Short Form Health Survey in 107 adult ASO survivors and compared their results with age and gender-matched population data [36]. Our results suggested that quality of life in ASO survivors is similar to that of the general population. Likewise, this topic was recently addressed by Kalfa and colleagues [37], who investigated cognitive and quality-of-life outcomes in 67 adult ASO survivors 18 to 31 years of age. In their study, despite patients reporting an overall satisfying quality of life, cognitive difficulties and impairments occurred in 31% of survivors compared with 16% in the general population. These cognitive issues may have significant effects on patients' daily functioning including the ability to achieve academic success. More research is needed in this area.

Challenging Subgroups Undergoing the ASO

Despite excellent early and long-term outcomes of the ASO in most patients, the ASO can be challenging in certain subgroups. These subgroups include patients with unusual coronary artery anatomy, concomitant AAO, VSD, TBA, low operative weight, and those with an intact IVS who present late.

Coronary Artery Anomalies

Anomalous coronary arteries are common in patients undergoing the ASO, making up approximately one-third of children operated [6, 38, 39]. The most common variant of coronary anatomy pattern is the left anterior descending artery arising from sinus 1 and right coronary and left circumflex coronary arteries arising from sinus 2 [6, 12, 38, 39]. Such variation occurred in 16.5% of our patients [6]. A single coronary artery is the next most common abnormal pattern and occurs in 6% to 7% [6, 12, 40].

There are conflicting data in the literature on whether abnormal coronary artery pattern is a risk factor for death [6, 38–48]. The meta-analysis by Pasquali and colleagues [41] of 1942 patients reported that any variant of coronary artery anatomy doubled the risk of death compared with normal coronary anatomy. In particular, the risk of death in patients with a single coronary artery or intramural coronary artery increased almost 3-fold and 7-fold,

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Table 1. Large Outcome Studies on the ASO

Author	Year Published	Number of Patients	Time Period Operated	Follow-Up Time (years)	Hospital Mortality (%)	Survival	Freedom From Reoperation	Neoaortic Root or Valve Reoperation
Losay et al [64]	2006	1,265	1982–2000	Median 6.3	8.4	NR	NR	Freedom of 98% at 10 years
Angeli et al [14]	2008	803	1987–2007	Mean 5.8	3.8	1.4% deaths after discharge	86% at 15 years, 88% at 10 years	1 patient
Fricke et al [6]	2012	618	1983–2009	Mean 10.6	2.8	96% at 10 and 20 years	87% at 15 years including catheter reintervention	Freedom of 97.7% at 15 years
Khairy et al [12]	2013	400	1983–1999	Median 18.7	6.5	96.7% at 20 years excluding hospital mortality	86% at 25 years	NR
Lo Rito et al [8]	2015	362	1988–1998	Median 16	8.6	98% at 10 years excluding hospital mortality	NR	Freedom of 99.3% at 10 years
Michalak et al [18]	2017	715	1991–2015	Mean 10.5	7.4	2.5% deaths after discharge	94% at 15 years	NR

ASO = arterial switch operation; NR = not reported.

respectively. As the patients included in this meta-analysis were operated on between 1977 and 1999, this study may not have direct clinical relevance to today's operative outcomes. In our cohort of 618 patients operated for TGA between 1983 and 2009, anomalous coronary artery patterns were not a risk factor for mortality [6]. This included patients with single coronary arteries, which can be managed even in the most difficult of scenarios. We have previously described the use of an interposition graft to translocate a single coronary from the nonfacing sinus (Fig 2) [49]. This patient was alive and well with angiographic evidence of a patent graft and coronaries 20 years after ASO.

In addition to single coronary arteries, patients with intramural coronary arteries also present a surgical challenge with conflicting results in the literature. New techniques to deal with this challenge are still being described [50, 51]. Metton and colleagues [43] reviewed 46 patients with intramural coronary arteries of a cohort of 919 patients who underwent ASO between 1987 and 2008. They found a mortality of 28%, including 11 deaths before discharge and 2 deaths at 51 and 105 days. Nine of the 11 deaths were deemed secondary to coronary complications. Conversely, Thrupp and colleagues [48] reported 1 death (5.6%) in 18 patients with intramural coronary arteries out of 215 patients who underwent ASO between 1996 and 2006. They found that an intramural coronary artery was not a risk factor for mortality in their cohort of 215 patients, and all survivors were asymptomatic after a median follow-up of 6.8 years. We have previously published outcomes of 28 patients with an intramural coronary artery and described the technique of coronary artery trasfer in detail [44] (Fig 3). No deaths occurred in the 28 patients at mean follow-up of 16.3 years. Although anomalous coronary arteries present a technical challenge during the ASO, children with single and intramural coronary arteries can undergo ASO with excellent long-term results.

Aortic Arch Obstruction

Patients with TGA and AAO, due to COA, hypoplastic aortic arch, or IAA, are uncommon, and constitute about 5% of all children undergoing the ASO [6]. IAA is a particularly rare problem in children undergoing ASO, and occurred in 0.7% of patients at our institution [10]. Only approximately 6% to 10% of children with IAA have TGA [52–54]. Because of the rarity of the combination of IAA and TGA, surgical experience is limited [10, 11, 16, 55]. Although a 2-stage repair of IAA via thoracotomy and subsequent ASO can be performed [10, 52], single-stage ASO with IAA repair is now the preferred approach [10, 56]. It should be kept in mind that some children with TGA-IAA-VSD may have concomitant hypoplasia of the morphological right ventricle. This may preclude VSD closure and require PA banding after ASO and IAA repair [56].

The favored arch repair at the Royal Children's Hospital in Melbourne is an end-to-side repair [54]. This involves dissection and divison of the first 3 pairs of intercostal arteries, a longitudinal incision in the inner curvature of the ascending aorta in front of the

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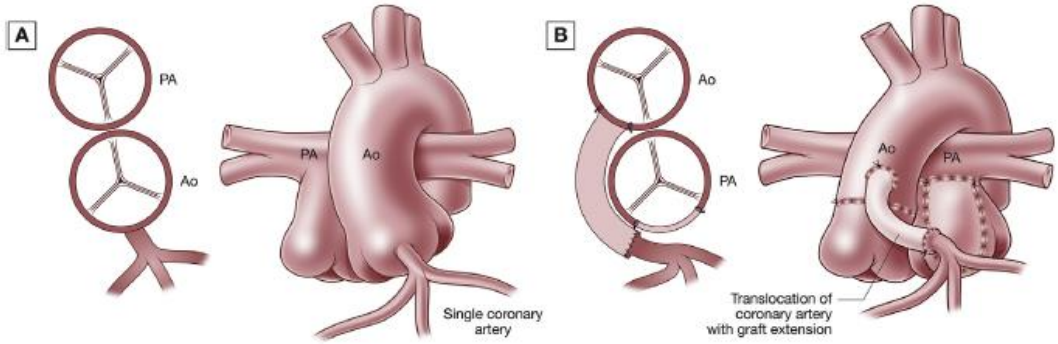

Fig 2. Single coronary artery transfer from nonfacing sinus. (A) The single coronary artery from the nonfacing sinus is translocated to (B) the neoaortic root faciliated by an interposition graft. (Ao = aorta; PA = pulmonary artery.)

emergence of the innominate artery, and anastomosis of the descending aorta to the ascending aorta (Fig 4). Others have described arch repair with patch augmentation and alternative techniques such as the swing-back technique [57].

Outcomes of single-stage ASO and AAO repair are limited to a few studies [10, 16, 55, 58]. The AAO is a risk factor for mortality [6], with early mortality in these patients reported from 7.9% to 24% [6, 16, 55]. Low operative mortality after concomitant AAO repair can be achieved

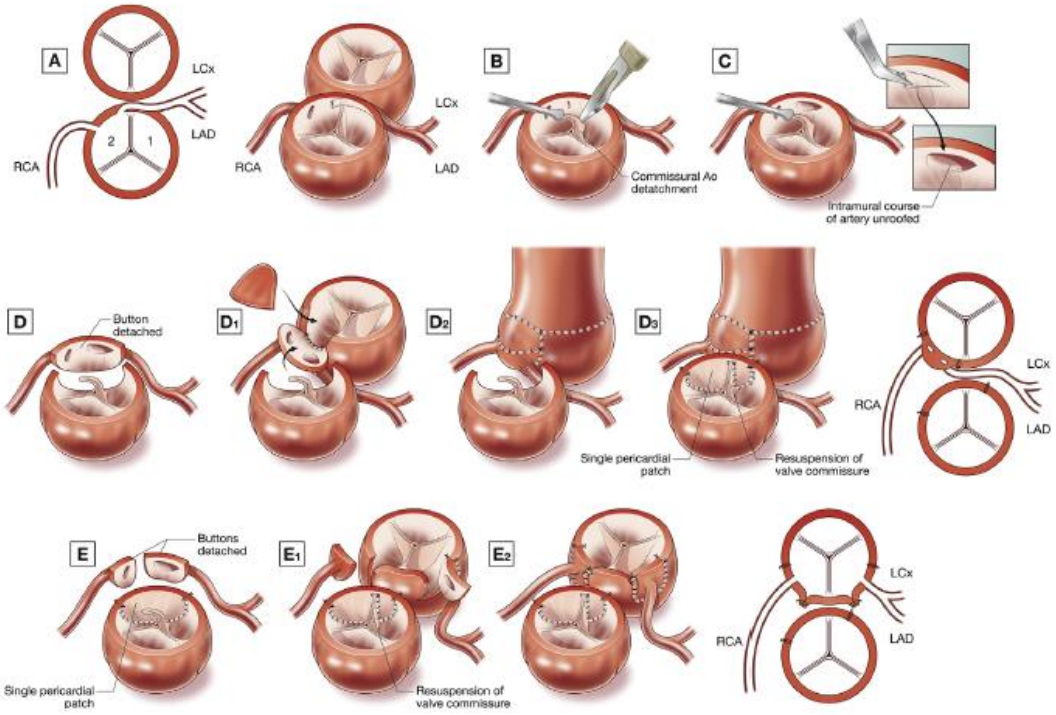

Fig 3. Transfer of intramural coronary. (A) Following identification of the intramural segment (1 = sinus 1; 2 = sinus 2), (B) the detachment of the posterior commissure of the aortic (neopulmonary) valve was performed in most patients (n = 25). (C) The unroofing of the intramural coronary artery was done in 16 patients. (D) Then the coronary arteries were detached and transferred either as a single button facilitated with a pericardial hood (D1–D3) in the first 3 patients or (E) as 2 separate buttons using the trapdoor technique (E1–E2) in the next 25 consecutive patients. In all patients the pulmonary artery was reconstructed with a single autologous pericardial patch and the posterior neopulmonary commissure was re-attached to it. (Reproduced from [44] with permission from The Society of Thoracic Surgeons.) (LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.)

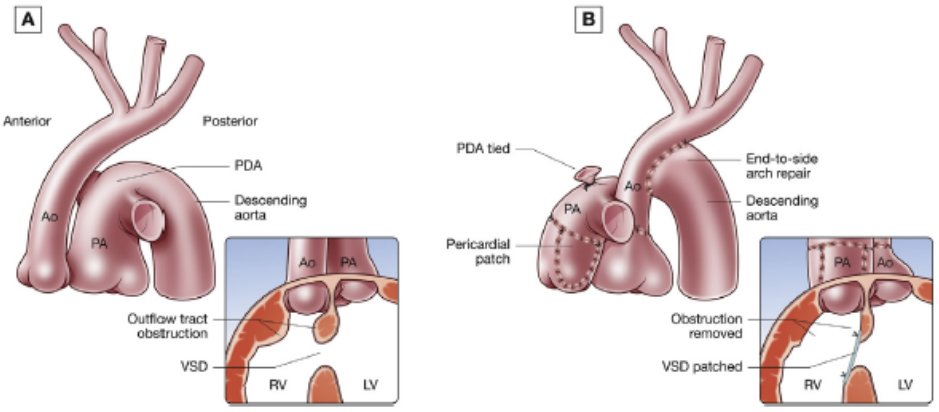

Fig 4. Repair of aortic arch obstruction and arterial switch operation. (A) Interrupted aortic arch with transposition of the great arteries and associated subneopulmonary obstruction. (B) Lecompte maneuver with end-to-side anastomosis of descending aorta (Ao) to ascending Ao, and resection of subneopulmonary obstruction is performed to reconstruct the aortic arch and prevent subpulmonary stenosis. (LV = left ventricle; PA = pulmonary artery; PDA = patent ductus arteriosus; RV = right ventricle; VSD = ventricular septal defect.)

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with [58] or without patch augmentation [6]. Hirata and colleagues [58] reported an operative mortality of 1.9% in 53 patients, including TGA (n = 33) and TBA (n = 20), who underwent ASO and COA repair from 1991 to 2006. Similarly, there were no operative deaths in 36 patients with both TGA (n = 19) and TBA (n = 17) operated from 1992 to 2009 at our institution [6, 9].

Reoperation is also higher in patients undergoing ASO with AAO repair [16, 55, 58]. We have previously reported a reintervention rate of 25.2% in patients with VSD and 23.4% in patients with AAO as compared with that of 5.9% in patients with an IVS at 15-year follow-up [6].

Late neo-ARD and neo-AR may also be concerns in patients with AAO and VSD. Of the 720 patients who underwent an ASO between 1983 and 2009 at our institution, 15 patients required reoperation on the neoaortic root or valve at mean follow-up of 14.5 years. Of these 15, 11 had a VSD, including 2 patients with concomitant IAA and 1 patient with isolated COA [34]. In as much as the need for reoperation for neo-ARD is infrequent, it may become more prevalent as the follow-up of these patients after ASO increases. It also appears that late PS and right ventricular outflow tract obstruction (RVOTO) are more common in patients with AAO, VSD, or TBA [16, 55, 58–61]. Patients may be at a risk of late PS due to the native aortic annulus often being relatively small with or without concomitant RVOTO [55, 58]. Bokenkamp and colleagues [55] found that 10 patients required reoperation for PS in 45 patients with prior AAO repair at a median follow-up of 6 years. Pocar and colleagues [16] reported 3 reoperations for PS in 38 patients with prior AAO repair after a follow-up of 8 years. Close follow-up of ASO survivors with repaired AAO is necessary given the increased risk of late reoperation.

Ventricular Septal Defect

A VSD is seen in approximately one-third of patients with TGA [6, 12]. Operative mortality is slightly higher in patients with VSD, although many studies examining mortality in TGA with VSD have included patients with more complex forms of transposition such as TBA and AAO [19, 46, 62, 63]. The presence of a VSD has not consistently been shown to be an independent risk factor for mortality across larger studies [6, 12, 19]. However, it is clear that patients with VSD require more re-interventions in the long term, with more than 20% of these patients requiring reintervention by 20 years [6, 12]. This is likely due to patients with VSD requiring more reintervention for PS as well as reoperation for a broader range of problems (eg, subaortic stenosis resection, pacemaker implantation, mitral valve repair, residual VSD closure) [6]. Furthermore, more patients with VSD seem to require neoaortic root or valve replacement in the second decade after repair [6, 34]. Statistical significance is difficult to demonstrate, owing to the rarity of these operations. However, it has been shown that the presence of a VSD is a significant risk factor for neo-AR, multiplying the risk of late neo-AR by 4 times [64].

Taussig-Bing Anomaly

Using the van Praagh definition, TBA is a form of true double-outlet right ventricle with the semilunar valves side by side and approximately at the same height, a bilateral conus in which both conal free walls are muscular and approximately equally developed, and a subpulmonary VSD [65, 66]. Owing to septal malalignment, subvalvular PS and AAO is very common in such patients [9, 59–61] (Fig 5). More than half of TBA patients have AAO [9, 59, 61].

Overall ASO carries higher mortality and reoperation rates in patients with TBA compared to patients with TGA [9, 42, 61, 67]. Operative mortality of 5% to 6% has been reported in the 2 largest studies [9, 60]. Our experience of 57 patients with TBA who underwent the ASO in our institution over a 25-year period demonstrated an operative mortality of 5% (3 of 57), survival of 94%, and

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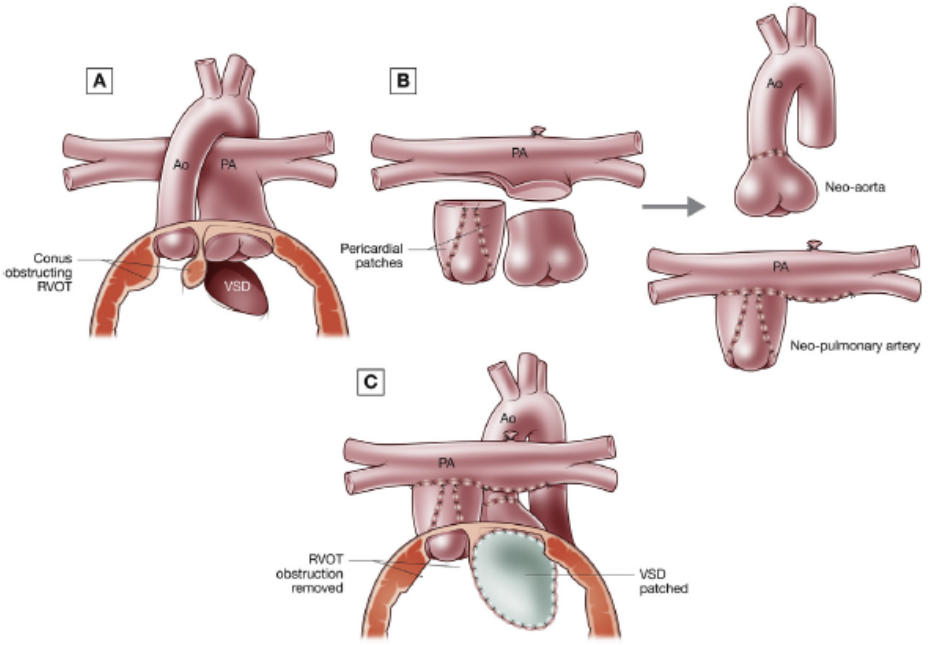

Fig 5. Arterial switch operation in Taussig-Bing anomaly. (A) Patients with Taussig-Bing anatomy often have size discrepancy between aorta (Ao) and pulmonary artery (PA) and may develop right ventricular outflow tract (RVOT) obstruction due to subaortic conus. (B) Due to side-by-side arrangement of the Ao and PA, a newly reconstructed main PA is reimplanted into the right PA. (C) Conal septum is resected before ventricular septal defect (VSD) closure to avoid RVOT obstruction.

freedom from reintervention of 75% at 15 years [9]. Technical complexity of repair due to associated anomalies likely accounts for the higher mortality and reoperation rate. The risk of recurrent subneopulmonary obstruction has been reported to be as high as 57% after 5 years [68]. At our institution, 6 (13.3%) of 45 survivors had RVOTO before ASO and all 6 underwent resection of this muscular subneopulmonary obstruction at the time of ASO. One (2.2%) of 45 survivors developed subneopulmonary obstruction after ASO and required resection. This patient was not 1 of the 6 patients who required resection at the time of ASO. Thus, we believe that resection at the time of ASO eliminated the recurrence of subneopulmonary obstruction in our patients [9]. While not seen in our group, possibly due to the number of patients and a mean follow-up time of 9.8 years, there is the risk of reoperation for neo-AR in these patients with TBA. Vergnat and colleagues [60] reported outcomes of 69 patients, the largest series of TBA to date, and demonstrated cumulative incidence of reinterventions at 10 years of 53%. After a median follow-up of 11.2 years, 5 patients required reoperation for RVOTO and 5 patients required neoaortic valve replacement. Their results highlight the frequent need for late reintervention in TBA survivors and the necessity of ongoing follow-up and surveillance for PS, neo-AR, and neo-ARD.

Low Operative Weight

Low body weight (LBW) remains a challenge when performing an ASO and is a risk factor for operative mortality [6, 69, 70]. Infants with LBW are often premature and are at a higher risk of infection, renal failure, respiratory disease, cerebral hemorrhage, and necrotizing enterocolitis [71]. At present, only 2 studies have dealt specifically with outcomes in LBW children undergoing the ASO [69, 72]. The first is by Roussin and colleagues [72], who examined 25 infants with TGA who were operated at a weight of less than 2 kg. These patients either underwent an ASO (n = 20), Senning procedure (n = 1), or various palliative procedures (n = 4). Operative mortality of 16% (4 of 25) in these LBW children. The second study comes from our institution, which studied 31 patients who underwent an ASO at less than 2.5 kg [69]. Our mortality for children less than 2.5 kg who underwent an ASO was 19% compared with a mortality of 1.9% in children above 2.5 kg. Only 1 of the 21 patients above 2.0 kg but less than 2.5 kg died, compared with 5 of the 10 children who were 2.0 kg or less. Long-term outcomes were comparable to children who were not LBW. At our institution, in LBW children all vascular anastomoses are performed with 8-0 Prolene (Ethicon, Somerville, NJ) and an 80-degree cannula placed from the right atrial appendage into the superior vena cava to avoid direct cannulation of the superior vena cava. These children represent a challenging and uncommon subgroup of patients with a high operative mortality.

Late ASO in Intact IVS

Delayed presentation of TGA with an IVS presents a rare and controversial clinical decision-making challenge. An ASO would usually be considered "late" in a child more than 3 or 4 weeks of age. Three options remain in this clinical situation. First, the possibility of an atrial switch exists; however, long-term results in atrial switch

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survivors may be suboptimal in regard to survival, systemic right ventricular failure, baffle obstruction, and arrhythmia [73]. Placement of a pulmonary artery band with an ASO being performed as soon as 7 to 10 days later (2-stage ASO) is another possibility [74]. However, early complications between stages as well as an increase in late complications such as left ventricular (LV) dysfunction, AR, and RVOTO have been documented [75, 76]. The largest study of late ASO outcomes is by Kang and colleagues [76]. They compared outcomes of 275 TGA-IVS patients operated within 3 weeks of age and 105 patients operated after 3 weeks. They found no significant difference in operative mortality (3.8% versus 5.5%) or need for mechanical circulatory support (3.6% versus 5.7%) between early and late ASO groups. The mechanical ventilation and length of hospital stay were longer in the late ASO group. Their experience and results lead them to perform a primary ASO in children up to 3 months of age; however, they advised that children beyond 3 months of age require careful assessment of LV conditioning before deciding between an ASO and atrial switch. Others have reported their experience with the late ASO [77].

Another approach to the late TGA-IVS presentation has been to perform a primary ASO and place a LV assist device (LVAD) at the same time if needed. The LVAD shares the burden of systemic pressures with the left ventricle and as soon as the left ventricle is deemed able to eject unaided, the LVAD is removed. A successful use of an elective LVAD at time of ASO for a 9-month-old child with TGA-IVS has been reported from our institution [78]. This child was supported with an LVAD for 8 days with normal LV function on echocardiography 3 months post-ASO. Two other single-case reports of successful late ASOs using a LVAD in 8-month-old and 9-month-old children have also been reported [79, 80]. It appears that this approach may be reasonable in the modern era; however, long-term results are still to be published.

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Conclusion

The ASO has excellent early outcomes. While the majority of patients are growing into healthy adults, a small subset require reoperation for PS as well as neo-ARD and neo-AR, especially as follow-up increases. Challenging subgroups include patients with anomalous coronary anatomy, concomitant AAO, TBA, VSD, low operative weight, and patients with an intact IVS who present late. Lifelong follow-up and research into the outcomes of adult survivors of the ASO is necessary.

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REVIEW

A.13. Fricke TA, Konstantinov IE. J Thorac Cardiovasc Surg 2019;157:504-505.

ADULT

EDITORIAL

A win in protection against ischemia-reperfusion injury?

Check for updates

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Igor E. Konstantinov, MD, PhD, FRACS, and Tyson A. Fricke, MBBS, BMedSci

Central Message

Synthetic cannabinoid agonists may provide protection against ischemia reperfusion injury.

See Article page 494.

The human race has used plant-derived cannabinoids, most commonly referred to today as marijuana, for more than 6000 years.[1] The first record of the medical application of the strong anti-inflammatory effect of cannabinoids comes from the world's oldest pharmacopoeia, which was found in China.[1] During the early 1990s, the endogenous ligand for cannabinoid receptors, anandamide, was identified.[2] The name of the naturally occurring fatty acid derivative anandamide comes from the Sanskrit word *ananda*, which means bliss, delight, or joy, a description that very well reflects its strong anti-inflammatory, pain-relieving properties.[2] Recently, the therapeutic anti-inflammatory effect of synthetic fatty acid derivative WIN55212-2, a nonselective cannabinoid agonist of cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors, has been explored. These cannabinoid receptors belong to the G-protein coupled receptor family and play a key role in downstream intracellular regulation of apoptosis and

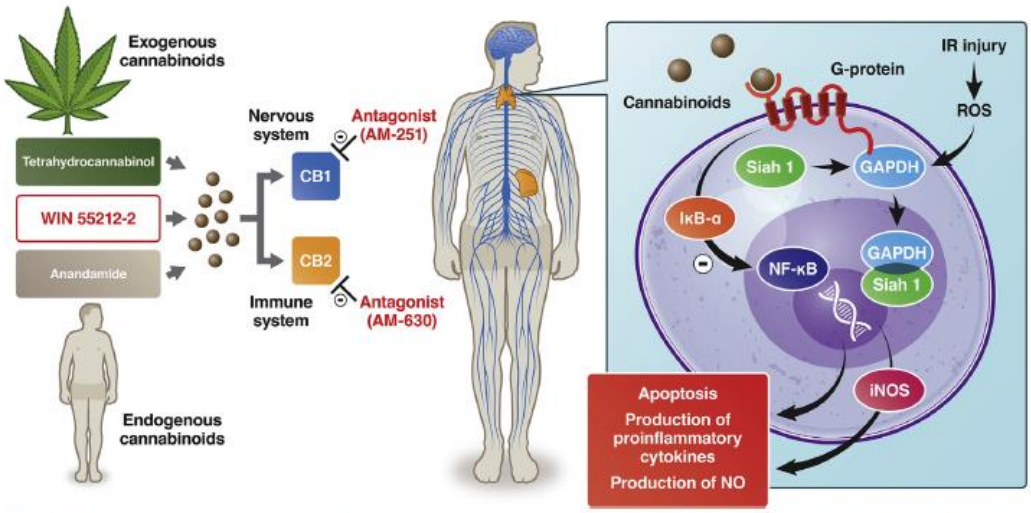

FIGURE 1. Pathways of cannabinoid receptor-mediated protection against ischemia-reperfusion (*IR*) injury. Cannabinoid receptor ligand (WIN55212-2) binding to cannabinoid receptors may reduce apoptosis and decrease proinflammatory cytokines and nitric oxide (*NO*) by increasing cytosolic inhibitory kBα, thus decreasing nuclear translocation of nuclear factor-kB (*NF-kB*) and decreasing nuclear translocation of the glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*)/Siah1 complex. *CB1*, Cannabinoid receptor 1; *CB2*, cannabinoid receptor 2; *IkBα*, inhibitory kBα; *iNOS*, inducible nitric oxide synthase; *ROS*, reactive oxygen species.

inflammation (Figure 1). CB1 receptors are located mostly in the central nervous system. In contrast, CB2 receptors are expressed mostly in the immune system, including the thymus, spleen, lymphatic nodes, and circulating leukocytes, where they mediate cytokine release.[3] Some CB2 receptors are also present in nervous system tissue.[4] In rat models, WIN55212-2 protected against ischemia-reperfusion (IR) injury in brain[5] and heart[6] tissue.

A fascinating article by Huo and colleagues[7] focuses on the protective effect of WIN55212-2 against IR injury. The authors used WIN55212-2 in a rat model of spinal cord IR injury and demonstrated that WIN55212-2 decreased nuclear translocation of both glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and nuclear factor-kB (NF-kB).

The ubiquitous cytoplasmic enzyme GAPDH is an important mediator in apoptosis. It appears that GAPDH binds with Siah1 in response to IR injury followed by nuclear translocation of the GAPDH/Siah1 complex that, in turn, is associated with increased apoptosis.[8] Huo and colleagues[7] speculated that the inhibitory action of WIN55212-2 on the GAPDH/Siah1 cascade might be due to the suppression of nitric oxide production, given the observation that the protein expression of inducible nitric oxide synthase in the spinal cord of IR injury was reduced in the presence of WIN55212-2. They also demonstrated that WIN55212-2 decreased nuclear translocation of NF-kB and increased cytosolic inhibitory kBα, a marker of NF-kB signaling activation.[7] NF-kB is a key mediator of inflammation in IR injury.[9,10]

Huo and colleagues[7] found that WIN55212-2 reduced the production of proinflammatory cytokines and reduced apoptosis of spinal cord cells, resulting in improved neurologic outcome and spinal neuron survival. The effects of WIN55212-2 were reversed by a CB2 receptor antagonist (AM630), but not by a CB1 antagonist (AM251), strengthening the evidence for a key role of the CB2 receptor-mediated pathway. This elegant study is a significant step in our understanding of cannabinoid-induced protection and may lead to important clinical translation in surgery. The ancient saga of cannabinoid receptors continues!

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A.14. Konstantinov IE et al. J Thorac Cardiovasc Surg 2019;158:742-743.

ADULT

Commentary: From bioprosthetic tissue degeneration to regeneration: A new surgical horizon in the era of regenerative medicine

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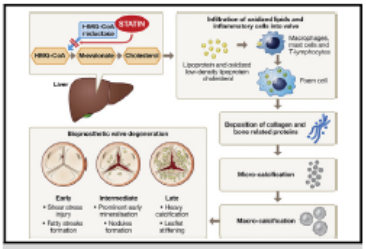

Statins and macrophages in bioprosthetic valve degeneration.

Central Message

Statins may decrease calcification of biologic tissue valve prostheses. Macrophages may play a key role in biologic valvular tissue longevity.

See Article page 731.

Just more than 100 years has passed since the very first studies showing the link between high-fat diet, increased cholesterol level, and development of atherosclerotic damage to cardiovascular the system.[1,2] Simplistically, it appears logical that controlling cholesterol at a normal level through various lipid-lowering strategies, including administration of statins, would reduce atherosclerotic degeneration. The statins are commonly used as a part of lipid-lowering therapy acting as a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor that is the rate-limiting enzyme in the synthesis of cholesterol (Figure 1). Could the same strategies by used to prevent bioprosthetic valve degeneration? Although the beneficial effect of statins to slow the progress of atherosclerosis has been demonstrated, the use of statins to prevent deterioration and calcification of bioprosthetic tissues remains controversial.[3,4]

A very interesting and thought-provoking article by Lee and colleagues[5] on the effect of statin treatment on bioprosthetic tissue calcification in rats is published in this issue of the *Journal*. Twenty rats were fed a high-fat diet for 1 month and then randomly assigned to receive either statin therapy with a high-fat diet or a high-fat diet alone. Tissues of 4 types of bioprosthetic valves were implanted subcutaneously and excised 12 weeks later. Lee and colleagues[5] found that rats treated with a statin had less calcification and a lower inflammatory infiltrate affecting the cusps of the excised valve.

It is tempting to take a closer look at the mechanism of the atherosclerotic damage. Macrophages constantly survey both native and implanted biologic tissues. Macrophages play a crucial role in the clearance of cellular debris and maintaining tissue homeostasis. Fatty streak formation occurs in areas of high shear stress. Macrophages infiltrating fatty streaks engulf lipoproteins and cholesterol in an attempt to clear the tissue of excessive lipoprotein deposits. Overwhelmed by engulfed lipoproteins, macrophages become foam cells that are incapable of effective clearance of debris and, in fact, contribute to tissue degeneration and calcification (Figure 1). Although the role of macrophages in atherosclerosis has been recognized for almost a century, the essential role of macrophages in tissue regeneration has only recently become apparent.[6]

Cellular senescence has recently been linked to the promotion of age-related pathologies and a decline in tissue regenerative capacity. Interestingly, it was previously demonstrated that senescent cells accumulate in patients with chronic inflammation of the pericardium.[7] Senescent cells produced more collagen, attracted more white blood cells, and deposited more calcium.[7] This may in part explain the fact that pericardial bioprostheses are particularly vulnerable to calcification. Effective immune clearance of senescent cells by macrophages could be important in both prevention of structural deterioration and tissue regeneration.[8] For example, salamanders have a remarkable ability to regenerate complex tissues, including

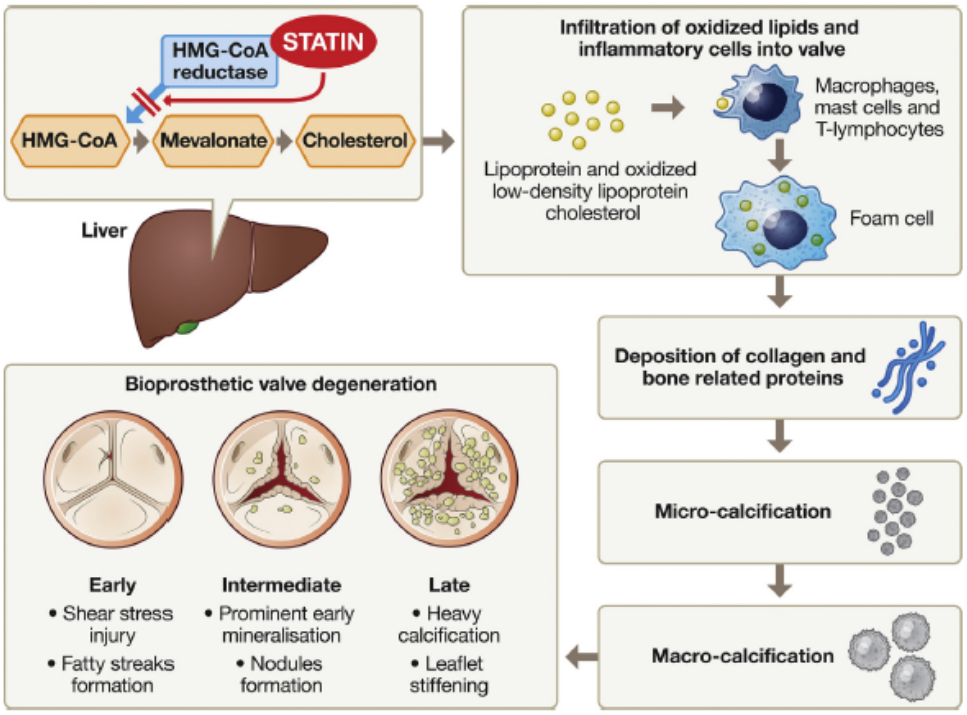

FIGURE 1. Schematic pathways of statins' lipid lowering strategy to reduce bioprosthetic valve degeneration. *HMG-CoA*, 3-hydroxy-3-methylglutaryl-coenzyme A.

heart tissues. Salamanders also have a superbly efficient mechanism of eliminating senescent cells through macrophage-dependent immune clearance.[9] Could such a regenerative pathway be emulated to prevent structural deterioration of implanted biologic tissues in patients? The use of a multifaceted strategy to improve macrophage-dependent clearance of metabolic and cellular debris may dramatically improve longevity of bioprosthetic heart valves.

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A.15. Khoo B et al. J Thorac Cardiovasc Surg 2019;158:1399-1409.

Outcomes of surgery for infective endocarditis in children: A 30-year experience

Check for updates

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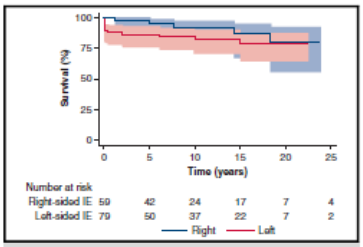
ABSTRACT

Background: Infective endocarditis (IE) is rare in children. Limited data have been reported on long-term outcomes of children who undergo surgery for IE.

Methods: Data were retrospectively obtained from medical records for all children who underwent surgery for IE.

Results: Between 1987 and 2017, 138 children with IE required surgery (mean age, 8.3 ± 6.5 years). The majority of children (80.4% [111 out of 138]) had underlying cardiac structural anomalies. Prior heart surgery was performed in 50.7% of patients (70 out of 138), including 19.6% (27 out of 138) who had valve replacement. Operative mortality was 5.8% (8 out of 138). Mean follow-up time was 9.7 ± 7.6 years. Long-term survival at 5 and 25 years was 91.5% (95% confidence interval, 85.1%-95.2%) and 79.1% (95% confidence interval, 66.3%-87.5%), respectively. Risk factors associated with death were: age (hazard ratio [HR], 0.88; $P = .015$), prosthetic valve IE (HR, 3.86; $P = .02$), coagulase-negative staphylococci (HR, 4.52; $P = .015$), increased duration of preoperative antibiotic therapy (HR, 1.02; $P = .009$), shock (HR, 3.68; $P = .028$), and aortic valve replacement (HR, 3.22; $P = .044$). In patients with left-sided IE, risk factors independently associated with death were heart failure (HR, 18.8; $P = .025$) and vegetation size adjusted to body surface area (HR, 1.06; $P = .008$). Freedom from recurrent endocarditis was 94.7% (95% confidence interval, 87.7%-97.8%) at 25 years.

Conclusions: Children undergoing surgery for IE had good long-term survival and recurrence of IE was uncommon. Surgery during the active phase of endocarditis did not increase risk of mortality or reoperation. In patients with left-sided IE, vegetation size adjusted for patient body surface area was identified as a risk factor for death, and a useful indicator of prognosis. (J Thorac Cardiovasc Surg 2019;158:1399-409)



Survival for left-sided and right-sided infective endocarditis.

Central Message

Children undergoing surgery for IE have good survival and a low recurrence of IE. In patients with left-sided IE, vegetation size adjusted for patient body surface area is a risk factor for death.

Perspective

Long-term data on the outcomes of surgery for IE in children is limited. This study describes outcomes of surgery for IE in the largest cohort of pediatric patients ever reported.

See Commentaries on pages 1410 and 1411.

Infective endocarditis (IE) accounts for 0.1 to 0.8 per 1000 pediatric admissions.[1] Recent studies have suggested that the incidence of IE in children is increasing due to improving survival of patients with corrected congenital heart disease (CHD).[2] Additionally, an increasing number of children without underlying cardiac defects are

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CONG

Abbreviations and Acronyms
CHD = congenital heart disease
CoNS = coagulase-negative staphylococci
IE = infective endocarditis

developing IE secondary to the use of central lines and other invasive procedures in neonatal and pediatric intensive care settings.[1]

Currently, pediatric recommendations for the management of IE are extrapolated from the guidelines developed for adults. A majority of children with IE are managed medically with antibiotic therapy and supportive care.[3] Cardiac surgery is performed in approximately 20% of pediatric admissions for IE.[2] Surgery is usually reserved for children, who are at increased risk of stroke, hemodynamic compromise, or failure of antibiotic therapy.[4]

Long-term data on the outcomes of surgery for IE in children is lacking. The aim of this study was to determine the outcomes of children who underwent surgery for IE at a single large-volume institution.

METHODS

Patients

All patients who underwent surgery for IE at the Royal Children's Hospital, Melbourne, Australia, from January 1, 1987, to January 1, 2017, were included in this study. Ethics approval was obtained from the Royal Children's Hospital Human Research Ethics Committee (No. 36250A).

Patients were identified using the modified Duke Criteria for possible or definite IE, accounting for microbiologic, echocardiographic, and clinical criteria.[5] Patients were also included if clear evidence of IE was found intraoperatively.

Data were obtained from retrospective chart review. Follow-up data were collected by correspondence with the general practitioners and cardiologists. Follow-up was complete if patient contact last occurred within 2 years of the end of the study period. Operative mortality was defined as death within 30 days of surgery or before hospital discharge. Early reoperation was defined as surgical reintervention occurring within 30 days of surgery or before hospital discharge. Patients were classified as having cardiogenic shock if they required parenteral inotropic/vasopressor agents or mechanical support in conjunction with documented clinical evidence of shock. Patients were considered to have active IE if they were receiving intravenous antibiotics until the time of surgery. Patients who had completed antibiotic treatment before surgery were classified as having treated IE.[6] The date of diagnosis of IE was recorded as the time point at which the patient met Duke Criteria for IE, otherwise, the start date of intravenous antibiotics or date of cardiac surgery was used.

Statistical Analysis

All data were analyzed using STATA version 14 (Stata Corp, College Station, Tex). Unless otherwise specified, all continuous data are expressed as mean ± standard deviation. Categorical data were compared between groups using the χ^2 test or the Fisher exact test if group size <10. Continuous data were compared between groups using the Kruskal-Wallis test.

Time dependent end points, such as survival and freedom from reoperation, were analyzed using the Kaplan-Meier method, with time commencing at the date of surgery for IE.

Risk factors evaluated using univariable Cox regression were age at operation, pre-existing CHD, history of cardiac surgery, prior IE, active infection, catheter-associated IE, left-sided IE, prosthetic valve IE, *Staphylococcus aureus* infection, coagulase-negative staphylococci (CoNS) infection, time from diagnosis to surgery, time from vegetation detection to surgery, time from first embolic event to surgery, length of preoperative antibiotic therapy, severe valvular insufficiency, embolic events, heart failure, shock, preoperative intensive care unit admission, perivalvular abscess, vegetation size to body surface area ratio, and replacement of individual valves at surgery.

Variables with at least moderate evidence against the null hypothesis ($P < .10$) were included in a multivariable model. Explanatory variables were tested for collinearity using the χ^2 test, t test, variance inflation factor, or Pearson correlation coefficient as appropriate. The weaker predictor from a pair of strongly correlated variables was excluded from the multivariable model. The model was then refined using the backward elimination method.

RESULTS

A total of 138 patients underwent surgery for 138 episodes of IE from January 1, 1987, to January 1, 2017. Mean follow-up time was 9.7 ± 7.6 years (median, 8.5 years; interquartile range [IQR], 3.3-16.4 years), 96.4% of patients (133 out of 138) had follow-up, 88.4% of patients (122 out of 138) had been reviewed within 12 months or had at least 5 years of follow-up. Baseline demographic characteristics of our cohort are in Table 1. The median age at operation was 8 years (mean, 8.3 ± 6.5 years; IQR, 1.3-14.0 years). Infants aged <1 year constituted 20.3% of all IE patients (28 out of 138).

Cardiac History

Underlying CHD was present in 77.5% of patients (107 out of 138) (Table 1). Ventricular septal defect was the most common lesion, found in 32.6% of patients (45 out of 138), followed by bicuspid aortic valve (17 out of 138 [12.3%]) and aortic stenosis (17 out of 138 [12.3%]).

In 50.7% of patients (70 out of 138), there was a history of at least 1 previous cardiac operation. Of these patients, 61.4% (43 out of 70) had previous valve surgery, 62.8% of whom (27 out of 43) had a total of 34 prosthetic valves: 82.4% of these prostheses (28 out of 34) had signs of IE. The mean time between the final operation and subsequent surgery for IE was 3.8 ± 4.4 years (median, 1.8 years; IQR, 0.2-6.3 years). Intracardiac synthetic material (other than suture) was present in 38.4% of patients (53 out of 138) before diagnosis of IE.

Location of IE

Patients with biventricular circulation had isolated left-sided IE (60 out of 138 [43.5%]), isolated right-side IE (59 out of 138 [42.7%]) or IE affecting both sides of the heart (9 out of 138 [6.5%]). The remaining patients (10 out of 138 [7.2%]) had IE in a univentricular

TABLE 1. Demographic characteristics of study patients (N = 138)

Characteristic	Result
Sex	
Male	66 (47.8)
Female	72 (52.2)
Age (y)	7.9 (1.3-14.0)
<1	28 (20.3)
≥1	111 (82.2)
Height (cm)	124 (77-159)
Weight (kg)	27.0 (9.5-49.7)
Indigenous Australian	11 (8.0)
Prior cardiac operation	70 (50.7)
Prior valve surgery	43 (31.2)
Prior valve replacement	27 (19.6)
Prior episode of infective endocarditis	4 (2.9)
Pre-existing congenital heart disease	107 (77.5)
Prior rheumatic heart disease	4 (2.9)
Cardiac anomalies	
Ventricular septal defect	45 (32.6)
Atrial septal defect/patent foramen ovale	20 (14.5)
Bicuspid aortic valve	17 (12.3)
Aortic stenosis	17 (12.3)
Pulmonary atresia	14 (10.1)
Coarctation of aorta	13 (9.4)
Patent ductus arteriosus	12 (8.7)
Transposition of great arteries	9 (6.5)
Tetralogy of Fallot	7 (5.1)
Hypoplastic left heart syndrome	6 (4.3)
Truncus arteriosus	5 (3.6)
Atrioventricular septal defect	5 (3.6)
Major aortopulmonary collateral arteries	5 (3.6)
Pulmonary stenosis	4 (2.9)
Double outlet right ventricle	3 (2.2)
Ebstein's anomaly	3 (2.2)
Hypoplastic right heart syndrome	3 (2.2)
Dextrocardia	1 (0.7)
Mitral stenosis	1 (0.7)
Tricuspid atresia	1 (0.7)
Double inlet left ventricle	1 (0.7)
Total anomalous pulmonary venous drainage	1 (0.7)
Valve involved	
Aortic	39 (28.3)
Mitral	37 (26.8)
Tricuspid	24 (17.4)
Pulmonary/conduit	39 (28.3)

Values are presented as n (%) or median (interquartile range).

TABLE 2. Infective organisms isolated by blood cultures

Organism	Result
Gram positive	
Staphylococcus spp	47 (34.1)
S aureus	35 (25.4)
Methicillin-sensitive *S aureus*	29 (21.0)
Methicillin-resistant *S aureus*	6 (4.3)
Coagulase-negative staphylococci	12 (8.7)
S epidermidis (or unspecified)	7 (5.1)
S capitis	2 (1.4)
S lugdunensis	2 (1.4)
S warneri and *S capitis*	1 (0.7)
Streptococcus spp	39 (28.3)
S viridans	25 (18.1)
Unspecified	10 (7.2)
S sanguis	6 (4.3)
S mitis	4 (2.9)
S mutans	1 (0.7)
S oralis	4 (2.9)
S pneumonia	7 (5.1)
Group B streptococci	3 (2.2)
Others	4 (2.9)
Corynebacterium diptheriae	5 (3.6)
Gram negative	
HACEK organisms	
Haemophilus influenzae	2 (1.4)
Kingella kingae	5 (3.6)
Pseudomonas spp	3 (2.2)
Klebsiella spp	3 (2.2)
Serratia marcesens	1 (0.7)
Enterococcus spp	3 (2.2)
Enterobacter cloacae	1 (0.7)
Streptobacillus moniliformis	1 (0.7)
Escherichia coli spp	1 (0.7)
Stenotrophomonas maltophilia	1 (0.7)
Fungi	
Candida parapsilosis	2 (1.4)

Values are presented as n (%). *HACEK*, Haemophilus, Aggregatibacter (previously Actinobacillus), Cardiobacterium, Eikenella, Kingella.

circulation. The outcomes of the patients with involvement of systemic circulation were analyzed together. Native valve IE (90 out of 138 [65.2%]) accounted for the majority of cases; 20.3% of patients (28 out of 138) had prosthetic valve IE, and 14.4% (20 out of 138) had nonvalvular IE. Among the cases involving a native valve, 25.6% (23 out of 90) had undergone previous valve repair. Across all patients with valvular IE, the aortic valve (39 out of 138 [28.3%]) was the most common site of infection.

Microbiology and Antibiotic Treatment

Positive blood cultures were obtained in 79.0% of patients (109 out of 138). The identified organisms are summarized in Table 2. More than 1 organism was isolated by blood culture in 8.0% of patients (11 out of 138). Gram-positive infections (93 out of 109 [85.3%]) were more common than gram-negative infections (16 out of 109 [14.7%]). *S aureus* (35 out of 138 [25.3%]), viridans group streptococci (25 out of 138 [18.1%]), and CoNS (12 out of 138 [8.7%]) were the 3 most commonly isolated organisms. Among patients with *S aureus* infection, 6 were methicillin-resistant organisms. The incidence of *S aureus* infection was significantly higher in patients who

underwent surgery during the active phase of IE, compared with patients who underwent surgery after treatment (31.9% vs 11.4%; $P = .01$). CoNS infection occurred more frequently in patients who had previous valve replacement (18.5% vs 6.3%; $P = .043$). No significant relationship was seen between left- or right-sided IE and the organism.

Invasive intravascular procedures had been performed in 15.2% of patients (21 out of 138) within 30 days before diagnosis of IE. Five patients (3.6%) had undergone a dental procedure within 30 days of diagnosis, and 15.9% of patients (22 out of 138) had intravascular catheters in situ at the time of diagnosis of IE. In 10.1% of cases (14 out of 138), the infection could have been related to an indwelling line.

For the entire cohort, patients received preoperative antibiotic drugs for a mean of 22.1 days (median, 15 days; IQR, 4-42 days). For patients who underwent surgery while still completing a course of intravenous antibiotics (94 out of 138 [68.1%]), the mean length of preoperative antibiotics was 16 days (median, 9 days; IQR, 3-20 days). The majority of patients continued their initially prescribed course of antibiotics. However, in 31.2% of patients (43 out of 138), preoperative antibiotic regimen was altered during treatment.

Preoperative Complications

Table 3 summarizes the preoperative complications of IE in our cohort. Embolic phenomena were noted in 29.0% of patients (40 out of 138). Embolic events occurred after diagnosis of IE in 14.5% of patients (20 out of 138). The median time from the embolic event to the date of surgery was 6 days (IQR, 2.5-38 days). Distal embolization to soft tissues or bone was the most commonly recorded event (22 out of 40 [55.0%]), followed by cerebral events (13 out of 40 [32.5%]). Embolization to multiple locations was recorded in 6.5% of patients (9 out of 138). Neither embolic phenomena overall nor embolization to specific locations were significant predictors of mortality ($P = .743$) or reoperation ($P = .558$). Vegetations were seen on preoperative echocardiography in 88.4% (122 out of 138). Vegetation size (largest dimension) was recorded in 43.5% of patients (60 out of 138). Mean size for all measured vegetations was 15.8 ± 9.3 mm. On average, left-sided vegetations were smaller than right-sided vegetations (mean, 13.5 ± 9.1 mm vs 16.6 ± 9.0 mm; $P = .461$). To account for vegetation size relative to patient size, we calculated a vegetation size to body surface area ratio. The mean value for all patients with measured vegetations was 26.2 ± 25.2 mm/m^2. These ratios were also lower in left-sided IE compared with right-sided (mean, 20.3 ± 15.9 mm/m^2 vs 36.3 ± 34.1 mm/m^2; $P = .203$). In patients without embolic complications at the time of diagnosis, the median time to embolism was 3 days.

TABLE 3. Preoperative complications and echocardiography findings

Complication	Result
Leaflet perforation	34 (24.6)
Perivalvular abscess	26 (18.8)
Mycotic aneurysm	11 (8.0)
Intracardiac fistula	5 (3.6)
Severe valvular insufficiency	46 (33.3)
Aortic	22 (15.9)
Mitral	15 (10.9)
Pulmonary	7 (5.1)
Tricuspid	4 (2.9)
Heart failure	38 (27.5)
Shock	13 (9.4)
Preoperative intensive care unit admission	27 (19.6)
Any embolic events	40 (29.0)
Cerebral	13 (9.4)
Pulmonary	9 (6.5)
Musculoskeletal	22 (15.9)
Splenic	5 (3.6)
Renal	5 (3.6)
Vegetations*	
Aortic valve	36 (26.1)
Mitral valve	29 (21.0)
Pulmonary valve	14 (10.1)
Tricuspid valve	18 (13.0)
Pulmonary artery	12 (8.7)
Artificial conduit or shunt	21 (15.2)
Intracardiac catheter tip	7 (5.1)
Other intracardiac	20 (14.5)

Values are presented as n (%). *Identified on preoperative echocardiogram.

For the whole cohort, the median time from diagnosis to surgery was 10 days (IQR, 3-64 days). In cases of left-sided IE, the median time from diagnosis to surgery was 5 days (IQR, 2-28 days), whereas in right-sided IE this was 28 days (IQR, 6-121 days). Surgery occurred within 24 hours of diagnosis in 13.8% of patients (19 out of 138). The median time to surgery from first detection of vegetation (by echocardiography or otherwise) was 9 days (IQR, 2-58 days). In the 36 patients for whom a date or time of initial embolic event was recorded, the median time from embolism to surgery was 6 days (IQR, 2.5-38 days). Patients with cerebral embolism (13 out of 138 [9.4%]) tended to receive surgery earlier (median, 4.3 days; IQR, 1.8-13.7 days).

Surgical Procedures

The nature of the surgical procedures performed for IE are summarized in Table 4 according to the active and treated IE groups. Heart failure was the most common indication for surgery in the active group (22 out of 94 patients [23.4%]). Most patients in the treated group (22

TABLE 4. Surgical procedures performed comparing active and treated groups

Procedure	Total (N = 138)	Active (n = 94)	Treated (n = 44)	*P* value
Valvular procedures				
Aortic	39 (28.3)	31 (33)	8 (18.2)	.112
Repair	16 (11.6)	10 (10.6)	6 (13.6)	.509
Replacement	23 (16.7)	21 (22.3)	2 (4.5)	**.013**
Autograft	12 (8.7)	11 (11.7)	1 (2.3)	.082
Homograft	8 (5.8)	7 (7.4)	1 (2.3)	.434
Mechanical	3 (2.2)	3 (3.2)	0 (0)	–*
Mitral	37 (26.8)	29 (30.9)	8 (18.2)	.174
Repair	31 (22.5)	24 (25.5)	7 (15.9)	.269
Replacement	6 (4.3)	5 (5.3)	1 (2.3)	.666
Homograft	1 (0.7)	0 (0)	1 (2.3)	–*
Mechanical	5 (3.6)	5 (5.3)	0 (0)	.322
Pulmonary	55 (39.9)	43 (45.7)	15 (34.1)	.073
Repair	17 (12.3)	14 (14.9)	3 (6.8)	.222
Replacement	38 (27.5)	29 (30.9)	12 (27.3)	.290
Homograft	26 (18.8)	21 (22.3)	6 (13.6)	.169
Xenograft	12 (8.7)	8 (8.5)	6 (13.6)	.815
Tricuspid repair	24 (17.4)	16 (17.0)	8 (18.2)	.728
Any replacement	52 (37.7)	41 (43.6)	11 (25.0)	.065
Any repair	79 (57.2)	58 (61.7)	21 (47.7)	.256
Concomitant/other procedures				
Ventricular septal defect closure	22 (15.9)	8 (8.5)	14 (31.8)	**<.001**
Pulmonary artery augmentation	15 (10.9)	11 (11.7)	4 (9.1)	.741
Atrial septal defect closure	8 (5.8)	7 (7.4)	1 (2.3)	.257
Repair of aortic arch/aneurysm	9 (6.5)	8 (8.5)	1 (2.3)	.276
Right ventricular outflow tract resection	7 (5.1)	4 (4.3)	3 (6.8)	.434
Shunt takedown	4 (2.9)	3 (3.2)	1 (2.3)	–*
Patent ductus arteriosus ligation	2 (1.4)	2 (2.1)	0 (0)	–*
Superior vena cava repair	2 (1.4)	2 (2.1)	0 (0)	–*
Blalock-Taussig shunt	2 (1.4)	1 (1.1)	1 (2.3)	–*

Significant *P* values are shown in bold. Values are presented as n (%). *Insufficient numbers to analyze.

out of 41 patients [53.7%]) primarily required surgery for repair of the cardiac lesion related to their IE episode. Aortic valve replacement was significantly more common in the active group (91.3% vs 8.7%; $P = .009$). Separate or nonvalvular procedures were sometimes performed alone or concurrently with surgery for IE. The most common concomitant procedure was ventricular septal defect closure (22 out of 138 patients [15.9%]), which includes cases of patch repair or replacement.

Over the study period, 41 patients required at least 1 reoperation. There were 7 cases (5.1%) of early reoperation, all of which occurred within 30 days of initial surgery. Twelve patients (8.7%) required reoperation for dysfunctional valves that were repaired or replaced at initial surgery. Reoperation was performed primarily due to somatic growth in 10 patients (7.2%). Eleven patients (8.0%) underwent planned reoperation for correction of pre-existing cardiac defects. There was a single case (0.7%) of late reoperation for recurrent endocarditis 2.5 years after initial surgery.

Outcomes

Overall operative mortality was 5.8% (8 out of 138) for the whole cohort and occurred exclusively in patients with IE in systemic circulation. Operative mortality in children with biventricular circulation was 8.7% (6 out of 69) in left-sided IE and 0% in 59 children with right-sided IE. Operative mortality in children with univentricular circulation was 20% (2 out of 10); both children had IE of the atrioventricular valve. Operative mortality for aortic valve IE was 12.8% (5 out of 39) and 3.3% (1 out of 30) for isolated mitral valve IE in children with biventricular repair. Overall survival at 5, 15, and 25 years was 91.5% (95% confidence interval [CI], 85.1%-95.2%), 84.7% (95% CI, 75.4%-90.7%), and 79.1% (95% CI, 66.3%-87.5%), respectively (Figure 1, *A*). When comparing active and treated subgroups, no significant differences in survival (log-rank test $P = .096$) or rates of reoperation (log-rank test $P = .397$) were noted (Figure 1, *B*). Survival for the subgroup of patients with IE involving systemic circulation, including those with univentricular physiology, at 5, 15, and

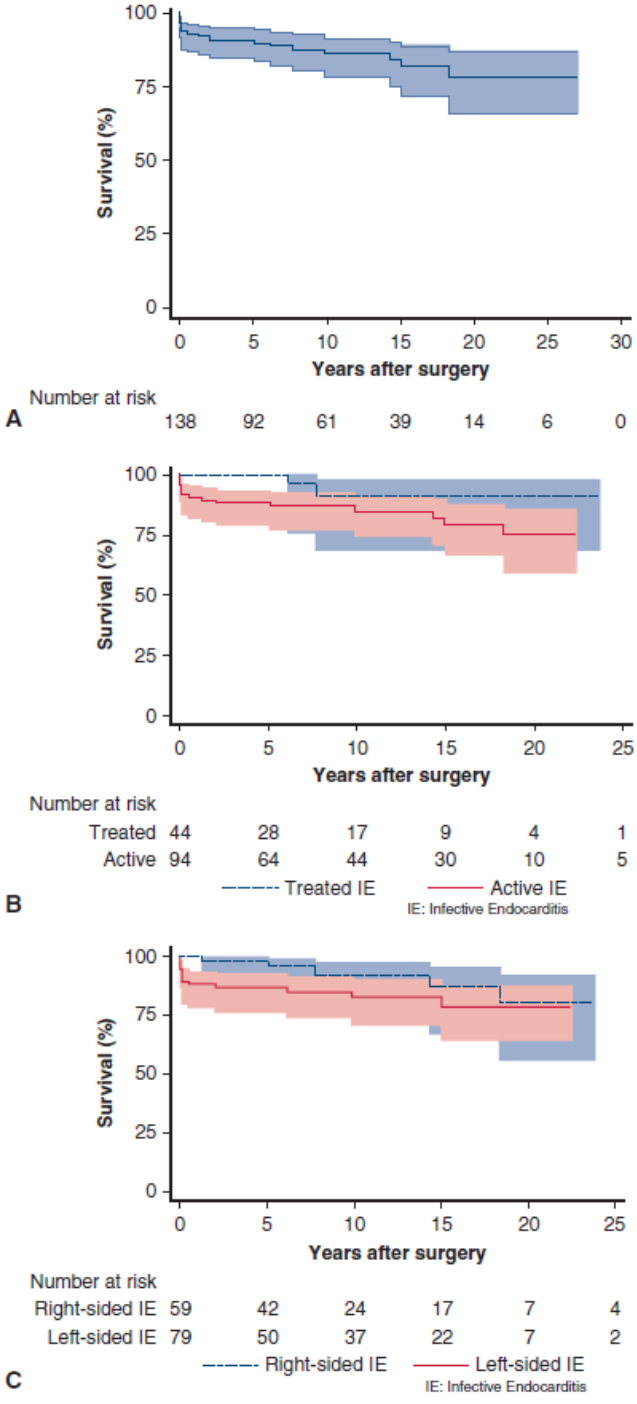

FIGURE 1. Kaplan-Meier curves. A, Survival for the entire cohort. B, Comparison of active and treated groups. C, Comparison of left and right-sided infective endocarditis (*IE*).

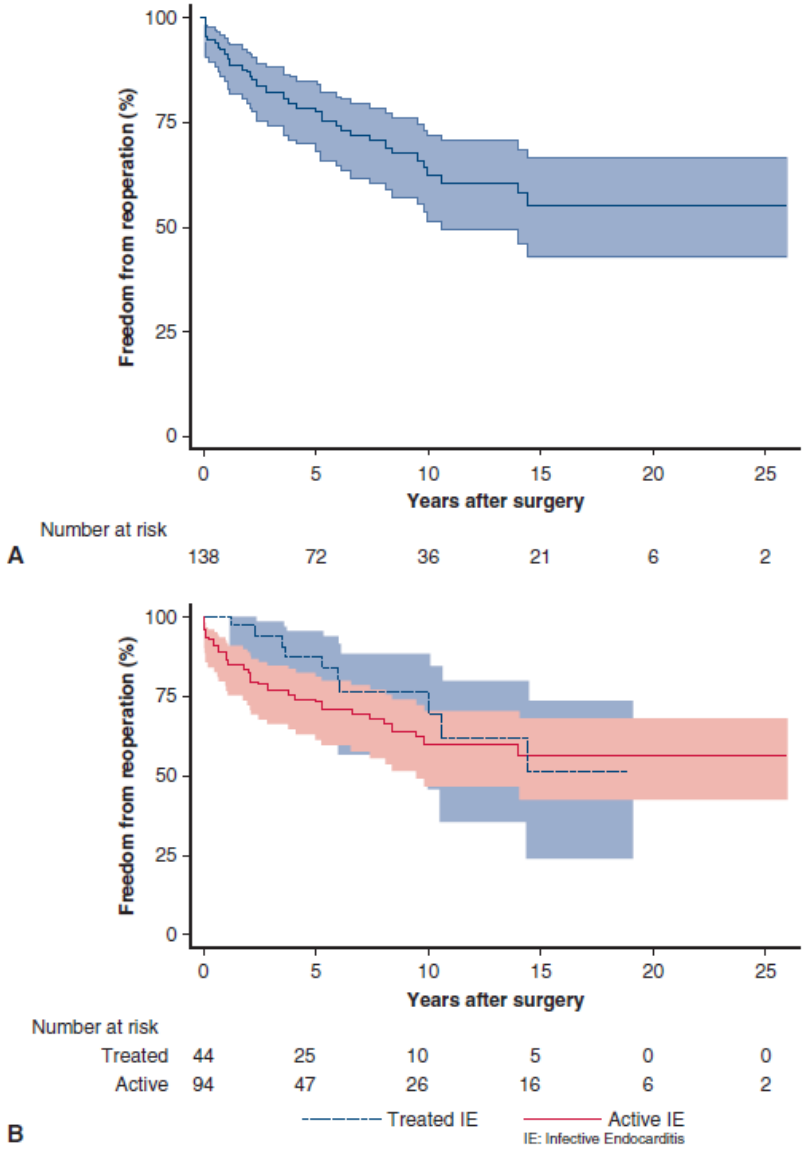

FIGURE 2. Kaplan-Meier curves. A, Freedom from all-cause reoperation for the entire cohort. B, Comparison of active and treated groups. *IE*, Infective endocarditis.

25 years was 86.6% (95% CI, 76.4%-92.5%), 82.5% (95% CI, 70.8%-89.8%), and 78.7% (95% CI, 64.5%-87.7%), respectively, whereas survival for those with isolated right-sided IE at the same time points was 98.1% (95% CI, 87.1%-99.7%), 87.2% (95% CI, 67.2%-95.4%), and 80.5% (95% CI, 55.8%-92.2%), respectively. Overall, late mortality occurred in 5 of 79 patients with IE in systemic circulation during the follow-up period, whereas this occurred in 5 of 59 patients with isolated right-sided IE. Long-term survival differences between left- and right-sided IE did not reach significance (log-rank test $P = .161$) (Figure 1, *C*). Freedom from all-cause reoperation at 5, 15, and 25 years was 77.3% (95% CI, 68.3%-84.0%), 55.5% (95% CI, 43.0%-66.3%), and 55.5% (95% CI, 43.0%-66.3%), respectively (Figure 2).

On multivariable analysis (Table 5), risk factors independently associated with death were age (HR, 0.88; $P = .015$), prosthetic valve IE (HR, 3.86; $P = .020$), CoNS (HR, 4.52; $P = .015$), increased duration of preoperative antibiotic therapy (HR, 1.02; $P = .009$), shock (HR, 3.68; $P = .028$), and aortic valve replacement

TABLE 5. Summary of multivariable predictors of outcome for the entire cohort

Risk factor	Hazard ratio (95% confidence interval)	*P* value
Multivariable predictor of death		
Age	0.88 (0.80-0.98)	.015
Prosthetic valve infective endocarditis	3.86 (1.24-12.0)	.020
Coagulase-negative staphylococci	4.52 (1.35-15.1)	.015
Duration of preoperative antibiotic therapy	1.02 (1.00-1.03)	.009
Shock	3.68 (1.15-11.7)	.028
Aortic valve replacement	3.22 (1.03-10.0)	.044
Multivariable predictors of reoperation		
Prior cardiac surgery	2.00 (1.04-3.85)	.037
Perivalvular abscess	2.83 (1.44-5.59)	.003

(HR, 3.22; $P = .044$). Risk factors independently associated with reoperation were prior cardiac surgery (HR, 2.00; $P = .037$) and perivalvular abscess (HR, 2.83; $P = .003$).

In children with left-sided IE (Table 6), risk factors independently associated with death were heart failure (HR, 18.8; $P = .025$) and vegetation size to body surface area ratio (in mm/m^2) (HR, 1.06; $P = .008$). This vegetation size ratio was also an independent predictor of mortality within 30 days (odds ratio, 1.07; $P = .024$), whereas cardiogenic shock was an independent predictor of postoperative embolic events (odds ratio, 5.91; $P = .019$). For 38 patients with left-sided IE with recorded vegetation size (range, 5.3-76.7 mm/m^2; mean, 20.3 $\pm$ 15.9 mm/m^2; median, 14.1 mm/m^2 [IQR, 9.0 to 27.5]) the operative mortality was 16% (6 of 38) and for every 1 mm/m^2 increase in vegetation size to the body surface area ratio, the relative risk of operative mortality increased by 7%, and the absolute risk of operative mortality increased by 1.1% (odds ratio, 1.069).

For patients with right-sided IE versus left-sided IE (Table 7), length of preoperative antibiotics (HR, 1.04; $P = .001$) and shock (HR, 18.8; $P = .033$) were independent predictors of death.

Freedom from recurrence of IE at 25 years was 94.7% (95% CI, 87.7%-97.8%) (Figure 3).

Among patients in whom evidence of cerebral embolism was detected, 15.4% (2 out of 13) had residual neurologic deficits at the time of final follow-up.

DISCUSSION

Currently, recommendations for surgical management of pediatric IE are an extension of guidelines for IE management in adults.[3] The decision on whether to operate to prevent primary embolic events remains problematic due to conflicting data on potential predictors of embolization.[7,8]

Reports on the outcome surgery for IE in children have been limited to small series of patients.[9] Russell and colleagues[10] described 34 IE patients who had surgery between 1990 and 2011. Overall operative mortality was 15% (5 out of 34 patients) but mortality for left-sided and right-sided IE was not specifically mentioned. They also reported a reoperation rate of 28% (10 out of 34 patients) mainly due to somatic growth. Long term outcomes were not reported. Hickey and colleagues[11] reported 30 patients who had surgery for IE between 1978 and 2007. Operative mortality was 10% (3 out of 30) and 5-year survival and freedom from reoperation was 84% and 80%, respectively. Rates of septic emboli were high in this study, occurring in 13 patients (46%). Few reports in children have investigated the influence of the timing of surgery on outcomes in children. Shamszad and colleagues[12] described 46 pediatric patients who underwent surgery for IE at a single center from 1996 to 2010, 76% (35 out of 46) of whom underwent surgery within 7 days of diagnosis, and 54% (25 out of 46) within 3 days or fewer. Overall mortality was 2.2% with 1 death (4%) in 25 patients with left-sided IE and no deaths in patients with right-sided IE. Estimated survival was 81% $\pm$ 11% at 10 years. They demonstrated that surgery within 3 days of diagnosis was safe and did not increase the risks of reoperation or mortality. In a report from our institution in 1992, Nomura and colleagues[13] highlighted the need for surgery during active or acute infection in select patients.

Overall, children who had surgery for IE at our institution had good long-term outcomes. Operative mortality in our cohort was 5.8% (8 out of 138). There was a gradual decline in survival over time, with 79.1% surviving at 25 years follow-up. In our patients, younger age, prosthetic valve IE, infection with CoNS, increased duration of preoperative antibiotic therapy, shock, and the need for aortic valve replacement were all independently associated with mortality in multivariable analysis.

In our study, age distribution was characterized by a peak in infancy and relatively even spread across other age

TABLE 6. Multivariable predictors of early adverse outcome for patients with left-sided infective endocarditis

Outcome	Risk factor	Odds ratio (95% confidence interval)	*P* value
Early mortality (within 30 d)	Vegetation size/body surface area ratio (mm/m^2)	1.069 (1.01-1.13)	.024
Postoperative embolic event	Shock	5.905 (1.33-26.1)	.019

TABLE 7. Multivariable predictors of death for patients with left-sided versus right-sided infective endocarditis (IE)

Patient group	Risk factor	Hazard ratio (95% confidence interval)	*P* value
Left-sided IE	Heart failure	18.81 (1.439-245.8)	.025
	Vegetation size/body surface area ratio	1.064 (1.017-1.114)	.008
Right-sided IE	Length of preoperative antibiotics	1.041 (1.015-1.067)	.001
	Shock	18.83 (1.275-278.3)	.033

IE, Infective endocarditis.

groups. Russell and colleagues[10] reported peaks in both infancy and adolescence. IE in younger patients has been attributed to the prolonged use of central venous catheters in infants and younger children.[1] Indeed, in our cohort, 77% of catheter-associated infections (17 out of 22) occurred in children under 10 years. However, no significant association was noted between nosocomial IE and poor outcomes. Younger children in our study were also more likely to undergo surgery while still receiving antibiotics (odds ratio, 0.90; 95% CI, 0.85-0.96; $P = .001$) suggesting elevated disease severity and awareness for the risks in this patient group.

Infection of prosthetic material or valve occurred in 21.5% of our patients (29 out of 138). Recommendations by the American Heart Association suggest valve replacement surgery in most patients with prosthetic valve infection caused by *S aureus*.[3] Our experience suggests that these patients also have poorer long-term survival. The reasons for this are likely to be multifactorial. The prosthetic material surface not only provides a surface susceptible to bacterial colonization but is also often difficult to sterilize.[14] Complications such as abscess formation are said to be more common in cases of prosthetic valve IE,[15] although, the incidence of perivalvular abscess was similar between cases of native IE and prosthetic IE in our study.

In our patients, the incidence of CoNS infection was approximately 3 times greater in patients with prosthetic IE in comparison to native IE. This relationship is consistent with reports from other studies in adults.[16] CoNS was the third most common bacterial isolate in our study, which supports recent data on microbiology trends in pediatric IE.[17] CoNS infection was also identified as a predictor of death in multivariable analysis. These organisms are sometimes multiresistant and can form biofilms that confer additional protection against sterilization.[18] In adults, the association of CoNS infection with greater morbidity and mortality in cases of prosthetic valve IE have been previously recognized.[16]

As expected, *S aureus* was the most commonly isolated organism in our patients. Unlike in other studies,[11,12,19] we did not find an association between *S aureus* infection and adverse outcomes. Relative to other patients, a greater proportion of patients with *S aureus* infection experienced embolic events. However, this difference did not reach statistical significance (41.2% vs 26.0%; $P = .095$). We

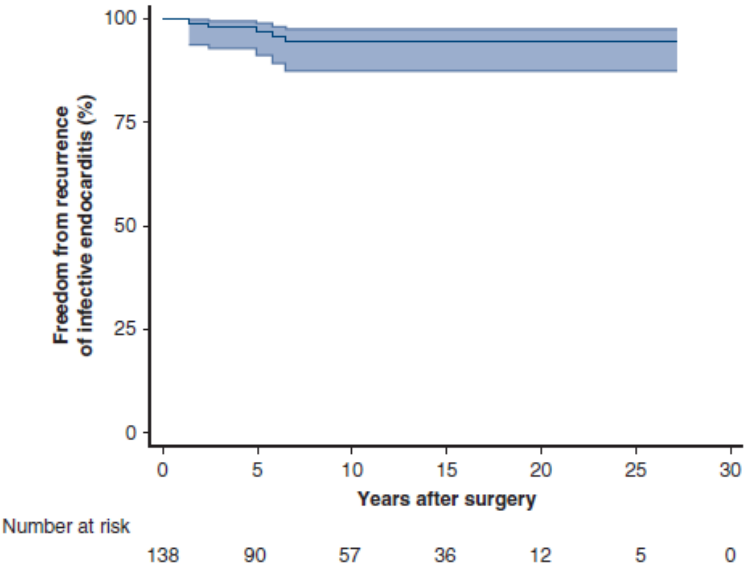

FIGURE 3. Kaplan-Meier curve showing freedom from recurrence of infective endocarditis.

noted that patients with *S aureus* IE were more than 3 times more likely to have surgery before completing antibiotic treatment. This suggests a tendency toward more aggressive surgical management in these patients, which may mitigate the risk associated with *S aureus* infection.

The ideal timing of surgery for IE is a controversial topic in both pediatric and adult medicine. The length of preoperative antibiotic treatment was the only measure that significantly correlated with increased mortality in our patients. Risk of death increased slightly for each additional day patients received antibiotics during the preoperative period (HR, 1.02; $P = .009$). Because our cohort does not include patients diagnosed with IE who were treated medically, we are unable to draw definite conclusions about the effectiveness of longer antibiotic therapy. The finding may be explained by the fact that our cohort selects for patients with right-sided IE that have failed medical therapy, and thus are more likely to have poor outcomes. We also observed that new embolic phenomena occurred at a median time of 3.2 days following diagnosis of IE. Furthermore, there was no difference in outcomes between patients who underwent surgery during the active phase of disease, and those who underwent delayed surgery. Based on these observations, it would seem reasonable to recommend surgery within 3 days of diagnosis in those patients with an indication for surgery.

Across many retrospective cohorts, vegetation size and location has been observed to influence the risk of death and adverse outcomes such as embolic phenomena.[8,20] In combined cohorts of adults and children, Yoshinaga and colleagues[21] observed that vegetation size 15 mm or larger was a risk factor for death and remarked that it may be more useful to account for vegetation size relative to patient body size especially in infants or children. Our study adjusted vegetation sizes (in patients with recorded measurements) for body surface area, calculated from height and weight. Indeed, we found that adjusted vegetation size was a significant independent predictor of early mortality (HR, 1.069; $P = .024$) and overall mortality (HR, 1.064; $P = .008$), but only in children with left-sided IE. Because infants comprised 20% of our cohort, absolute vegetation size was not correlated with any adverse outcomes. There is a close correlation between age and body size, so these findings demonstrate the need to consider relative vegetation size, especially in cases of left-sided IE in small, young children.

IE of the aortic valve was present in 28.3% of our patients (39 out of 138 patients). According to European guidelines, heart failure due to severe aortic valve dysfunction is an indication for surgery.[22] Heart failure in IE is strongly related to mortality, with the highest degree of failure associated with aortic valve destruction.[23] Periannular extension of infection occurs most commonly in aortic valve endocarditis,[24] a feature of more severe disease. In our cohort, aortic valve replacement was performed in 16.7% of our patients (23 out of 138) and was associated with poorer long-term survival. In contrast, none of the 16 patients who underwent aortic valve repair died during the follow-up period. Hickey and colleagues[11] advocated for the avoidance of valve replacement where possible and reported good outcomes following valve repair despite advanced disease in some patients. Our findings support this approach, with our group favoring valve repair when feasible, utilizing treated autologous pericardium for native valve reconstruction where possible.[25,26]

Freedom from recurrence of IE occurred was 95% at 25 years follow-up, and only 2 patients in our study required reoperation for recurrent endocarditis after transition to adult care. The last recurrence of endocarditis occurred at 6.5 years of follow-up. This suggests that surgery is highly effective in curing IE in children, and recurrent episodes are very uncommon.

However, all-cause reoperation rates were high. Russell and colleagues[10] reported a similar finding, where most reoperations were in children who initially underwent valve replacement and subsequently required a larger prosthesis. In our study, pre-existing heart defects and perivalvular abscess were independently associated with reoperation, whereas valve replacement on its own was not. Perivalvular abscess is said to indicate uncontrolled infection, and is most often related to the aortic valve or mitral valve.[27] Annuloplasty, extensive reconstruction, or valve/root replacement are often required and are associated with higher morbidity and mortality.[15,28] It is possible that the complex nature of procedures performed in these patients may necessitate earlier reoperation.

This study is limited by its retrospective nature. Due to the long follow-up period, time-related bias could potentially affect results as treatment approaches change over time. The association between adjusted vegetation size and increased mortality in left-sided IE was an important finding of our study; however, vegetation size was only recorded in 43.5% of patients. Also, the close correlation between patient age and body size was a potential confounder. Although this is the largest study on surgery in children with IE, our relatively limited sample size may have prevented further detailed analysis or demonstration of potential risk factors. The lack of data on IE patients who did not have surgery prevented more direct comparisons of approaches to therapy.

CONCLUSIONS

Children undergoing surgery for IE had good long-term survival, and recurrence of endocarditis was uncommon. However, the long-term burden of reoperation was high, with 45% of patients requiring reoperation by 25 years. Surgery during the active phase of endocarditis did not increase risk of mortality or reoperation. In children with

left-sided IE, vegetation size indexed to body surface area was identified as a risk factor for both adverse events and death, suggesting that it may be a useful prognostic factor.

Conflict of Interest Statement

Dr d'Udekem is a consultant for Actelion and MSD. Dr Brizard serves on the advisory board of Admedus. All other authors have nothing to disclose with regard to commercial support.

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Key Words: infective endocarditis, surgery, pediatric, outcomes, mortality, reoperation, timing, valve replacement

CONG

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Long-term quality of life in adults following truncus arteriosus repair

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Key question

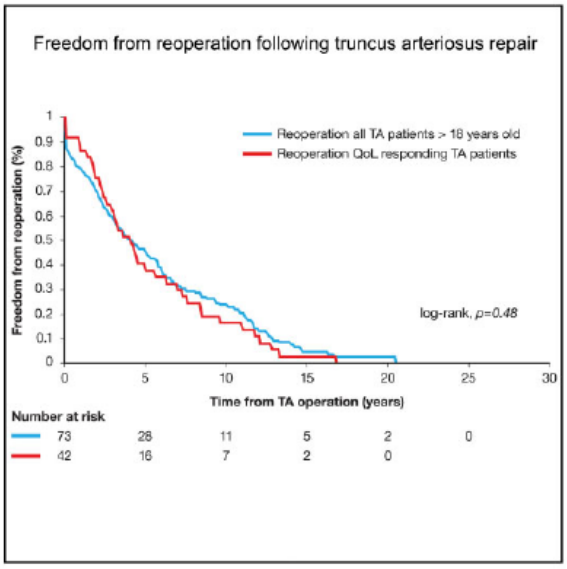
What is the quality of life of adult patients following repair of truncus arteriosus (TA)?

Key finding(s)

We found no difference in quality of life in patients with TA versus Australian controls or patients who had an arterial switch operation.

Take-home message

Patients with TA have a quality of life similar to that of Australian controls.



Abstract

OBJECTIVES: To date, few studies have assessed the quality of life following congenital cardiac surgery. In this study, we aimed at determining the quality of life after truncus arteriosus (TA) repair using the Short Form 36 questionnaire in adult survivors.

METHODS: Seventy-three patients (age >18 years) who underwent TA repair at the Royal Children's Hospital, Australia were identified for the study. Of these, 42 patients (58%, 42/73) participated in the study and completed the Short Form 36 questionnaire. The results of the 8 domains and the derived health state summary score (Short Form Six Dimension, SF-6D) were compared with age-matched Australian population controls, and with patients who underwent the arterial switch operation (ASO).

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RESULTS: Compared with the age-matched Australian population, 18- to 24-year-old TA patients (31%, 13/42) had lower scores in 6 of 8 domains; 25- to 34-year-old TA patients (36%, 15/42) scored lower in 5 of 8 domains; and 35- to 44-year-old TA patients (33%, 14/42) scored lower in 4 of 8 domains. SF-6D scores were not significantly different between TA patients and the age-matched Australian population. Compared with patients who underwent ASO, 18-to 24-year-old TA patients scored lower in 3 of 8 domains; and 25- to 34-year-old TA patients scored lower in 2 of 8 domains. There was no significant difference in SF-6D scores between TA and patients who underwent the ASO.

CONCLUSIONS: Adult survivors of TA have similar quality of life compared with age-matched Australian controls measured by SF-6D. Despite a higher reoperation rate in TA patients, they have similar quality of life compared with ASO patients.

Keywords: Truncus arteriosus • Quality of life • Short form six dimension

INTRODUCTION

To date, few studies have assessed the long-term health-related quality of life in adult survivors of congenital cardiac surgery. We therefore sought to assess the long-term health-related quality of life in adults following truncus arteriosus (TA) repair using the Short Form 36 (SF-36) questionnaire—a widely validated generic instrument [1]—and compare this with age-matched Australian population controls. Despite a good understanding of the long-term surgical outcomes, there are no data on the health-related quality of life following TA repair in those who reach adulthood. However, there is general concern and evidence that patients with congenital heart disease are at risk of worse emotional functioning and mental health in adulthood [2, 3]. The SF-36 addresses health-related quality of life from 8 dimensions including physical functioning, social functioning and mental health. Furthermore, most patients who undergo TA repair require the use of a conduit to re-establish continuity between the right ventricle and pulmonary artery, and thus invariably require reoperation/s throughout their lives [4, 5]. Therefore, we also compared the health-related quality of life in patients who underwent TA repair to those who underwent the arterial switch operation (ASO)—an operation with comparatively similar complexity, but with low reoperation rates. We had previously reported the quality of life in adult survivors after ASO [6].

Table 1: Patient characteristics

Variables	
Total TA patients over 18 years of age	39% (73/188)
Total number of responses	58% (42/73)
Females	52% (22/42)
Median age surgical repair	
18–24 age group	44 days (mean 60 days, range 12–218 days)
25–34 age group	43 days (mean 46 days, range 6–100 days)
35–44 age group	164 days (mean 278 days, range 51–1413 days)
Reoperations	
18–24 age group	
Total	26
Median time to reoperation	4.4 years (mean 7.3 years, range 7 days–15.5 years)
25–34 age group	
Total	26
Median time to reoperation	7.2 years (mean 6.8 years, range 1.1–12.9 years)
35–44 age group	
Total	12
Median time to reoperation	4.6 years (mean 5 years, range 0.9–12.1 years)

TA: truncus arteriosus.

METHODS

Patients

The study was approved by the Human Research Ethic Committee at the Royal Children's Hospital. All patients ($n = 188$) who underwent TA repair between 1979 and 2018 were identified from the hospital database. The study population was limited to survivors above the age of 18 years. The overall survival was 73.6% at 30 years [4, 5]. Seventy-three patients above 18 years of age were selected for the study. Of which, 42 (58%, 42/73) patients agreed to participate in the study. Thirteen (31%, 13/42) patients were 18–24 years old; 15 (36%, 15/42) patients were 25–34 years old; and 14 (33%, 14/42) patients were 35–44 years old. Table 1 presents the clinical characteristics of the group. There were 2 patients with DiGeorge syndrome included in the study. Participants were contacted via telephone and completed SF-36 quality of life questionnaire between December 2017 and April 2018.

Definitions

As previously described [6], the SF-36 quality of life questionnaire is a validated health-related survey that is composed of 36 questions that measures 8 domains. These domains include physical functioning (impact of health on physical activities), body pain (frequency and impact of pain on activities), general health, vitality (perception of energy and fatigue), social functioning (impact of physical or emotional problems on social activities), mental health, role limitations caused by physical health problems (impact of physical health on vocational and avocational activities) and role limitations caused by emotional problems (impact of emotional problems on vocational and avocational activities) [1]. A higher domain score represents a more favourable health-related quality of life. Responses to the 36 questions indicate the presence or absence of limitations and are scored and averaged so that a higher score in a domain indicates more favourably ranked quality of life. While the SF-36 questionnaire is commonly conducted as a written survey, telephone administration has been shown to be equivalent to the written form [7]. The SF-36 scores are then converted into a summary score, the Short Form 6-Dimension (SF-6D) score, to present a generic single-index health state that is comparable across different disease states and the general population. The SF-6D has interval scale property, i.e. a difference between 0.2 and 0.4 is equally valued as a difference

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Table 2: SF-36 domain and SF-6D scores for truncus arteriosus patients and Australian age-matched population

Domain	18–24 years old			25–34 years old			35–44 years old		
	TA patients ($n = 13$)[a]	Aust population[a] ($n = 1762$)	*P*-value	TA patients ($n = 15$)[a]	Aust population[a] ($n = 2679$)	*P*-value	TA patients ($n = 14$)[a]	Aust population[a] ($n = 2274$)	*P*-value
PF	**76.5 ± 26.6 (60.4–92.6)**	**91.1 ± 20.3 (90.1–92.0)**	**0.011**	**74.7 ± 26.2 (60.2–89.2)**	**91.6 ± 18.3 (90.9–92.3)**	**<0.001**	84.6 ± 22.6 (71.6–97.7)	89.7 ± 18.5 (88.9–90.4)	0.31
Pain	87.8 ± 17.2 (77.5–98.3)	81.1 ± 20.5 (80.1–82.0)	0.23	81.5 ± 26.5 (66.8–96.2)	78.8 ± 21.0 (78.0–79.6)	0.62	84.6 ± 21.2 (72.4–96.9)	75.2 ± 22.3 (74.3–76.1)	0.12
GH	65.8 ± 21.1 (53.0–78.5)	70.3 ± 19.6 (69.4–71.2)	0.41	**54.0 ± 25.9 (39.7–68.3)**	**70.9 ± 19.0 (70.2–71.6)**	**<0.001**	**60.7 ± 27.3 (45.0–76.5)**	**69.0 ± 19.8 (68.2–69.8)**	**<0.001**
Vit	55.9 ± 14.3 (47.2–64.6)	59.5 ± 19.1 (58.6–60.4)	0.50	57.7 ± 25.7 (43.4–71.9)	58.3 ± 19.0 (57.6–59.0)	0.90	57.1 ± 24.8 (42.8–71.5)	57.0 ± 20.6 (56.1–57.8)	0.97
SF	77.9 ± 25.6 (62.4–93.4)	83.2 ± 22.2 (82.1–84.2)	0.39	80.0 ± 30.9 (62.9–97.1)	84.6 ± 31.5 (83.8–85.4)	0.41	85.7 ± 18.9 (74.8–96.6)	82.6 ± 23.6 (81.6–83.5)	0.62
EW	69.9 ± 23.5 (55.6–84.1)	70.4 ± 18.3 (69.6–71.3)	0.91	75.7 ± 20.1 (64.6–86.9)	72.1 ± 17.0 (71.4–72.7)	0.40	80.3 ± 13.1 (72.7–87.8)	72.0 ± 17.8 (71.3–72.8)	0.084
RLPH	80.8 ± 34.1 (60.2–101.4)	88.8 ± 26.4 (87.5–90.0)	0.28	80.0 ± 35.6 (60.3–99.7)	88.2 ± 27.7 (87.1–89.2)	0.26	80.4 ± 32.8 (61.4–99.3)	83.7 ± 32.6 (82.4–85.0)	0.70
RLEP	87.2 ± 25.6 (71.7–102.7)	82.6 ± 32.3 (81.1–84.1)	0.61	88.9 ± 30.0 (72.3–105.5)	84.6 ± 31.5 (83.4–85.7)	0.59	69.1 ± 46.2 (42.4–95.7)	82.5 ± 33.2 (81.1–83.9)	0.13
SF-6D	0.729 ± 0.095 (0.672–0.786)	0.772 ± 0.121 (0.767–0.778)	0.20	0.765 ± 0.151 (0.682–0.849)	0.780 ± 0.116 (0.775–0.784)	0.64	0.788 ± 0.109 (0.725–0.851)	0.767 ± 0.123 (0.762–0.772)	0.52

Values in boldface indicate statistical significance.

[a]All data are reported as mean ± standard deviation (95% confidence interval).

Aust: Australian; EW: emotional well-being; GH: general health; PF: physical functioning; RLEP: role limitations due to emotional problems; RLPH: role limitations due to physical health; SF: social functioning; SF-6D: Short Form 6 Dimension; TA: truncus arteriosus; Vit: vitality.

between 0.6 and 0.8, and thus is easily interpretable. The Australian population SF-36 and SF-6D scores are estimated from the Household, Income and Labour Dynamics survey [8]. The Household, Income and Labour Dynamics survey is an Australian government funded longitudinal study of >17 000 Australians.

Statistical analysis

Stata version 12 (Stata Corp, College Station, TX, USA) was used for data analysis. Continuous data are expressed as means ± standard deviations (95% confidence interval), while skewed continuous data are expressed as medians (mean, range). Categorical data are summarized as frequencies and percentages. The results derived from the 8 individual SF-36 domains and SF-6D scores were compared with the mean scores from age-matched Australian population data derived from the Household, Income and Labour Dynamics survey [8]. A two-sample *t*-test was used to determine any statistically significant difference between SF-36 domains and SF-6D scores between groups. The Kaplan–Meier survivor functions were used to plot and analyse time-related end points. The log-rank test was used to compare survivor functions. Statistical significance was set a *P*-value <0.05.

RESULTS

A total of 73 patients identified by the hospital database were eligible to participate in the study, of whom 42 (58%, 42/73) agreed to participate. The scores for each age group from the 8 SF-36 domains compared with the general age-matched Australian population are summarized in Table 2. Compared with the age-matched Australian population, 18- to 24-year-old TA patients had lower scores in 6 out of the 8 domains; 25- to 34-year-old TA patients scored lower in 5 out of the 8 domains; and 35–44 years old age group patients (33%, 14/42) scored lower in 4 out of the 8 domains. Physical functioning was significantly lower in TA patients compared with the Australian population in both the 18–24 years old ($P = 0.011$), and 25–34 years old groups ($P < 0.001$). General health was also significantly lower in the 25- to 34-year-old TA patients compared with the Australian population ($P < 0.001$). There were no significant differences in the SF-6D scores between TA patients and the Australian population in any age group (18–24 years old, 0.729 ± 0.095 vs 0.772 ± 0.121, respectively, $P = 0.20$; 25–34 years old, 0.765 ± 0.151 vs 0.780 ± 0.116, respectively, $P = 0.64$; and 35–44 years old, 0.788 ± 0.109 vs 0.767 ± 0.123, respectively, $P = 0.52$).

Forty-two patients who participated in the study had a total of 64 reoperations (Table 2). In all TA patients above 18 years old, overall freedom from reoperation was 3 ± 2% (95% CI 1–8) at 20 years (Fig. 1A). In TA patients who undertook the SF-36 questionnaire, freedom from reoperation was 0% at 20 years. There was no significant difference in reoperation rates between TA patients who did and did not undertake the SF-36 questionnaire ($P = 0.48$). The most common reason for reoperation was right ventricular outflow tract obstruction. In contrast, for patients who underwent the ASO, freedom from reoperation was 85 ± 2% (95% CI 80–88) at 20 years (Fig. 1B). In patients who underwent the ASO and undertook the SF-36 questionnaire, freedom from reoperation was 82 ± 4% (95% CI 73–89) at 20 years. There was

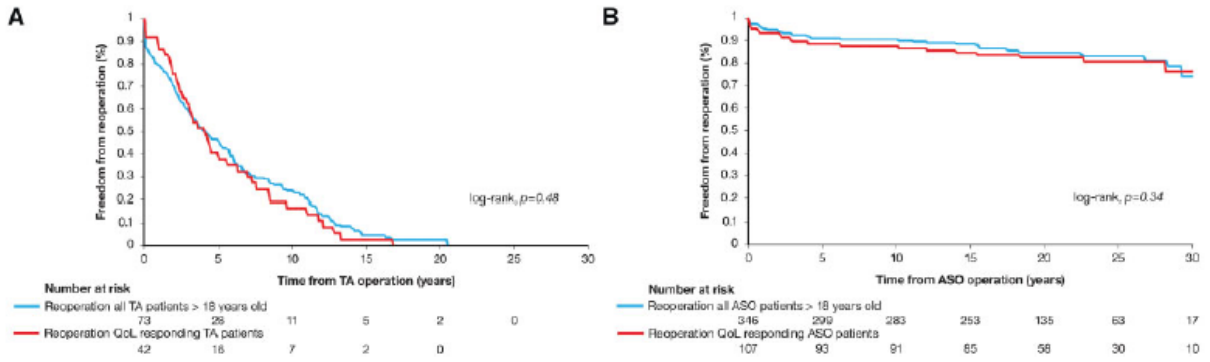

Figure 1: Freedom from reoperation. (**A**) Freedom from reoperation in all TA patients (blue) and TA patients who participated in quality of life survey (red). (**B**) Freedom from reoperation in all ASO patients (blue) and ASO patients who participated in quality of life survey (red). ASO: arterial switch operation; QoL: quality of life; TA: truncus arteriosus.

Table 3: SF-36 domain and SF-6D scores for truncus arteriosus patients and arterial switch operation patients

Domain	18–24 years old			25–34 years old		
	TA patients ($n = 13$)[a]	ASO patients ($n = 51$)[a]	*P*-value	TA patients ($n = 15$)[a]	ASO patients ($n = 56$)[a]	*P*-value
PF	**76.5 ± 26.6 (60.4–92.6)**	**92.5 ± 10.1 (89.6–95.3)**	**<0.001**	**74.7 ± 26.2 (60.2–89.2)**	**92.9 ± 12.1 (89.6–96.1)**	**<0.001**
Pain	87.8 ± 17.2 (77.5–98.3)	88.7 ± 17.7 (83.7–93.7)	0.87	81.5 ± 26.5 (66.8–96.2)	85.2 ± 20.8 (79.7–90.8)	0.57
GH	65.8 ± 21.1 (53.0–78.5)	69.7 ± 18.5 (64.5–74.9)	0.51	**54.0 ± 25.9 (39.7–68.3)**	**69.4 ± 18.5 (64.4–74.3)**	**0.011**
Vit	**55.9 ± 14.3 (47.2–64.6)**	**69.7 ± 14.7 (65.6–73.8)**	**0.004**	57.7 ± 25.7 (43.4–71.9)	68.0 ± 18.8 (63.0–73.1)	0.09
SF	77.9 ± 25.6 (62.4–93.4)	84.6 ± 21.0 (78.7–90.5)	0.33	80.0 ± 30.9 (62.9–97.1)	90.0 ± 18.1 (85.1–94.8)	0.11
EW	**69.9 ± 23.5 (55.6–84.1)**	**81.3 ± 16.6 (76.7–85.6)**	**0.047**	75.7 ± 20.1 (64.6–86.9)	83.5 ± 14.7 (79.6–87.4)	0.087
RLPH	80.8 ± 34.1 (60.2–101.4)	87.3 ± 27.1 (79.6–94.9)	0.47	80.0 ± 35.6 (60.3–99.7)	92.4 ± 20.7 (86.9–98.0)	0.086
RLEP	87.2 ± 25.6 (71.7–102.7)	83.0 ± 30.1 (74.5–91.5)	0.65	88.9 ± 30.0 (72.3–105.5)	92.4 ± 24.4 (86.9–98.0)	0.64
SF-6D	0.729 ± 0.095 (0.672–0.786)	0.769 ± 0.098 (0.742–0.797)	0.19	0.765 ± 0.151 (0.682–0.849)	0.795 ± 0.102 (0.768–0.822)	0.37

Values in boldface indicate statistical significance.

[a]All data are reported as mean ± standard deviation.

ASO: arterial switch operation; EW: emotional well-being; GH: general health; PF: physical functioning; RLEP: role limitations due to emotional problems; RLPH: role limitations due to physical health; SF: social functioning; SF-6D: Short Form 6 Dimension; TA: truncus arteriosus; Vit: vitality.

no significant difference in reoperation rates in ASO patients who did and did not undertake the SF-36 questionnaire ($P = 0.34$).

Compared with patients who underwent the ASO, 18- to 24-year-old TA patients had lower scores in 7 out of the 8 domains; and 25- to 34-year-old TA patients scored lower in all 8 domains (Table 3). Again, physical functioning was significantly lower in TA patients in both the 18–24 years old ($P < 0.001$), and 25–34 years old groups ($P < 0.001$). There were no significant differences in the SF-6D scores between TA patients and ASO patients in any age group (18–24 years old, 0.729 ± 0.095 vs 0.769 ± 0.098, respectively, $P = 0.19$; and 25–34 years old, 0.765 ± 0.151 vs 0.795 ± 0.120, respectively, $P = 0.37$).

DISCUSSION

We have previously reported good long-term surgical outcomes following TA patients, albeit with a high reoperation rate [4, 5]. Over a 35-year period between 1979 and 2014 we reported on 171 patients who underwent TA repair with an early mortality of 12%, and overall survival of 75% ± 3% at 20 years. This has resulted in an evergrowing adult population of those who have undergone TA repair. Although similar long-term results have been reported from other centres [9–12], there are no current data on the quality of life of adult survivors of TA. Therefore, the focus of this study was to assess the long-term quality of life following TA repair. By understanding the health-related quality of life outcomes in patients with surgically repaired TA, it may allow us to assess the overall impact of the condition and provide a reference to adjust the therapeutic interventions to address the physical and psycho-social issues in adults.

To the best of our knowledge, our study represents the only study of adult survivors of TA repair to have their quality of life examined and compared with an age-matched population. O'Byrne *et al.* [13] reported on the quality of life in 25 children who underwent TA repair using the Child Health Questionnaire-Parent Form 50, and Parent Child Quality of Life Inventory. However, the study population only included children from 8 to 10 years old who volunteered to participate and did not investigate any long-term quality of life beyond adolescent years [13]. O'Byrne *et al.* [13] demonstrated similar results of psycho-social functional status in TA patients compared with the general population but recorded significantly diminished physical functioning score. Similarly, we noted significantly reduced physical functioning compared with the age-matched Australian population.

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We have previously reported on the quality of life of patients who underwent the ASO [6]. While TA patients and those who undergo the ASO obviously have different malformations, both cohorts of patients undergo complex cardiac surgery during infancy. Stark differences arise in the reoperation rates between TA patients and those who undergo the ASO [14] (Fig. 1). As nearly all patients with TA undergo surgical repair with the use of a conduit, this inevitably requires reoperation as the patient matures. Thus, freedom from reoperation was 3% at 20 years in TA patients, and 85% at 20 years in patients who underwent the ASO. One would therefore expect the quality of life of TA patients to be lower than those who underwent the ASO. Compared with patients who underwent the ASO, TA patients scored lower in nearly all domains across all age groups. Again, physical functioning was significantly lower in TA patients in all age groups when compared with patients who underwent the ASO. However, the overall quality of life as demonstrated by the SF-6D were comparable in both cohorts.

Our results as demonstrated by SF-6D show that TA patients have similar overall quality of life as the general age-matched Australian population and patients who underwent the ASO. The SF-6D is a universally accepted health measurement derived from a selection of SF-36 domains which has been used to describe over 18 000 health states and generate quality-adjusted life years. While TA patients had lower scores in many of the SF-36 domains—most significantly in physical functioning—the absolute differences in the domains are difficult to interpret. Furthermore, there were no statistically significant differences in the SF-6D scores across all TA age groups. These initial results are reassuring and suggest that the overall quality of life of TA survivors is comparable to the general population and other congenital cardiac surgical patients, despite the high reoperation rates. Larger studies are required to further evaluate the quality of life in these complex patients.

Limitations

Our study has several limitations. Patients without contact details were unable to be investigated. The small population sample size limits the power of statistical analysis. Our results are from a single institution and thus cannot be generalized for TA patients worldwide. The study was limited to survivors of TA repair and thus could lead to an overestimation of quality of life for all those with TA.

CONCLUSION

Survivors of TA repair have similar quality of life outcomes compared with the age-matched Australian population as measured by the SF-6D. Despite a higher reoperation rate in TA patients, they have similar quality of life to patients who underwent the ASO.

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