

LONG-TERM OUTCOMES OF TRUNCUS ARTERIOSUS REPAIR

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“The more you read,
the more things you will know.

The more that you learn,
the more places you’ll go”

- *Dr. Seuss*

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ABSTRACT

Truncus arteriosus is a rare congenital cardiac defect which results in a single common arterial trunk exiting the heart which supplies the systemic, pulmonary, and coronary circulations. The truncus itself is guarded by a single, often large common valve – the truncal valve – which separates the truncus from both the left and right ventricle. Truncus arteriosus has an incidence of 3 to 10 per 100,000 live births. Although only 0.7% – 3% of all congenital cardiac anomalies are due to truncus arteriosus, it accounts for 4% of all critical congenital cardiac anomalies. Patients typically present early in life with symptoms of cyanosis and congestive cardiac failure. Nowadays, surgery is undertaken early in life prior to the development of irreversible pulmonary hypertension. Improvements in surgical techniques and perioperative management has drastically reduced early mortality to 3 – 20%. Therefore, many children who have undergone truncus arteriosus repair are living well into adulthood. Despite this, there are few large studies addressing the long-term outcomes of truncus arteriosus repair. Furthermore, the impact of concomitant anomalies and the truncal valve are insufficiently described.

This Doctor of Philosophy focuses on the long-term outcomes of truncus arteriosus repair in order to determine the current results and risk factors for poor outcomes. This research constitutes the largest single-institutional and multi-institutional experience assessing the long-term outcomes of truncus arteriosus repair with the longest follow-up time.

I demonstrated that the majority of mortality following truncus arteriosus repair occurs within the first year after repair, and survival beyond the first year is excellent. I found that the presence of a coronary artery anomaly was associated with both early and late mortality and suggest that the coronary anatomy be clearly identified intraoperatively. Furthermore, patients with DiGeorge syndrome are at risk of late mortality, most commonly due to infection.

Interestingly, I found that patients with mild or less truncal valve insufficiency are free from truncal valve surgery for up to 25 years, despite their truncal valve anatomy. In contrast, most patients with moderate or greater truncal valve insufficiency – particularly those with a quadricuspid truncal valve – will require truncal valve surgery at some stage in their lifetime. Of note however, the durability of truncal valve repair as a whole is poor, with most patients requiring reoperation on the truncal valve. In those with a quadricuspid truncal valve, repair by tricuspidization appears to be the most durable option with good long-term outcomes. Tricuspidization provided better long-term outcomes even if the non-tricuspidization group included younger children (less than 6 years of age), in whom truncal valve replacement was performed. This is an important finding as it suggests that younger children may benefit from truncal valve repair rather than a replacement with a smaller (non-adult sized) mechanical prosthesis which may require repeat replacement. Furthermore, if repair of the truncal valve is possible, this would avoid life-long anti-coagulation and the associated risks.

In the long-term, patients had an excellent functional status following truncus arteriosus repair but had a high rate of reoperation due to the use of a conduit for reconstruction of the right ventricular outflow tract. Despite the high reoperation rate, patients have similar quality of life compared to age-matched Australian controls.

This Doctor of Philosophy has redefined our understanding of the long-term outcomes of truncus arteriosus repair. The findings presented will impact clinical decision making, and I envision an improvement in the outcomes of these rare and complex patients.

DECLARATION

This is to certify that:

- (i) This thesis comprises only my own original work towards the Doctor of Philosophy except where specifically indicated in the text;
- (ii) Due acknowledgements have been made in the text to all other material used;
- (iii) In accordance with the Department of Paediatrics guidelines, this thesis is fewer than 100,000 words in length, exclusive of tables, bibliographies, and appendices.

Dr Phillip Naimo, MD, BSc (Hons)

Signed: _____

Date: _____

PREFACE

This is original work, except where acknowledgements and references are made to previous work. This thesis contains large cohort studies where a small proportion of information was necessarily collected with the assistance of others. Nevertheless, the majority of data collection, as well as data analysis, writing, and revision of manuscripts were all performed primarily by myself.

This work was supported by the scholarship presented on page XXIX.

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List of Abbreviations and Acronyms

AA	aortic arch
Ao	aorta
ASD	atrial septal defect
AVSD	atrioventricular septal defect
CI	confidence interval
CoA	coarctation of the aorta
CPB	cardiopulmonary bypass
ECMO	extracorporeal membrane oxygenation
HR	hazard ratio
IAA	interrupted aortic arch
ICU	intensive care unit
LA	left atrial
LCA	left coronary artery
LV	left ventricle
MAPCA	major aortopulmonary collateral artery
OR	odds ratio
PDA	patent ductus arteriosus
RA	right atrium
RCA	right coronary artery
RV	right ventricle
RVOT	right ventricular outflow tract
ST junction	sino-tubular junction

SVC	superior vena cava
TAPVD	total anomalous pulmonary venous drainage
TV	truncal valve
TVI	truncal valve insufficiency
VSD	ventricular septal defect
XC	cross clamp

Manuscripts submitted during candidature

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2. **Naimo PS**, Buratto E, Konstantinov IE. Surgery for an anomalous aortic origin of a coronary artery: to do, or not to do? That is the question. *J Thorac Cardiovasc Surg.* 2020. In Press
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Conference presentations during candidature

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Poster presentations

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2. **Naimo PS**, Fricke TA, Yong MS, d'Udekem Y, Brizard CP, Konstantinov IE. Surgery for congenital tracheal stenosis in children.

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Chapter 1: Background and literature review

The incidence of congenital cardiac anomalies range from 4 to 50 out of every 1000 live births (1). They are 6 times more common than chromosomal abnormalities, and 4 times more common than neural tube defects (2). Truncal anomalies occur due to malformation of the aortopulmonary septum. Although rare, truncal anomalies are responsible for significant morbidity and mortality if not repaired early in life. As with many cardiac anomalies, there is a spectrum of disease with truncal anomalies due to variable development of the aortopulmonary septum. A partial defect in aortopulmonary septation may result in an aortopulmonary window, while total defects can result in a common arterial trunk, or truncus arteriosus.

Truncus arteriosus is a rare congenital cardiac defect which results in a single common arterial trunk exiting the heart which supplies the systemic, pulmonary, and coronary circulations. Additionally, patients with truncus arteriosus have a single, often large, common valve – the truncal valve – which separates the truncus itself from both the left and right ventricles. Truncus arteriosus has an incidence of 3 to 10 per 100,000 live births (3, 4). Although only 0.7% – 3% of all congenital cardiac anomalies are due to truncus arteriosus, it accounts for 4% of all critical congenital cardiac anomalies (3, 5, 6). Truncus arteriosus was first reported in an autopsy case by Wilson in 1798 (7), and later the anatomical details were described by Buchanan in a six-month-old infant in 1864 (8). Patients typically present early in life with symptoms of cyanosis and congestive cardiac failure. If left untreated, patients will develop progressive pulmonary vascular obstructive disease and clinically significant truncal valve insufficiency, and will often die within the first year of life (9). There has been remarkable improvement in perioperative and surgical management of truncus arteriosus, which now means an early mortality of 3 – 20% (10-21). Thus, many children who have undergone truncus arteriosus repair are now living well into adulthood, albeit with several reoperations. Despite this, little is known about the

long-term outcomes of truncus arteriosus repair, and this is the focus of this Doctor of Philosophy.

1.1 Anatomy and embryology of the truncal region

From the third week of gestation, the tubular heart elongates and develops alternate dilations and constrictions forming the sinus venosus, an atrium, a ventricle, and the bulbus cordis. The bulbus cordis will subsequently flow into a common outflow tract – the truncus arteriosus (22). Embryonically, the truncus arteriosus – common arterial trunk or *truncus arteriosus communis* – exits the developing heart. Together, the bulbus cordis and the truncus arteriosus form the conotruncus collectively. The truncus arteriosus itself extends distally to the margins of the pericardial cavity, where it becomes continuous with the aortic sac (22). The eventual fate of the embryonic truncus arteriosus is that it will be divided to form the proximal portions of the main pulmonary artery and ascending aorta; while the bulbus cordis will be incorporated as the infundibulum of the right ventricle (22). However, at this stage in embryonic life, the truncus arteriosus is unpartitioned, and thus supports the entire circulation of the embryo.

During the fifth week of gestation, active proliferation of mesenchymal cells within the truncus arteriosus and aortic arches cause a variety of swellings to develop within the vessel wall (23). Initially, a mesenchymal wedge of tissue develops between the fourth and sixth aortic arches and begins projecting inferiorly towards the heart (23). Additional swellings develop in both the walls of the bulbus cordis and truncus arteriosus, resulting in the formation of bulbar and truncal ridges, respectively (collectively named conotruncal ridges) (**Figure 1.1A**). The bulbar and truncal ridges, which are just beginning to separate the outflow tract, run in a spiral course along the walls of the bulbus cordis and truncus arteriosus. The spiral course is paramount for the right ventricle to connect to the future pulmonary circulation and the left ventricle to connect to the systemic circulation (22-24). As the truncal ridges continue to grow, they meet and fuse with the mesenchymal wedge of tissue between the fourth and sixth aortic arch (23). Following this, fusion of the spiraled bulbar and truncal ridges

occurs, commencing distally and progressing proximally (**Figure 1.1B**). Once fused, the now aortopulmonary septum divides both the bulbus cordis and truncus arteriosus into two separate arterial channels – the main pulmonary artery and the ascending aorta (22, 23). Meanwhile, the atrioventricular cushions and septa continue to develop within the heart itself. Complete segregation of the right and left ventricles and their respective outflow tracts is only complete when the interventricular septum fuses with the aortopulmonary septum and the ventricular side of the atrioventricular septum (24).

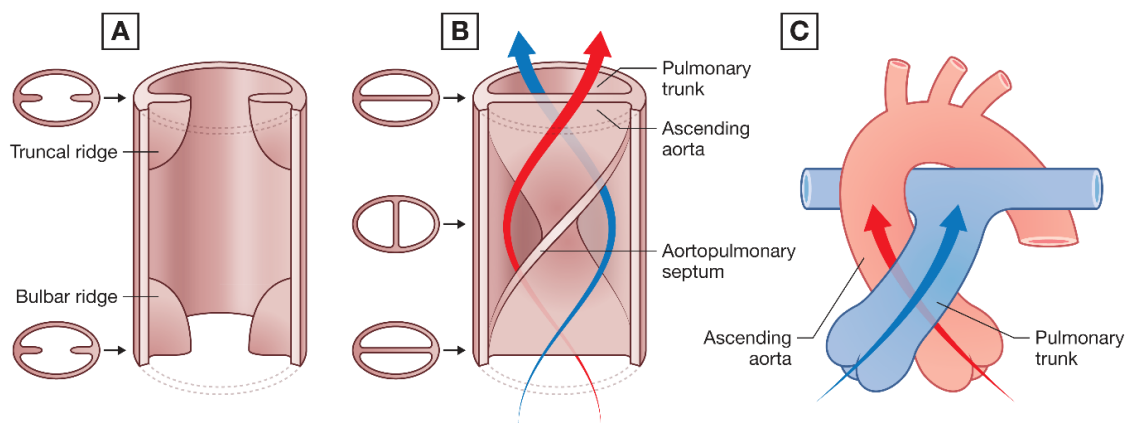


Figure 1.1 Embryological development of the conotruncal region. (A) Development and approximation of the bulbar and truncal ridges. (B) Rotational arrangement of the fused bulbar and truncal ridges. (C) Final anatomical relationship between the ascending aorta and main pulmonary artery.

As a result of the spiral course of the bulbar and truncal ridges, the left and right ventricular outflow tracts and, eventually, the main pulmonary artery and ascending aorta, form a helical arrangement. The cause of and ultimate reason for this spiraling is unknown. Several theories have been proposed, including rotational and torsional forces on the outflow tract generated as a consequence of cardiac looping, and the forces caused by streaming of blood from the ventricles (23-25). The eventual helical arrangement results in the great arteries almost perpendicular to each other (**Figure 1.1C**).

When partitioning of the bulbus cordis and truncus arteriosus is nearly complete, the semilunar valves begin to develop from three swellings around the orifices of the soon to be main pulmonary artery and ascending aorta, respectively. These swellings are reshaped to form three, thin-walled cusps on each outflow tract, which are completed by the ninth week of gestation (23). These will be the pulmonary and aortic valves, respectively.

Truncal anomalies result from a failure of the truncal and bulbar ridges developing normally. Without complete fusion of these ridges, and subsequent aortopulmonary septum, the main pulmonary artery and ascending aorta are in communication with one another. Partial fusion results in an aortopulmonary window, while a total defect of fusion results in *persistent* truncus arteriosus (or truncus arteriosus). The discriminating factor separating these two conditions clinically is that an aortopulmonary window will have two separately formed semilunar valves. As malformations in the conotruncal ridges can cause disruption in the development of the semilunar valves, truncus arteriosus will result in a single truncal valve separating the truncus arteriosus from both the right and left ventricles (26).

1.2 Classification

Classification of truncus arteriosus has been based around the branching of the pulmonary arteries from the truncus itself. Collett and Edwards (27) described four types of truncus arteriosus in 1949: type I, truncus arteriosus with a main pulmonary artery arising from the truncus; type II, truncus arteriosus with separate right and left pulmonary arteries arising adjacent to each other on the posterior aspect of the truncus; type III, truncus arteriosus with right and left pulmonary arteries taking origin from the posterolateral aspect of the truncus; and type IV, truncus arteriosus with no pulmonary artery arising from the truncus itself, rather arising from the thoracic aorta or ductus. The type IV of the Collett and Edwards classification system has often been referred to as 'pseudo-truncus arteriosus'; however, it is no longer considered to be a part of the truncus

arteriosus complex, rather it is a form of pulmonary atresia with a ventricular septal defect (26, 28).

In 1965, the truncus arteriosus classification was revised by Van Praagh & Van Praagh (29) who specified the presence (A) or absence (B) of a ventricular septal defect, as well as describing an associated interrupted aortic arch, if present. Van Praagh and Van Praagh described four types of truncus arteriosus (29): type 1, was the same as Collett and Edwards type I in that the main pulmonary artery arises from the truncus; type 2 included Collett and Edwards type II and type III with separate orifices of the pulmonary arteries; type 3, was an absence of one branch pulmonary artery branch from the truncus and a ductal or aortic origin of the second branch pulmonary artery; and type 4 was a truncus arteriosus with an interrupted aortic arch. The Van Praagh classification is most commonly used when describing truncus arteriosus.

1.3 Concomitant anomalies

Truncus arteriosus is associated with concomitant cardiovascular anomalies in up to 50% of patients (13, 20, 30-32). While patients with truncus arteriosus may present with any number of concomitant anomalies, two important concomitant anomalies are an interrupted aortic arch and a coronary artery anomaly. Both concomitant anomalies have been associated with an increased risk of mortality (32-36).

One of the most significant concomitant anomalies in patients with truncus arteriosus is an interrupted aortic arch. An interrupted aortic arch is present in approximately 10 – 20% of patients with truncus arteriosus, and is commonly type B (13, 28, 32, 37-40) interruption of the Celoria and Patton classification (41). Several previous studies have shown an interrupted aortic arch to be a risk factor for mortality (11, 13, 20, 30, 32, 42, 43). The largest multi-institutional study to date, which was published by the Congenital Heart Surgeon's Society (32), described 50 patients with truncus arteriosus and interrupted aortic arch between 1987 and 1997, with 34 deaths and an overall survival of 31% at 10 years. McCrindle and colleagues reported the outcomes of truncus arteriosus and

concomitant interrupted aortic arch to be worse than interrupted aortic arch alone (43). Furthermore, it appears that truncus arteriosus with interrupted aortic arch and clinically significant truncal valve insufficiency have very poor surgical outcomes. The Congenital Heart Surgeon's Society study (32) demonstrated that patients with an interrupted aortic arch and truncal valve insufficiency had a mortality of 75% (18/24). While concomitant interrupted aortic arch adds significant complexity to patients with truncus arteriosus, many single centre studies associating concomitant interrupted aortic arch and mortality have been from the 1990s. More contemporary studies may have mitigated the risk of mortality likely due to improved surgical techniques and perioperative management of these complex patients. However, the overall experience with truncus arteriosus and interrupted aortic arch is limited. Within the confines of the current literature, it is difficult to ascertain the appropriate surgical management and the long-term outcomes of these complex patients.

Coronary artery anomalies have been reported in 10 – 20% of patients with truncus arteriosus (33, 44-50). Lenox and colleagues (47) reviewed 30 pathological specimens of truncus arteriosus and noted that all hearts had some form of coronary anomaly. Coronary artery anomalies mostly consist of an abnormal origin of a coronary artery, a single coronary artery giving rise to the entire coronary circulation, or a variable epicardial course (48). de la Cruz and colleagues (50) in 1990 described 17 distinct epicardial coronary artery patterns in 39 hearts, though there was no particular association with truncus arteriosus. It has been demonstrated that the presence of a coronary artery anomaly is a risk factor for mortality in patients with truncus arteriosus (13, 34-36). However, given that many studies have small numbers of patients with coronary artery anomalies, it is difficult to determine the best surgical approach. Furthermore, little is known about the long-term outcomes of these patients.

1.4 Genetics

The specific aetiology of truncus arteriosus is unknown. Limited data has suggested both environmental and genetic factors contribute to its development.

The Baltimore-Washington Infant Study assessed that self-reported first-trimester maternal cigarette smoking was associated with an almost two-fold increased risk of truncus arteriosus (51). Additionally, Long and colleagues reported an association between advancing maternal age and truncus arteriosus (52). On a genetic level, associations have been found between truncus arteriosus and deletions in chromosome 22q11.2 (53-56). Approximately 20 – 40% of patients with truncus arteriosus have deletions of 22q11.2 (31, 55-57). Complete deletion of 22q11.2, known as DiGeorge syndrome, results in cardiac defects – often conotruncal anomalies – hypocalcaemia secondary to parathyroid hypoplasia, midline facial clefts, and immunodeficiency secondary to thymic hypoplasia.

Deletions of 22q11.2 are also associated with a dysplastic truncal valve in up to 30% of patients (30, 58), interrupted aortic arch in up to 20% (32, 59), and coronary anomalies in up to 20% (50). Furthermore, truncus arteriosus patients with 22q11.2 deletions have a higher incidence of discontinuity of the pulmonary arteries (53, 58). Deletions of 22q11.2 do not appear to be associated with mortality, but require longer mechanical ventilation, intensive care time, and hospital stay (60-62). Furthermore, these patients are at higher risk of postoperative complications, particularly infections likely due to their immunodeficiency (55, 62).

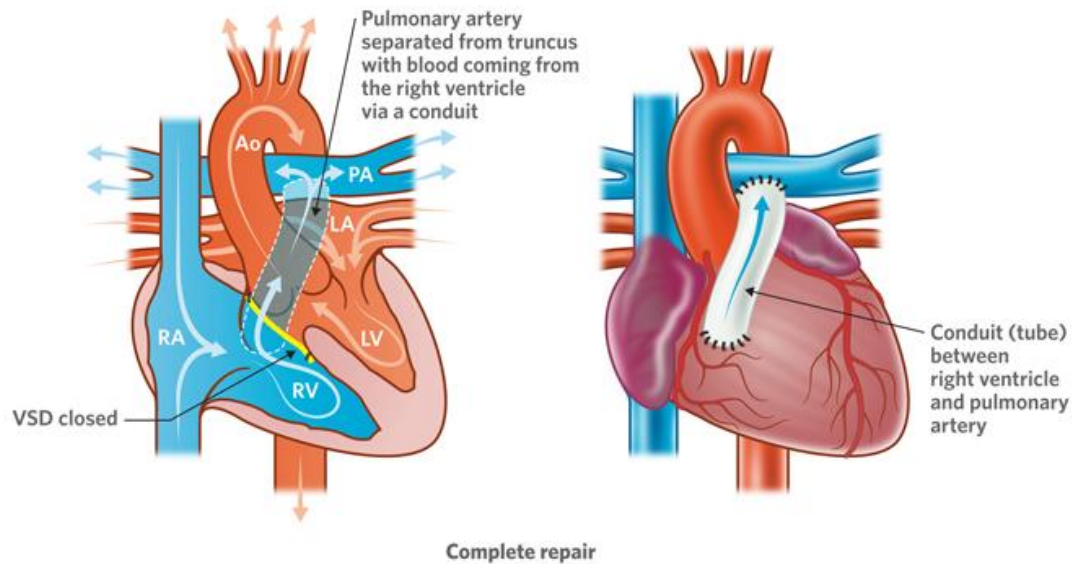
1.5 Surgical management

Early era surgical management of truncus arteriosus involved palliation with pulmonary artery banding which had suboptimal results (63, 64). The first successful intracardiac repair of truncus arteriosus was performed in 1963 (reported in 1974) by Herbert Sloan using a non-valved polytetrafluoroethylene conduit (65). Meanwhile, Giancarlo Rastelli in 1967 described the use of a homograft to connect the right ventricle to the pulmonary arteries – which were detached from the truncus – closing the ventricular septal defect, leaving the original truncus to function as the neo-aorta (66). Dwight McGoon performed the first truncus arteriosus repair using this technique with a valved conduit in 1967

(67). Common practice at the time was for staged repair using pulmonary artery banding early in life, followed by repair of truncus arteriosus when the child was 1 to 3 years of age. This changed in 1976 when Paul Ebert described using a 12mm Hancock (Medtronic, Minneapolis, MN) porcine aortic valve conduit in infants under 6 months of age (68). Though these were pioneering surgical techniques, the policy of the time was to delay repair until patients were a few months of age, which produced mixed results. It was not uncommon for patients to worsen – or even die – whilst awaiting complete repair. This saw a shift to truncus arteriosus repair within the first days of life with positive results as reported by Edward Bove in the early 1990s (69). Pulmonary hypertensive crises became a thing of the past once this approach was adopted for truncus arteriosus and many other forms of congenital heart disease. Nowadays it is well accepted that complete surgical repair of truncus arteriosus is done within the first weeks of life (10, 20, 28, 31, 32, 70, 71). Furthermore, single-staged repair of all concomitant cardiac anomalies is now advocated for, despite the procedure being more time consuming and carrying a greater perioperative risk (13, 32). The basis of reparative surgery is to re-establish continuity between the right ventricle and pulmonary artery and close the ventricular septal defect (**Figure 1.2**).

During surgery, the truncus arteriosus itself is transected and separated from the pulmonary arteries. Transection of the truncus arteriosus allows a symmetrical reconstruction, as there is often a significant size mismatch from the truncal root to the ascending aorta (28). A ventriculotomy is then performed to close the ventricular septal defect and establish a connection between the right ventricle and the pulmonary artery. Reconstruction of the right ventricular outflow tract can be established with a conduit or direct anastomosis of the pulmonary artery to the right ventricle. The best method of right ventricular outflow tract reconstruction is unknown and is usually centre specific. The use of a conduit to reconstruct the right ventricular outflow tract is the most common. However, conduits have limited durability as they cannot grow or regenerate, and therefore inevitably require reoperation (6, 72, 73). Additionally, like any foreign material, they are prone to infection, immunological reactions, and thrombosis (72).

Repair of truncus arteriosus



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Figure 1.2. Complete repair of truncus arteriosus. The pulmonary artery is separated from the truncus itself, the defect closed, and the pulmonary artery connected to the right ventricle with use of a conduit. The ventricular septal defect is closed. *Ao*, aorta; *LA*, left atrium; *LV*, left ventricle; *PA*, pulmonary artery; *RA*, right atrium; *RV*, right ventricle; *VSD*, ventricular septal defect. Reproduced with permission from The Royal Children's Hospital, Melbourne.

Bioprosthetic conduits

The choice of conduit depends on several factors, not limited to homograft availability, patient size and haemodynamics, availability and success of xenografts, and surgeon preference. The Contegra (Medtronic, Minneapolis, MN) bovine jugular vein conduit is predictable in performance and lacks immunogenic properties (74). Dave and colleagues in 2011 reported their experience with Contegra conduits in a variety of patient cohorts, which included 13 patients with truncus arteriosus (75). The overall survival in their study was 92% at 8 years, and freedom from conduit replacement of conduits less than 16mm of 48%, while over 16mm was 98% (75) at 8 years. Similarly, Prior and colleagues noted that conduits over 16mm had fewer deaths and lower rates of conduit failure (76). An issue with oversized conduits however, is that there is an increased risk for coronary artery compression, truncal valve or pulmonary artery distortion, and

they require a larger ventriculotomy (77). An alternative is the Hancock porcine aortic valve conduit which is a bioprosthetic conduit made of a Dacron – woven fabric – tube. The Hancock conduit may be used for patients with high pulmonary artery pressures (78). Belli and colleagues (79) assessed the Hancock conduit for right ventricular outflow tract reconstruction in 268 patients, including 62 truncus arteriosus patients with freedom from conduit reoperation of 32% at 10 years. Its main disadvantage is the rigidity of the Dacron tube, which may cause compression of adjacent structures, particularly the coronary artery (79).

Homografts

An alternative to the bioprosthetic conduits above are the pulmonary and aortic homografts. Homografts have been the conduit of choice in recent decades, but have been limited due to smaller sizes, availability, and potential for obstruction. Homografts reportedly have better haemodynamic properties and increased longevity (80). Vohra and colleagues (81) in 2010 reported on 32 patients who underwent truncus arteriosus repair with 24 aortic homograft and 8 pulmonary homograft reconstructions, resulting in a freedom from reoperation of 68% at 10 years, 37% at 20 years, and 27% at 30 years. As with bioprosthetic conduits, larger homograft sizes increase longevity and improve freedom from reoperation. Vohra and colleagues (81) showed that oversizing the homograft increased longevity of the graft to up to 12 years. Several studies have suggested homografts less than 12mm in diameter fail earlier, requiring earlier replacement (5, 20, 30, 31, 75, 82).

Direct right ventricle to pulmonary artery anastomosis

The biggest hindrance to long-term freedom from conduit reoperation is the lack of living material with the capacity for growth or regeneration. Any child who requires a conduit as part of their truncus arteriosus repair will invariably require reoperation. In an attempt to circumvent this issue, direct anastomosis of the pulmonary artery to the right ventricle, with or without the use of autologous tissues, has been explored (14, 18, 21, 83). In the case of truncus arteriosus type

1, the main pulmonary artery can be sutured to the right ventriculotomy with the anterior portion of the right ventricular outflow tract being reconstructed with a pericardial patch and a monocusp valve created of autologous pericardium. This method has been shown to have comparable mortality to conduit repair, with observed interval growth of the right ventricular outflow tract, and subsequent delayed reoperation (14, 18). Danton and colleagues (14) reported a freedom from right ventricular outflow tract reoperation of 89% at 4 years in patients who underwent direct anastomosis of the main pulmonary artery to the right ventricle compared to 58% at 4 years in patients who underwent conduit repair. An issue with direct anastomosis of the pulmonary artery to the right ventricle is that without favourable anatomy, it often leads to pulmonary artery distortion which necessitates early reoperation (84). Another draw-back to this method is the potential for severe pulmonary regurgitation, which has not yet been observed likely due to short follow-up (14, 18, 21, 83). Augmentation of the anastomosis with a patch anteriorly has been suggested to avoid pulmonary artery distortion, which would also allow for interval growth and avoid or delay obstruction to the right ventricular outflow tract or the branch pulmonary arteries (14). While early mortality is similar between direct anastomosis and using a conduit, there is limited long-term data (14, 18, 21).

1.6 Truncal valve

Truncal valve insufficiency occurs in approximately 25% of patients (42, 81, 85). The truncal valve is bicuspid in 7 – 22% of patients; tricuspid in 55 – 70%; quadricuspid in 9 – 25%; and pentacuspid in less than 2% (71, 86-88). Some have suggested that truncal valve insufficiency was one of the most important factor influencing early outcomes (15, 20, 32, 42, 89, 90). It seems that mild truncal valve insufficiency is often well tolerated and often does not require intervention (71), while moderate or greater truncal valve insufficiency is associated with mortality (30, 34, 35, 42, 71, 85, 91).

There is no uniform approach in managing truncal valve insufficiency. Various techniques for truncal valve repair have been described, including

suturing partially developed commissures, resuspension of leaflets, resection of redundant portion of leaflets, annuloplasty of commissures and pericardial leaflet extension, tricuspidization of a quadricuspid valve, or repair of the bicuspid valve. Each of these techniques have been reported with varying success with concomitant truncal valve surgery having an early mortality rate as high as 30% (42). As such, there are varying opinions as to when truncal valve repair should be undertaken. Most surgeons tend to agree that mild or less truncal valve insufficiency will be well tolerated and does not require surgical intervention. Similarly, most agree that severe truncal valve insufficiency is problematic and often requires attention. However, contention arises when discussing moderate truncal valve insufficiency. Several studies have shown that moderate to severe truncal valve insufficiency was a risk factor for early reoperation for truncal valve replacement (20), early mortality, and generally poorer long-term outcomes if not adequately addressed during the initial operation (30, 34, 35, 42, 85, 91). Conversely, Tlaskal and colleagues (20) determined that persistent moderate insufficiency is usually well tolerated and does not lead to an increase in early mortality, although was associated with the need for eventual truncal valve replacement.

Furthermore, little is known about how the truncal valve function is in the long-term. In particular, it is unclear whether addressing moderate truncal valve insufficiency at initial truncus arteriosus repair is beneficial in the long-term, or if leaving the truncal valve untouched leads to progressive insufficiency and eventual surgical intervention.

1.7 Quality of life

As the previous sub-chapters have identified, there is a reasonable understanding of the short term outcomes following truncus arteriosus repair. However, the long-term outcomes are not well understood. There is an ever growing population of truncus arteriosus patients reaching adulthood, yet there is no information about their quality of life. As most patients who undergo truncus

arteriosus repair require reoperation throughout their lifetime, it is unclear whether this negatively impacts their quality of life.

O'Bryne and colleagues (92) reported on 25 patients with a median age of 11.8 years who underwent truncus arteriosus repair and assessed their health status. Factors such as exercise tolerance, VO₂ max, maximal work, and forced vital capacity were all lower than normal for age and sex (92). Additionally, health-related quality of life was diminished and comparable with that of children with severe heart disease, represented by the Fontan population (92). However, psychosocial functional status was not significantly diminished. These findings collectively represent moderate morbidity and disability (92). Of note, patients with DiGeorge syndrome have significantly worse neurodevelopmental and functional outcomes than do those without 22q11.2 deletions (62).

By understanding the health-related quality of life following truncus arteriosus repair, we may be able to assess the overall impact of this condition on the individual, and potentially provide a reference for management to address physical or psychosocial issues that may arise.

1.8 Current outcomes

Early mortality for truncus arteriosus is 3 – 20%, depending on perioperative status and the presence of concomitant anomalies (10-21, 31, 71). Long-term survival after truncus arteriosus repair has been reported to be approximately 75% at 20 years (10-21, 31, 71). As the previous sub-chapters of this thesis have demonstrated, there are several factors which may determine the success of truncus arteriosus repair, including but not limited to, truncal valve insufficiency, an interrupted aortic arch, a coronary artery anomaly, or the presence of DiGeorge syndrome. The current mortality following truncus arteriosus repair are summarised in **Table 1.1**.

Many of the current studies on truncus arteriosus have several limitations. Firstly, most are single centre reports with patient cohorts of less than 100 patients. This makes assessment of risk factors for mortality and reoperation

limited due to the small number of patients and outcomes. Secondly, follow-up time of patients seldom exceeds 10 years. A large proportion of patients who have had truncus arteriosus repair as children are now well into adulthood. Therefore, there is little known about the long-term implications of truncus arteriosus in the current literature. Importantly, there is limited understanding on the long-term cardiac function, frequency of reoperation, and the quality, durability, and function of the truncal valve. Lastly, though there has been recent focus on quality of life following congenital heart surgery, there are no studies assessing the long-term quality of life of patients with repaired truncus arteriosus.

Table 1.1 Reported outcomes of truncus arteriosus repair

Study	Year	Study Period	Patients (n)	Age at Repair (median, days)	Early Mortality	Overall survival	Follow-up (mean, years)
Lacour-Gayet et al (83)	1996	1988-1995	56	41	16.1% (9/56)	80% at 7 years	3.2
Rajasinghe et al (30)	1997	1975-1995	165	106	Not reported	85% at 10 years	10.5#
Urban et al (10)	1998	1987-1997	46	62	4.3% (2/46)	93% at 5 years	3.0
Williams et al (97)	1999	1953-1997	148	38	50.0% (74/148)	83% at 10 years	Not reported
Jahanjiri et al (11)	2000	1992-1998	50	14	4.0% (2/50)	96% at 3 years	1.9#
Schrieber et al (96)	2000	1976-1998	106	134	17.9% (19/106)	61% at 10 years	6.0
Alexiou et al (12)	2001	1974-1994	23	51	17.4% (4/23)	79% at 10 years	14.8
Brown et al (37)	2001	1978-2000	60	76*	16.7% (10/60)	82% at 10 years	9.4
Danton et al (14)	2001	1988-2000	61	34	13.1% (8/61)	73% at 5 years	4.2
Thompson et al (15)	2001	1992-1999	65	10	4.6% (3/65)	92% at 3 years	2.7#
Kalavrouziotis et al (16)	2006	1993-2005	29	28	3.4% (1/29)	93% at 6 years	6.2
Henaine et al (17)	2008	1986-2003	153	35	17.0% (26/153)	79% at 10 years	8.1
Raisky et al (18)	2009	2000-2006	32	74*	15.6% (5/32)	76% at 5 years	3.3
Hawkins et al (95)	2010	1999-2008	42	31	9.5% (4/42)	82% at 5 years	5.0
Tlaskal et al (20)	2010	1981-2009	83	54	22.9% (19/83)	75% at 10 years	10.9
Vohra et al (81)	2010	1964-2008	32	14	9.4% (3/32)	91% at 20 years	24.5#
Xu et al (21)	2010	2000-2006	23	350	8.7% (2/23)	91% at 5 years	4.1
Buckley et al (94)	2019	2009-2016	216	10	6.9% (15/216)	87% at 5 years	2.9#
Ivanov et al (93)	2019	1997-2017	97	32	17.5% (17/97)	68% at 10 years	2.5#

* denotes mean age at repair; # denotes median follow-up time.

1.9 Thesis outline

Aims and scope of this thesis

Truncus arteriosus is a rare condition with high morbidity and mortality. As I have demonstrated in the previous subchapter, there is a limited cumulative experience with this condition, particularly the surgical techniques, risk, and long-term management. This Doctor of Philosophy primarily aimed to determine the long-term outcomes after surgical repair of truncus arteriosus. A broad range of factors were explored including surgical technique, additional cardiac conditions, and quality of life. Each of these factors is the subject of a large retrospective review.

This thesis has refined our understanding and management of truncus arteriosus and will ultimately improve the short- and long-term outcomes of many patients with this rare condition.

The aims of this thesis were therefore:

- To assess the risk factors for poor outcomes following repair of truncus arteriosus, with particular focus on concomitant anomalies;
- To determine the impact and management of the truncal valve, with a focus on the long-term outcomes and function of the truncal valve; and
- To examine the quality of life of patients following truncus arteriosus repair.

Chapter objectives

- Chapter 2: Determine the short and long-term single centre outcomes of truncus arteriosus repair, with a focus on risk factors for poor outcomes.
- Chapter 3: Evaluate the short and long-term outcomes of truncus arteriosus repair from a multi-centre perspective. A focus was placed on the impact of concomitant anomalies and age of repair.
- Chapter 4: Evaluate the long-term outcomes of truncus arteriosus and a concomitant intramural coronary artery.
- Chapter 5: Evaluate the long-term outcomes of truncus arteriosus and concomitant interrupted aortic arch, with particular focus on reoperation on the aortic arch.
- Chapter 6: Investigate the impact of truncal valve insufficiency on truncus arteriosus repair and determine the optimal management of truncal valve.
- Chapter 7: Evaluate the surgical management and outcomes of patients with a quadricuspid truncal valve.
- Chapter 8: Investigate the long-term quality of life in adult survivors of truncus arteriosus repair, with comparison to an age-matched Australian control population and comparable complex cardiac defects with low reoperation rates.

Chapter 2: Outcomes of truncus arteriosus repair in children: 35 years of experience from a single institution

2.1 Introduction

Truncus arteriosus is rare congenital cardiac defect which is often repaired in the first few weeks of life. Over time, there has been remarkable improvement in perioperative and surgical management of truncus arteriosus. Nowadays, early mortality has been reported to be between 3 to 20%, with overall survival of 65 – 90% at 10 years (10-21). Many children who have undergone truncus arteriosus repair are now living well into adulthood, albeit with several reoperations.

However, most literature on truncus arteriosus is comprised of small studies of less than 100 patients and lack significant long-term follow up. Previous reports on risk factors for mortality and reoperation are conflicting, likely due to the low number of patients and events. The Royal Children's Hospital, Melbourne, has one of the largest single centre experiences with truncus arteriosus with the longest reported follow-up time.

The following two chapters aim to address the current mortality and risk factors for poor outcomes following truncus arteriosus repair, as well as the impact of associated cardiac anomalies. In order to establish the local outcomes and predictors of survival and reoperation, a review was conducted of all patients who underwent truncus arteriosus repair at The Royal Children's Hospital between 1979 and 2015. During this period, there were 171 consecutive patients with truncus arteriosus who underwent surgical repair at The Royal Children's Hospital. There were no deaths whilst awaiting truncus arteriosus repair.

This study demonstrated an early mortality of 11.7% (20/171) and overall survival of 73.6% at 30 years. Over half of all deaths occurred within the first year following truncus arteriosus repair. Low operative weight (less than 2.5kg) and the presence of a coronary artery anomaly were identified as risk factors for early mortality. Interestingly, 3 of 6 patients who had a coronary artery anomaly and

died had a major branch coronary artery crossing the right ventricular outflow tract. DiGeorge syndrome was identified as a risk factor for late mortality, with a high proportion of these deaths being attributed to infection.

It was also found that freedom from right ventricular outflow tract reoperation was only 4.6% at 20 years. Despite this, all surviving patients were in New York Heart Association Class I/II after a median follow-up time of 19 years. Most patients had normal or mildly reduced right ventricular function.

Another important finding in this study was that both concomitant interrupted aortic arch and truncal valve insufficiency, which have been previously been reported as risk factors for mortality (20, 32, 42), appear to have been ameliorated at The Royal Children's Hospital.

Overall, this study suggested that the long-term outcomes following truncus arteriosus repair are excellent following the first year after repair, albeit with a high rate of reoperation.

2.2 Naimo PS, et al. Semin Thoracic Surg. 2016;28:500-11

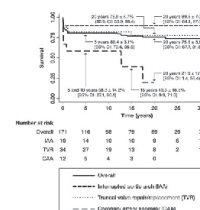
ORIGINAL SUBMISSION

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.



Kaplan-Meier overall survival following truncus arteriosus repair.

Central Message

Postoperative extracorporeal membrane oxygenation, operative weight < 2.5 kg, 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.

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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.

OUTCOMES OF TRUNCUS ARTERIOSUS REPAIR

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 used³. 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 (Stata-Corp LP, College Station, TX). Continuous data were expressed as means $\pm$ 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 $80.4 \pm 3.1\%$ (95% CI: 73.6-85.6) at 10 years and $73.6 \pm 4.0\%$ (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	<i>n</i> = 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

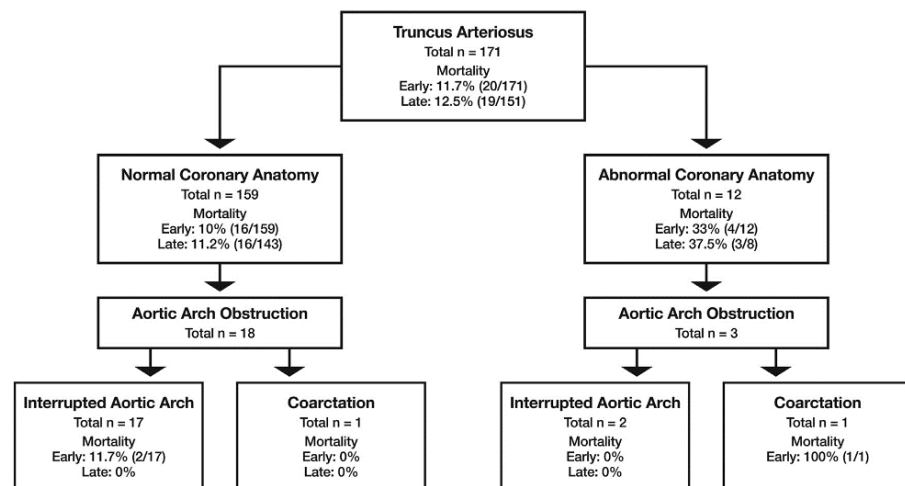
There have been 207 reoperations in 114 patients. Freedom from any reoperation was $23.3 \pm 3.7\%$ (95% CI: 16.3-31.0) at 10 years and $3.2 \pm 1.8\%$ (95% CI: 0.9-8.2) at 20 years. Freedom from reoperation for RVOT obstruction, aortic arch obstruction, and TV insufficiency is shown in Figure 4.

OUTCOMES OF TRUNCUS ARTERIOSUS REPAIR

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.

OUTCOMES OF TRUNCUS ARTERIOSUS REPAIR

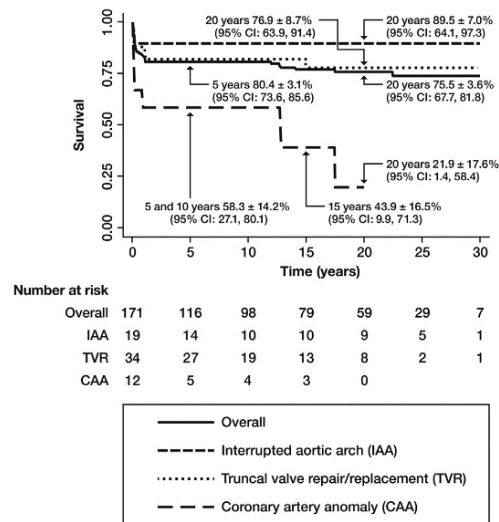


Figure 2. Kaplan-Meier overall survival following truncus arteriosus repair.

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.

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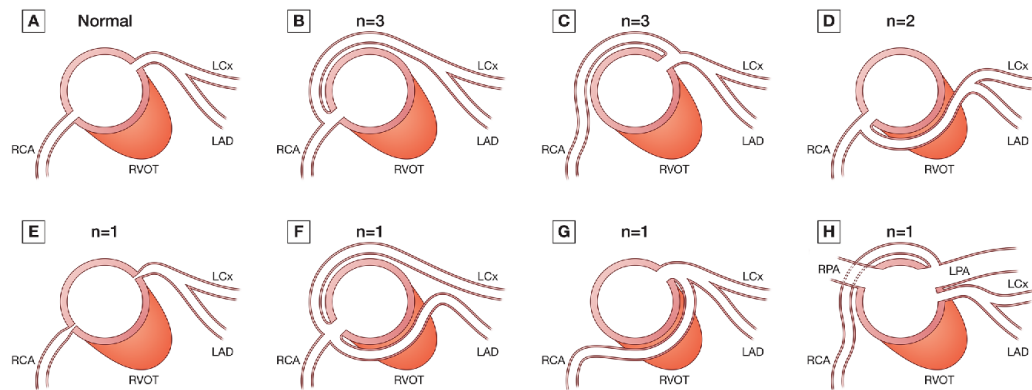


Figure 3. Coronary artery anomalies. Most patients had normal coronary anatomy (A). Most common coronary anomaly was a single coronary orifice (B-D, F, and G). One patient had narrow coronary ostia immediately on top of the commissures of a bicuspid truncal valve (E). In 1 patient, the right coronary 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 $29.2 \pm 4.4\%$ (95% CI: 20.9-38.0) at 10 years and $4.6 \pm 2.4\%$ (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 $70.7 \pm 14.3\%$ (95% CI: 33.7-89.5) at 5 years and $47.1 \pm 21.5\%$ (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 $89.5 \pm 7.0\%$ (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 $70.1 \pm 11.5\%$ (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

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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, tricuspid valve; VF, ventricular fibrillation.

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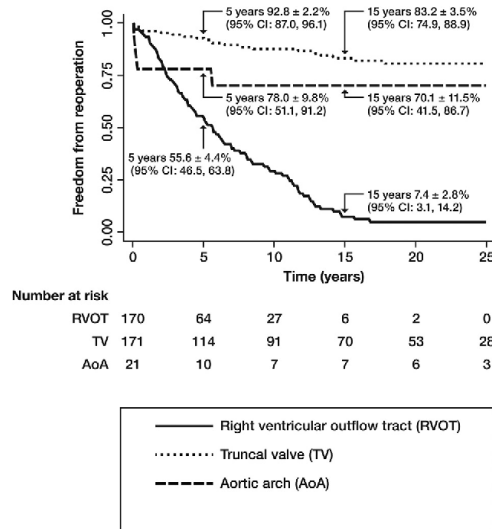


Figure 4. Freedom from reoperation following truncus arteriosus repair.

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 $51.4 \pm 12.2\%$ (95% CI: 25.8-72.3) at 10 years and $25.8 \pm 19.1\%$ (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 $92.6 \pm 2.4\%$ (95% CI: 85.9-96.3) at 10 years and $86.5 \pm 3.6\%$ (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 $82.4 \pm 6.5\%$ (95% CI: 64.9-91.7) at 10 years and $76.9 \pm 8.7\%$ (95% CI: 63.9-91.4) at 20 years (Fig. 2). Neither TV

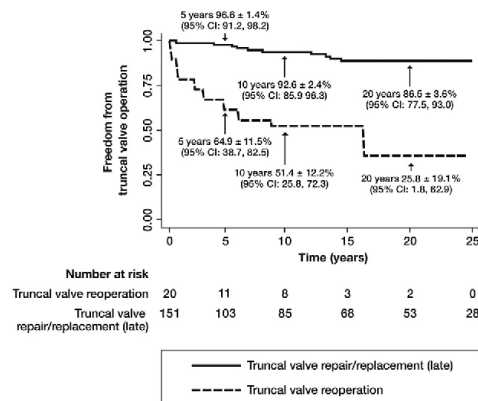


Figure 5. Freedom from truncal valve operation in those ($n = 20$) who had concomitant truncal valve repair during the initial complete repair of the truncus (dashed line) and those ($n = 151$) who did not (solid line).

OUTCOMES OF TRUNCUS ARTERIOSUS REPAIR

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 al⁹ also noted that 56% (13/23) of late deaths occurred within the first year following repair. Similarly, Tlaskal et al⁶ 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 al¹³ 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 al¹⁴ described their experience with 61 patients with TA between 1988 and

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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 al¹⁵ 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 al² 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

OUTCOMES OF TRUNCUS ARTERIOSUS REPAIR

study was 13.2% (5/38). Brown et al¹⁵ 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 al²⁷ 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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Chapter 3: Truncus arteriosus repair: a 40-year multi-centre perspective

3.1 Introduction

In the previous Chapter, it was shown that the long-term outcomes of truncus arteriosus repair at The Royal Children's Hospital are good. However, given the small number of outcomes it is difficult to completely elucidate risk factors for mortality and reoperation. I therefore extended the scope of review to include paediatric centres in Queensland, Australia. An additional 66 patients underwent truncus arteriosus repair at the Queensland Children's Hospital (formerly Lady Cilento Children's Hospital), and The Prince Charles Hospital. To our knowledge, this is the largest experience assessing the long-term outcomes of truncus arteriosus repair.

During the study period of 1979 to 2018, 255 patients underwent truncus arteriosus repair across the three centres in Australia. Early mortality was 13.3% (34/255) and overall survival was 76.8% at 20 years. Consistent with our single centre results, neither truncal valve insufficiency nor the presence of an interrupted aortic arch were identified as risk factors for mortality. However, neonatal surgery and low operative weight (less than 2.5kg) were found to be risk factors for early mortality. This was an interesting finding given that worldwide common practice nowadays is to operate early in the neonatal period. When examining neonatal deaths closely, it was found that many of these patients had significant concomitant defects or presented in a more critical state.

The presence of a coronary artery anomaly and the need for early reoperation were both identified as risk factors for late mortality. Taken in combination with our single centre report which found coronary artery anomalies to be a significant risk factor for early mortality, I suggest that it is paramount the ostia and epicardial course of the coronary arteries are clearly identified. It is clear that coronary artery anomalies play a significant role in the successful outcome of truncus arteriosus repair.

Interestingly, this study demonstrated that most deaths – 82.5% (47/57) – in fact occurred within the first year following repair. If a patient survives to 1 year after repair, survival thereafter is excellent, with an estimated survival of 93.5% at 20 years. This is an important prognostic factor and important information for the patient's family.

3.2 Naimo PS, et al. J Thorac Cardiovasc Surg. 2020

The following study has been accepted for publication in the Journal of Thoracic and Cardiovascular Surgery.

3.2.1 Background

Truncus arteriosus is a rare and complex congenital cardiac anomaly associated with significant morbidity and mortality. Previous studies have reported an early mortality of 4 – 20%, depending on perioperative status and the presence of concomitant anomalies (10-21, 31, 71). Long-term survival after truncus arteriosus repair has been reported to be approximately 75% at 20 years (10-21, 31, 71). While long-term functional outcomes are reportedly good, there is a significant reoperation rate (10-21, 31, 71). There are few large cohort studies adequately assessing the long-term outcomes of these complex patients. We therefore sought to determine the long-term surgical outcomes of patients who underwent truncus arteriosus repair at 3 Australian institutions with a similar approach to truncus arteriosus repair.

3.2.2 Methods

Data were obtained by review of medical records from initial admission until last cardiology follow-up at The Royal Children's Hospital, Melbourne; Queensland Children's Hospital, Brisbane; and The Prince Charles Hospital, Brisbane. The Royal Children's Hospital Human Research Ethics Committee and the Children's Health Queensland Hospital and Health Service Research Governance approved the current study.

Between 1979 and 2018, 255 consecutive patients underwent truncus arteriosus repair and were included in the study. Patient characteristics are summarised in **Table 3.1**. Twenty patients underwent surgical procedures prior to truncus arteriosus repair. This included pulmonary artery banding (n=12),

pulmonary artery reconstruction (n=4), major aortopulmonary collateral artery ligation (n=3), modified Blalock-Taussig shunt (n=2), interrupted aortic arch repair (n=2), and tracheoesophageal fistula repair (n=2). Most patients (16/20, 80%) who had prior surgical procedures presented before 1998. There were 78 patients who required admission to the intensive care unit prior to truncus arteriosus repair, 2 of whom required extracorporeal membrane oxygenation (ECMO).

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. A modified Van Praagh classification for truncus arteriosus was used (29).

Data analysis

Data was analysed using STATA 14 (StataCorp LP, College Station, TX). Continuous data are expressed as mean $\pm$ standard deviation (range), whilst skewed continuous data are expressed as median (range). Categorical data are summarised as frequencies and percentages. Chi-squared, Student's t-test, and Mann-Whitney U test were used as appropriate. Univariable and multivariable logistic regression, and Cox-proportional hazard modelling were used to determine risk factors for mortality and reoperation. A step-wise forward selection model was used to create the multivariable model. Variables were selected based on significance in the univariable model to a threshold of $p = 0.2$, and variables previously known to impact the outcome of interest. The likelihood ratio test was used upon addition and subtraction of variables to assess benefit to the model. With regard to Cox-proportional hazard modelling, the proportional hazard assumption was tested and valid for the outcomes described. Kaplan-Meier survival curves were used to analyse and plot time-related endpoints. Log-rank test was used to compare survivor functions. Statistical significance was set at $p < 0.05$.

Table 3.1. Characteristics of patients who underwent truncus arteriosus repair (n=255)

Variable	% (N)
Neonates	36.5% (93/255)
Male	54.5% (139/255)
Median age at repair	44 days (range 1 day to 8.7 years)
Median weight at repair	3.5kg (range 1.2kg to 23.0kg)
Classification	
Type 1	61.6% (157/255)
Type 2	26.7% (68/255)
Type 3	11.0% (28/255)
Unspecified	0.8% (2/255)
Truncal valve anatomy	
Bicuspid	10.6% (27/255)
Tricuspid	58.0% (148/255)
Quadricuspid	30.2% (77/255)
Truncal valve insufficiency	
None	54.9% (140/255)
Mild	29.8% (76/255)
Moderate	11.8% (30/255)
Severe	2.4% (6/255)
Syndromes	21.2% (54/255)
DiGeorge Syndrome	15.3% (39/255)
Other Syndromes	4.7% (12/255)
Concomitant anomalies	
ASD	32.5% (83/255)
PDA	21.2% (54/255)
Aortic arch obstruction	14.1% (36/255)
IAA	12.9% (33/255)
Type A	21.2% (7/33)
Type B	72.7% (24/33)
Type C	6.1% (2/33)
CoA	1.2% (3/255)
Coronary artery anomaly	10.6% (27/255)
MAPCA	3.1% (8/255)
AVSD	0.4% (1/255)
TAPVD	0.4% (1/255)

ASD, atrial septal defect; *AVSD*, atrioventricular septal defect; *CoA*, coarctation of aorta; *IAA*, interrupted aortic arch; *MAPCA*, major aortopulmonary collateral artery; *PDA*, patent ductus arteriosus; *TAPVD*, total anomalous pulmonary venous drainage.

3.2.3 Results

Median age at repair was 44 days (range 1 day to 8.7 years) and median weight at repair was 3.5kg (range 1.2kg to 23.0kg). Median age at repair was 81.5 days (range 1 day to 8.7 years) between 1979 and 1988; 68.5 days (range 3 days to 1.9 years) between 1989 and 1998; 31 days (range 2 days to 2.0 years) between 1999 and 2008; and 21 days (range 1 day to 3.1 years) between 2009 and 2018 ($p < 0.001$). Surgery was performed via midline sternotomy with cardiopulmonary bypass in all patients. The pulmonary arteries were detached from the truncus arteriosus and continuity between the right ventricle and pulmonary artery was established via a conduit ($n=239$) or direct anastomosis ($n=16$) of the main pulmonary artery to the right ventricle, with or without a monocusp valve. Concomitant cardiovascular surgery at truncus arteriosus repair included: atrial septal defect closure in 93 patients; aortic arch reconstruction in 34 patients; pulmonary artery reconstruction in 23 patients; coronary artery repair in 5 patients; major aortopulmonary collateral artery ligation in 4 patients; placement of an aortopulmonary shunt in 1 patient; and total anomalous pulmonary venous drainage repair in 1 patient; Median cardiopulmonary bypass time was 133min (range 33min to 439min) and median aortic cross clamp time was 75min (range 31min to 263min).

Mortality

Early mortality was 13.3% (34/255). In the last 20 years, median age at surgery decreased from 70.5 days (range 1 day to 8.7 years) between 1979 and 1998, to 26 days (range 2 days to 3.1 years) between 1999 and 2018 ($p < 0.001$). Early mortality between 1979 and 1998 was 11.9% (15/126); and 14.7% (19/129) between 1999 and 2018 ($p = 0.507$). Risk factors for early mortality are summarised in **Table 3.2**. There was no difference in early mortality between centres (18%, 12/67 vs. 12%, 22/188; $p = 0.199$).

There were 23 late deaths (10.4%, 23/221) and overall survival was $76.8 \pm 2.9\%$ (95% CI: 70.4, 81.9) at 20 years. Most deaths (82.5%, 47/57) occurred within the first year following repair. If a patient survived to 1 year, survival

thereafter was excellent with Kaplan-Meier survival of $93.5 \pm 2.2\%$ (95% CI: 87.6, 96.7) at 20 years (**Figure 3.1**). Causes of death are presented in **Table 3.3**. The rate of late deaths was not impacted by era of surgery, with 13 late deaths between 1979 and 1998, and 10 late deaths between 1999 and 2018 ($p = 0.524$). Risk factors for overall mortality are summarised in **Table 3.2**.

Table 3.2. Risk factors for mortality following truncus arteriosus repair

Early Mortality					
Variable	Early Mortality (%)	Univariable		Multivariable-regression	
		OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
Moderate TVI	20.0% (6/30)	1.8 (0.7, 4.8)	0.238		
Severe TVI	33.3% (2/6)	3.5 (0.6, 19.7)	0.161		
AA obstruction	27.8% (10/36)	3.1 (1.3, 7.3)	0.008	1.7 (0.6, 4.3)	0.299
Coronary anomaly	22.2% (6/27)	2.0 (0.8, 5.5)	0.158		
Preoperative ICU	20.5% (16/78)	2.3 (1.1, 4.7)	0.028		
Neonate	23.7% (22/93)	3.9 (1.8, 8.3)	<0.001	2.9 (1.3, 6.8)	0.012
Low weight (< 2.5kg)	41.2% (7/17)	5.5 (1.9, 15.6)	0.001	4.0 (1.3, 12.1)	0.013
TV surgery	18.2% (6/33)	1.5 (0.6, 4.1)	0.383		
Overall Mortality					
Variable	Univariable		Cox-proportional hazard		
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	
AA obstruction	1.7 (0.8, 3.3)	0.142			
Coronary anomaly	2.7 (1.3, 5.4)	0.005	2.4 (1.2, 4.9)	0.013	
DiGeorge syndrome	1.1 (0.5, 2.1)	0.870			
Neonate	2.4 (1.3, 4.1)	0.002			
Low weight (< 2.5kg)	3.9 (1.8, 8.3)	< 0.001	3.5 (1.6, 7.6)	0.001	
TV surgery	1.3 (0.6, 2.8)	0.468			
Early reoperation	1.7 (0.9, 3.4)	0.103			

AA, aortic arch; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; TV, truncal valve; TVI, truncal valve insufficiency

Table 3.3. Causes of death following truncus arteriosus repair

Cause of death	Number of patients
Early deaths	13.3% (34/255)
Cardiac failure	4.7% (12/255)
Myocardial ischaemia	1.6% (4/255)
Respiratory failure	1.6% (4/255)
Sepsis	1.2% (3/255)
Sudden cardiac arrest	1.2% (3/255)
Unable to wean from CPB	1.2% (3/255)
Unknown	0.8% (2/255)
Brain haemorrhage and respiratory failure	0.4% (1/255)
Exsanguination from conduit	0.4% (1/255)
Seizure disorder	0.4% (1/255)
Within one year	6.3% (14/221)
Unknown	2.3% (5/221)
Respiratory failure	1.4% (3/221)
Respiratory tract infection	0.9% (2/221)
Cardiac failure	0.5% (1/221)
Progressive pulmonary hypertension	0.5% (1/221)
Sudden cardiac arrest	0.5% (1/221)
Unknown infection	0.5% (1/221)
After one year	4.8% (10/207)
Acute respiratory failure secondary to infection	1.4% (3/207)
Unknown	0.9% (2/207)
Candida sepsis with T-cell lymphoma	0.5% (1/207)
Cardiac failure	0.5% (1/207)
Sudden cardiac arrest	0.5% (1/207)
Thromboembolism following catheterisation	0.5% (1/207)

CPB, cardiopulmonary bypass

Neonatal Surgery

There were 93 neonates who underwent truncus arteriosus repair. The proportion of neonates increased over time from 19% (24/126 – 23/110 from Melbourne, 1/16 from Queensland) between 1979 and 1998, to 53% (68/128 – 40/77 from Melbourne, 28/51 from Queensland) between 1999 and 2018 ($p < 0.001$). There were no significant differences in neonatal volume between centres over time ($p = 0.163$ between 1979 and 1988; $p = 0.74$ between 1999 and 2018). The median age of neonates was 13 days (range 1 day to 28 days), while the median age of older patients was 70.5 days (range 30 days to 8.7 years). Early mortality in neonates was 23.7% (22/93) compared to 7.4% (12/162) in older patients ($p < 0.001$). Neonatal surgery was a risk factor for early mortality on multivariable analysis (OR 2.9, 95% CI: 1.3, 6.8, $p = 0.012$). The proportion of neonates increased over the study period (**Figure 3.2A**) from 21% between 1979–1988, to 63% between 2009–2018 ($p < 0.001$), however the proportion of neonatal early deaths (25%, 6/24 between 1979 and 1998 vs. 23%, 16/69 between 1999 to 2018) did not significantly change over time ($p = 0.322$). Overall survival in neonates was $68.9 \pm 4.9\%$ (95% CI: 58.2, 77.4) at 20 years, compared to $82.2 \pm 3.4\%$ (95% CI: 74.4, 87.8) at 20 years in older patients ($p = 0.002$, **Figure 3.2B**).

Total deaths within one year was 38% (9/24) in neonates who underwent truncus arteriosus repair in week one, 21% (6/29) in week two, 19% (5/27) in week three, and 46% (6/13) in week four (**Figure 3.3A**). The highest proportion of total deaths within one year occurred in neonates in week one and four, though these did not reach statistical significance. A 10-year survival of neonates who underwent surgery in the first week of life ($n=24$) was $60.9 \pm 10.2\%$ (95% CI: 38.3, 77.4); in the second week of life ($n=29$) was $71.8 \pm 8.5\%$ (95% CI: 51.5, 84.8); in the third week of life ($n=27$) was $81.3 \pm 7.5\%$ (95% CI: 60.8, 91.8); and in the fourth week of life ($n=13$) was $53.9 \pm 13.8\%$ (95% CI: 24.8, 76.0) (**Figure 3.3B**). Both neonates in the first week (log-rank $p = 0.007$), and fourth week (log-rank $p = 0.002$) had worse survival than those operated in weeks two and three.

Neonates had a higher proportion of significant comorbidities, i.e., 1) significant concomitant anomalies (moderate or greater truncal valve

insufficiency, interrupted aortic arch, coronary artery anomaly, low operative weight) and/or 2) requiring preoperative intensive care, when compared to older patients (78%, 73/93 vs. 39%, 63/162, $p < 0.001$). Within the neonatal group, significant comorbidities were present in 96% (23/24) who were underwent TA repair in the first week of life, 76% (22/29) in the second week; 67% (18/27) in the third week; and 77% (10/13) in the fourth week. Neonates in the first week had a higher proportion of significant comorbidities as compared to weeks two to four combined (96%, 23/24 vs. 72%, 50/69, $p = 0.019$). When including only patients who only had significant concomitant anomalies (i.e. excluding those who solely required intensive care and did not have concomitant anomalies), we observed that significant concomitant anomalies were present in 92% (22/24) of neonates in the first week; 62% (18/29) in the second week; 41% (11/27) in the third week; and 31% (4/13) in the fourth week. Neonates who required TA repair in the first week of life had a higher proportion of significant concomitant anomalies than those who had repair in week two ($p = 0.001$), week three ($p < 0.001$), and week four ($p < 0.001$). Furthermore, neonates in week four had the highest proportion of patients solely requiring intensive care for management of heart failure (46%, 6/13) which was statistically significant compared to week one (4%, 1/24; $p = 0.004$) and week two (14%, 4/29; $p = 0.045$), but not statistically different to week three (26%, 7/27; $p = 0.28$). Additionally, neonates in week four appeared to have more intensive care admissions for the management of heart failure than the following 8 weeks of life (46%, 6/13 vs. 20%, 19/93; $p = 0.074$).

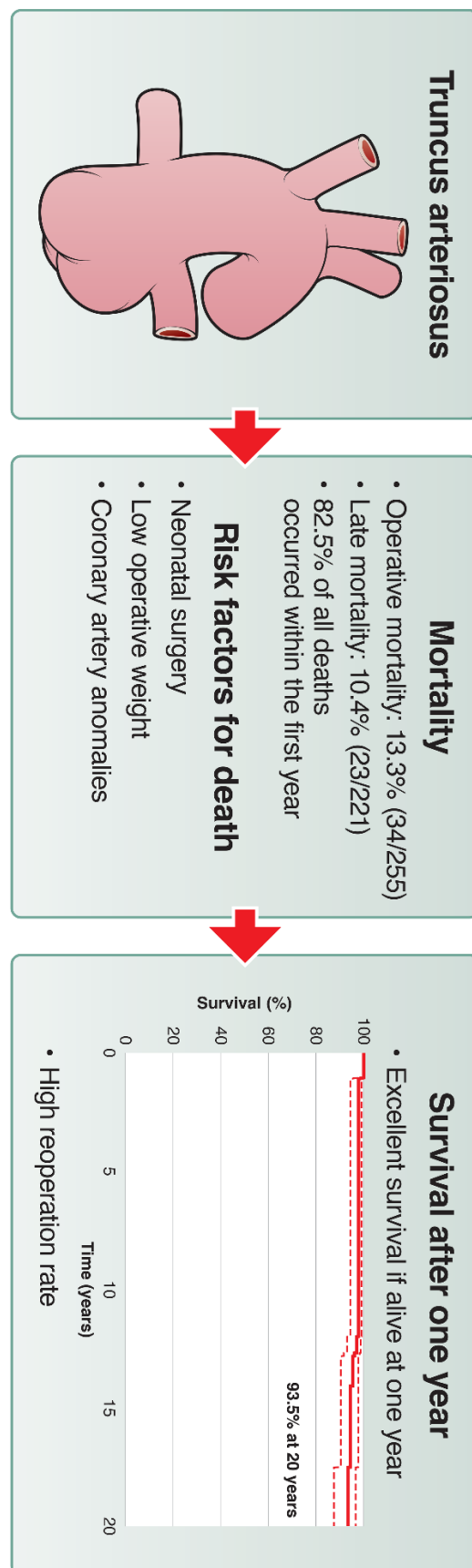


Figure 3.1. Outcomes following truncus arteriosus repair. Risk factors for mortality and Kaplan-Meier survival given survival to the first year after repair.

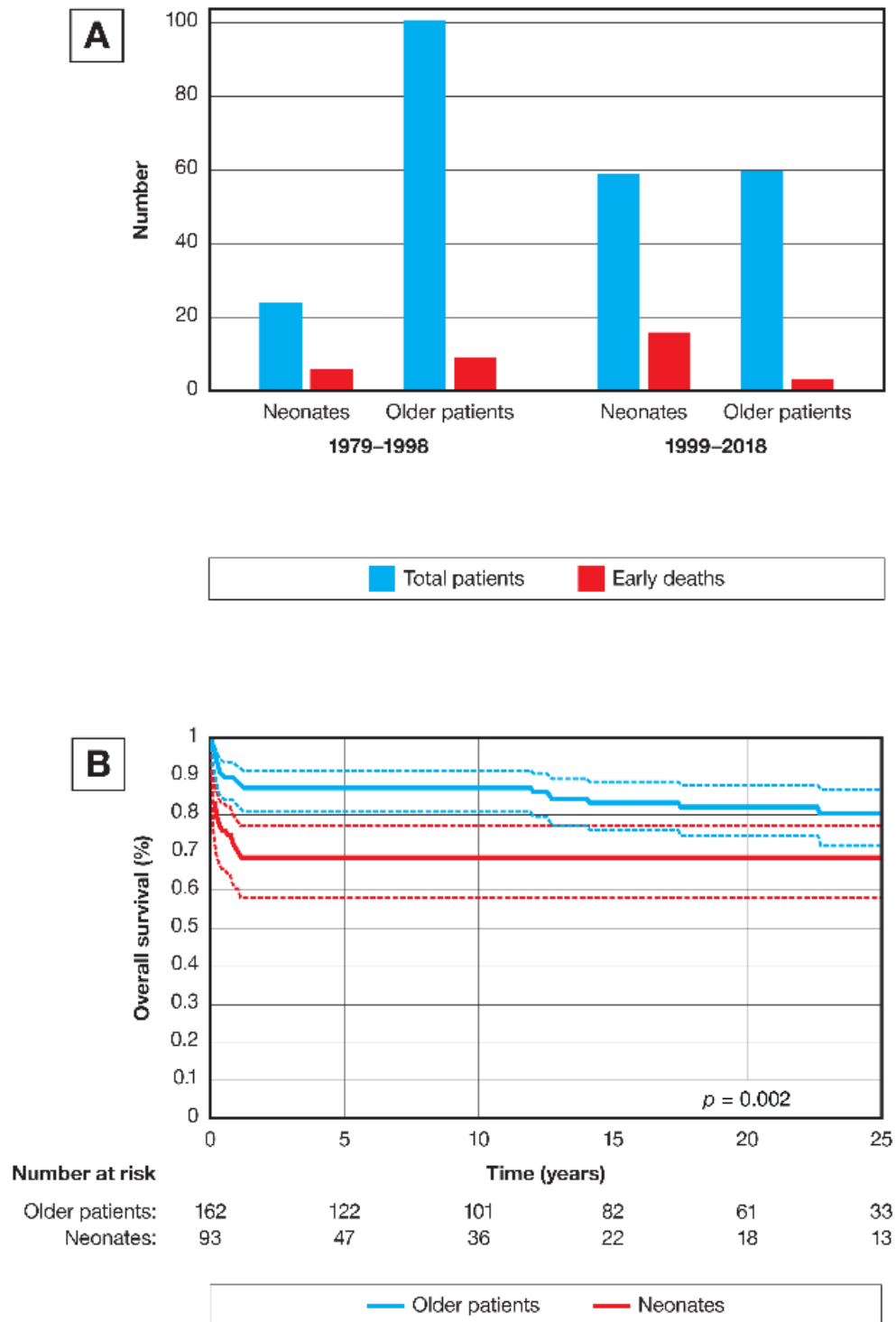


Figure 3.2. Early mortality over time and Kaplan-Meier overall survival in neonates versus older patients following truncus arteriosus repair. Proportion (blue) of neonates and older patients and associated early mortality (red) by era (A). Kaplan-Meier overall survival in neonates (red) versus non-neonates (blue) (B). Solid lines represents overall survival, dashed lines represents 95% confidence interval. P -value represents log-rank testing.

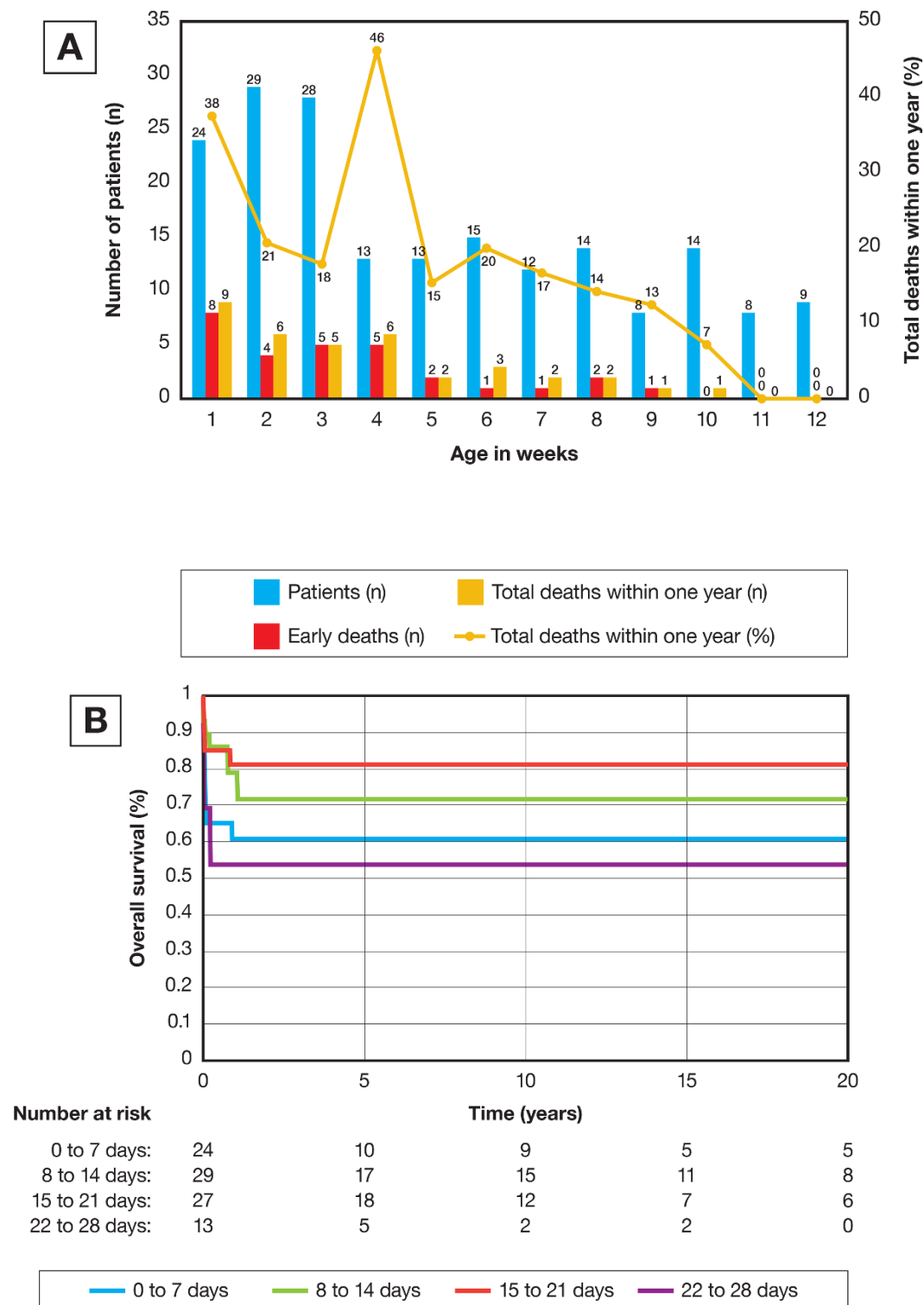


Figure 3.3. Kaplan-Meier overall survival in neonates by week of truncus arteriosus repair.

A) Age in weeks at the time of truncus arteriosus repair (total patients, blue) with the number of early deaths (red) and one-year deaths (yellow) on the primary axis. Percentage of one-year deaths (yellow line) on secondary axis. B) Kaplan-Meier overall survival of neonates by week of truncus arteriosus repair. Neonates aged 0 to 7 days (blue), survival $60.9 \pm 10.2\%$ (95% CI: 38.3, 77.4) at 10 years; neonates aged 8 to 14 days (green), survival $71.8 \pm 8.5\%$ (95% CI: 51.5, 84.8) at 10 years;

neonates aged 15 to 21 days (red), survival $81.3 \pm 7.5\%$ (95% CI: 60.8, 91.8); and neonates aged 22 to 28 days (purple) survival $53.9 \pm 13.8\%$ (95% CI: 24.8, 76.0) at 10 years.

Coronary artery anomalies

There were 27 patients identified with a coronary artery anomaly. The most common coronary artery anomaly was a single coronary artery in 14 patients (single left coronary artery, $n=8$; single right coronary artery, $n=6$), of whom 7 had a major branch crossing the right ventricular outflow tract. Five patients had an intramural coronary artery, 3 had slit-like coronary ostia, and 2 had a coronary artery arising from the pulmonary artery. Of the 27 patients identified with a coronary artery anomaly, only 12 were noted on preoperative transthoracic echocardiogram. Five patients underwent repair of their anomalous coronary artery which included unroofing of an intramural coronary artery in 4 patients, and reimplantation of a coronary artery from the pulmonary artery in 1 patient. Three patients required early reoperation for unroofing of an anomalous coronary artery. In patients with a coronary artery anomaly, there were 6 early deaths (22.2%, 6/27) and 4 late deaths (19.0%, 4/21). Overall survival was $39.6 \pm 15.6\%$ (95% CI: 11.8, 66.9) at 20 years in patients with a coronary artery anomaly, compared to $78.4 \pm 3.1\%$ (95% CI: 71.6, 83.8) at 20 years in patients without a coronary artery anomaly ($p = 0.004$) (**Figure 3.4**). Of the 10 deaths, 40% (4/10) had a major coronary artery branch crossing the right ventricular outflow tract. The presence of a coronary artery anomaly was identified as a risk factor for late mortality on Cox regression (HR 3.7, 95% CI: 1.2, 11.2, $p = 0.019$). Fourteen neonates had a coronary artery anomaly with 4 deaths (all early).

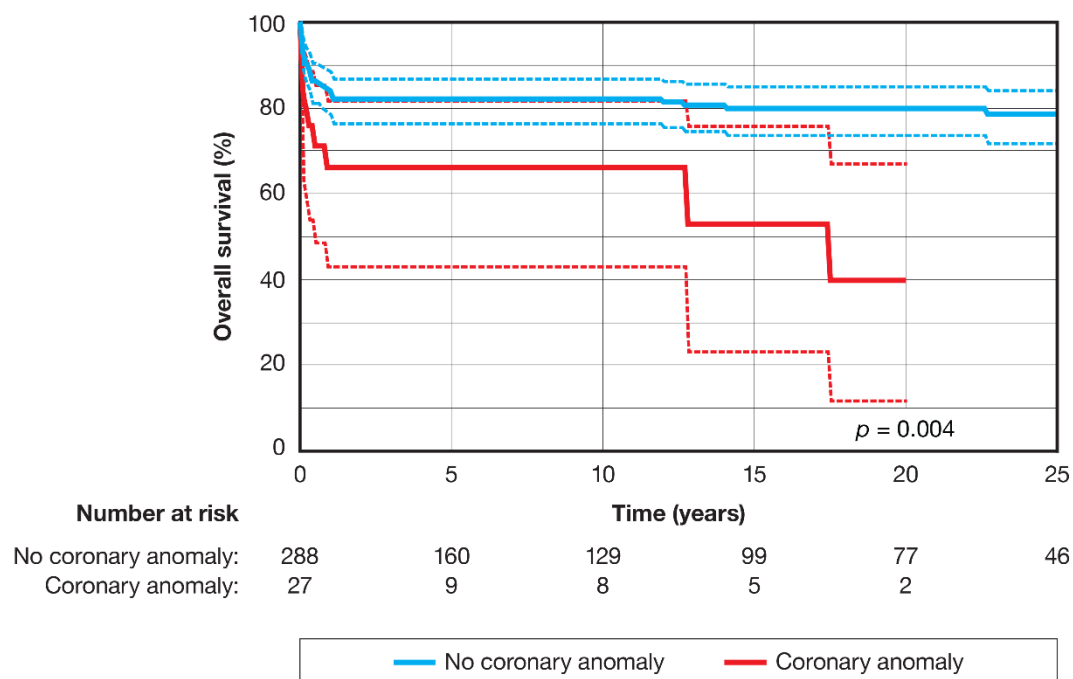


Figure 3.4. Kaplan-Meier overall survival in patients with (red) and without (blue) a coronary artery anomaly. Coronary artery anomalies include a single coronary artery, major coronary artery crossing the right ventricular outflow tract, intramural coronary artery, slit-like coronary ostia, or a coronary artery arising from the pulmonary artery. Solid line represents overall survival, dashed lines represents 95% confidence interval. P -value represents log-rank testing.

Reoperation

A total of 175 patients have required at least 1 reoperation with overall freedom of reoperation of $2.9 \pm 1.5\%$ (95% CI: 0.9, 7.1) at 20 years. Early reoperation was required in 34 patients (13.3%, 34/255). Early reoperative procedures are summarised in **Table 3.4**. Risk factors for reoperation are summarised in **Table 3.5**. Neonatal surgery was a risk factor for early reoperation on multivariable analysis (OR 4.2, 95% CI: 1.9, 9.1, $p < 0.001$). Freedom from any reoperation in neonates was $39.9 \pm 6.2\%$ (95% CI: 27.7, 51.8) at 5 years and $21.2 \pm 6.0\%$ (95% CI: 10.9, 33.7) at 10 years, compared to $50.8 \pm 4.4\%$ (95% CI: 41.9, 59.0) at 5 years, and $22.2 \pm 3.8\%$ (95% CI: 15.2, 29.9) at 10 years in older patients. There was no significant difference in freedom from reoperation between neonates and older patients ($p = 0.087$).

During the follow-up period, 45 patients had percutaneous transcatheter reinterventions including pulmonary artery dilation in 36 patients, Melody (Medtronic, Minneapolis, MN) pulmonary valve insertion in 4 patients, aortic arch dilation in 2 patients, coiling of major aortopulmonary collateral arteries in 1 patient, PFO closure in 1 patient, and superior vena cava dilation in 1 patient.

Right ventricular outflow tract

Continuity between the right ventricle and pulmonary artery was established using a conduit in 239 patients and direct right ventricle to pulmonary artery anastomosis in 16 patients. The median conduit size was 12mm (range 5mm to 20mm).

There have been 231 right ventricular outflow tract reoperations in 159 patients. Of these reoperations, 64 patients have had at least 2 conduit replacements, and 8 have had 3 conduit replacements. Median time to right ventricular outflow tract reoperation was 4.3 years (range 7 days to 18.3 years). Freedom from right ventricular outflow tract reoperation was $25.4 \pm 3.4\%$ (95% CI: 19.0, 32.3) at 10 years, and $3.4 \pm 1.8\%$ (95% CI: 3.1, 11.8) at 20 years. Freedom from right ventricular outflow tract reoperation was $54.2 \pm 6.6\%$ at 5 years, and $28.5 \pm 6.7\%$ at 10 years compared to $55.5 \pm 4.4\%$ at 5 years, $23.7 \pm 3.9\%$ at 10

years in older patients. There was no significant difference in freedom from right ventricular outflow tract reoperation between neonates and older patients (log-rank $p = 0.98$). There was no *early* mortality *following* right ventricular outflow tract reoperation. DiGeorge syndrome (HR 1.9, 95% CI: 1.2, 2.8, $p = 0.005$), use of a Hancock conduit (HR 2.3, 95% CI: 1.6, 3.4, $p < 0.001$), and conduit size (HR 0.91, 95% CI: 0.85, 0.97, $p = 0.006$) were identified as a risk factor for right ventricular outflow tract reoperation on Cox regression analysis. Seven patients who underwent direct right ventricle to pulmonary artery anastomosis required reoperation with conduit placement at a median time of 1.4 years (range 8 days to 8.8 years). There was no difference in median time to reoperation between direct anastomosis and conduit placement ($p = 0.116$). Freedom from right ventricular outflow tract reoperation in patients who underwent direct anastomosis was $35.2 \pm 15.4\%$ (95% CI: 9.3, 63.3) at 10 years ($p = 0.274$, when compared to conduit patients).

Truncal valve

The truncal valve anatomy is summarised in **Table 3.1**. Overall mortality at 20 years was $79.5 \pm 3.7\%$ (95% CI: 71.2, 85.7) in patients with no truncal valve insufficiency; $76.8 \pm 5.4\%$ (95% CI: 64.1, 85.6) with mild insufficiency; $76.9 \pm 8.3\%$ (95% CI: 55.4, 88.9) with moderate insufficiency; and $22.2 \pm 19.3\%$ (95% CI: 1.0, 61.5) at 10 years with severe insufficiency. The degree of truncal valve insufficiency was not associated with mortality (**Table 3.2**).

Concomitant truncal valve surgery was undertaken in 33 patients (truncal valve repair, $n=31$; truncal valve replacement, $n=2$) – including 20 neonates. Concomitant truncal valve surgery was undertaken in 3 patients with no insufficiency, 7 with mild insufficiency, 17 with moderate insufficiency, and 6 with severe insufficiency. Of the 3 patients with no truncal insufficiency on initial preoperative transthoracic echocardiogram: 2 had moderate-severe truncal valve stenosis which was addressed at the time of truncus repair, while 1 patient required resuspension of truncal commissures to facilitate unroofing of an

intramural coronary artery. Of the 7 patients with mild insufficiency on initial preoperative transthoracic echocardiogram: 4 were deemed to have at least moderate insufficiency on subsequent imaging, 2 had large myxoid nodules on the valve leaflets which were deemed problematic, and 1 had moderate truncal valve stenosis. Overall survival at 20 years in patients who underwent concomitant truncal valve surgery was $74.3 \pm 7.9\%$ (95% CI: 55.0, 86.2) compared to $77.4 \pm 3.1\%$ (95% CI: 70.6, 82.8) without concomitant truncal valve surgery ($p = 0.467$).

Overall freedom from late truncal valve surgery (including truncal valve *reoperation*) was $79.3 \pm 3.3\%$ (95% CI: 71.9, 85.0) at 20 years. Concomitant truncal valve surgery was identified as a risk factor for late truncal valve surgery (HR 6.5, 95% CI: 3.1, 13.3, $p < 0.001$). Sixteen patients underwent truncal valve *reoperation* at median time of 2.6 years (range 1 day to 17.8 years). Freedom from truncal valve *reoperation* was $27.5 \pm 11.2\%$ (95% CI: 9.0, 49.9) at 20 years.

Of the 222 patients who did not require concomitant truncal valve surgery, 20 have required late truncal valve surgery. Freedom from late truncal valve surgery was $86.3 \pm 3.0\%$ (95% CI: 79.1%, 91.2) at 20 years. Of these 20 patients, 9 had a quadricuspid truncal valve, 6 of whom initially had mild insufficiency, and 3 had moderate insufficiency. Interestingly, freedom from late truncal valve surgery at 20 years in patients with a quadricuspid truncal valve was $73.9 \pm 7.8\%$ (95% CI: 55.1, 85.8) compared to $90.3 \pm 3.0\%$ (95% CI: 82.3, 94.8) without a quadricuspid valve ($p = 0.023$) (**Figure 3.5**). At last follow-up 89.5% (171/191) of surviving patients had none or mild truncal insufficiency, while 6.3% (12/191) had moderate or severe truncal insufficiency. Follow-up truncal valve data was unavailable in 8 patients. There were no patients who had an aortic dissection or aortic rupture over the study period, however 2 patients had a dilated truncal root requiring repair.

Table 3.4. Reoperative procedures

Reoperative procedure	Number of patients*
Early reoperations	
Right ventricular outflow tract reconstruction	12
Residual ventricular septal defect closure	4
Aortic arch reconstruction	3
Branch pulmonary artery reconstruction	3
Coronary artery unroofing	3
Truncal valve replacement	3
Bidirectional cavopulmonary shunt	2
Interposition graft to aorta to relieve bronchial obstruction	2
Laparotomy	2
Aortic root repair	1
Pulmonary embolectomy	1
Replacement of superior vena cava and innominate vein due to obstruction	1
Vascular ring division	1
All reoperations	
Right ventricular outflow tract reconstruction	159
Branch PA reconstruction	48
Truncal valve reoperation	36
Truncal valve repair	19
Truncal valve replacement	17
Right ventricular outflow tract myectomy	10
Residual ventricular septal defect closure	6
Aortic arch reconstruction	6
Left ventricular outflow tract repair	5
Aortic root repair	3
Coronary artery unroofing	4
Laparotomy	3
Bidirectional cavopulmonary shunt	2
ASD closure	1
Cardiac transplant	1
Excision of supra-mitral ring	1
PAPVC repair	1
Pulmonary embolectomy	1
Replacement of superior vena cava and innominate vein due to obstruction	1
Tricuspid annuloplasty	1
Vascular ring division	1

**patients may have undergone a combination of procedures outlined*

Table 3.5. Risk factors for reoperation following truncus arteriosus repair

Early Reoperation				
Variable	Univariate		Multivariate-regression	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Severe TVI	6.9 (1.3, 35.9)	0.021	4.1 (0.7, 22.6)	0.105
AA obstruction	2.1 (0.9, 5.1)	0.096		
Neonate	4.5 (2.1, 9.8)	<0.001	4.2 (1.9, 9.1)	<0.001
Preoperative ICU	1.1 (0.5, 2.4)	0.810		
TV surgery	0.9 (0.3, 2.7)	0.826		
Right ventricular outflow tract reoperation				
Variable	Univariate		Cox-proportional hazard	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Neonate	1.0 (0.7, 1.4)	0.906		
DiGeorge syndrome	1.5 (1.0, 2.2)	0.067	1.9 (1.2, 2.8)	0.005
Direct anastomosis	0.7 (0.3, 1.4)	0.277		
Hancock conduit	1.9 (1.4, 2.8)	<0.001	2.3 (1.6, 3.4)	<0.001
Conduit size	0.9 (0.9, 1.0)	0.044	0.9 (0.9, 1.0)	0.006
Truncal valve reoperation				
Variable	Univariate		Cox-proportional hazard	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Tricuspid TV	0.3 (0.1, 0.6)	<0.001		
Quadricuspid TV	3.4 (1.7, 6.5)	<0.001		
Quadricuspid TV and greater than moderate TVI	10.4 (5.0, 21.4)	<0.001	2.4 (0.9, 6.8)	0.088
No TVR	0.2 (0.1, 0.4)	<0.001	0.3 (0.1, 0.7)	0.009
Moderate TVI	9.9 (4.5, 20.3)	<0.001		
Severe TVI	33.9 (9.0, 127.9)	<0.001		
Neonate	2.5 (1.3, 4.9)	0.007		
TV surgery	8.5 (4.3, 16.8)	<0.001	2.9 (1.1, 7.7)	0.037

AA, aortic arch; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; TV, truncal valve; TVI, truncal valve insufficiency

Follow-up status

Follow-up was 96% (191/198) complete for survivors. Seven patients were lost to any follow-up. Median follow-up time was 16.4 years (range 6 months to 38.1 years). At last follow-up, 190 patients were in New York Heart Association Class I/II, while 1 patient was in Class III. Right ventricular function was normal in 59.7% (114/191) of patients, mildly reduced in 12.0% (23/191), and moderately reduced in 1.6% (3/191).

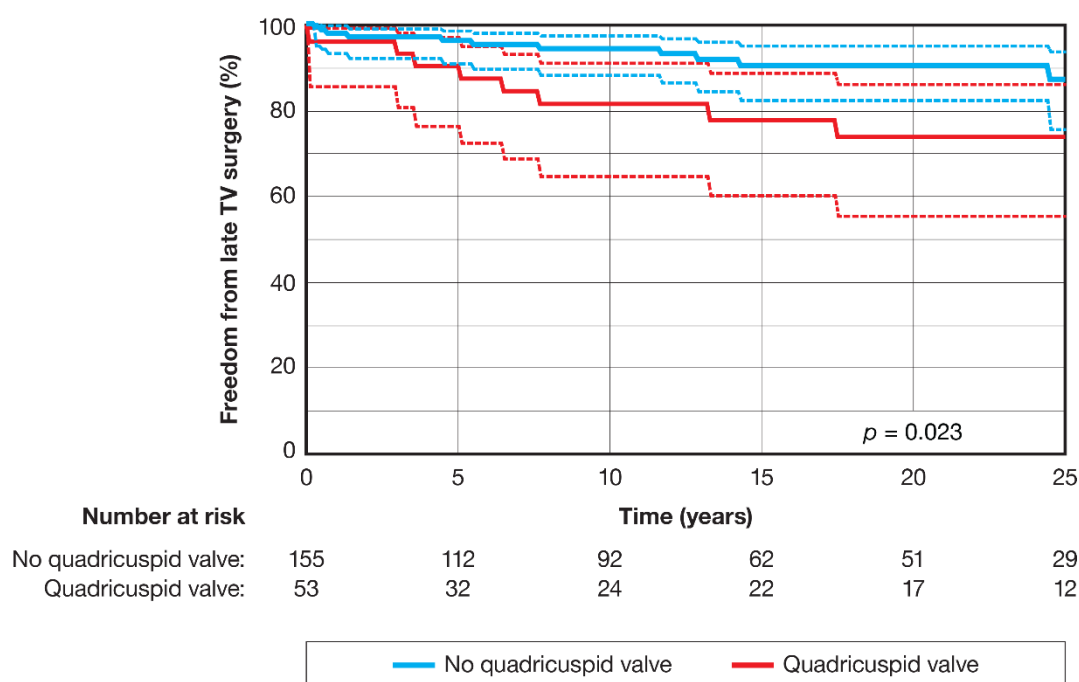


Figure 3.5. Freedom from late truncal valve surgery in patients with and without a quadricuspid truncal valve. Solid lines represents freedom from truncal valve surgery, dashed lines represents 95% confidence interval. *P*-value represents log-rank testing.

3.2.4 Discussion

Herein, we present our experience of truncus arteriosus repair spanning 4 decades. Despite a 40-year period, there was no impact of era on mortality or reoperation. Neonatal surgery was identified as risk factor for early mortality with a neonatal mortality of 23.7% compared to 7.4% in older patients. There was a total of 93 neonates who underwent truncus arteriosus repair, and while the

proportion of neonates increased over the study period, their early mortality remained unchanged. Neonatal surgery has become common practice in patients with truncus arteriosus. However, neonatal surgery is not without its challenges, particularly in patients with complex concomitant cardiac anomalies. When closely examining the 22 early deaths amongst neonates in this study, 6 patients had moderate or severe truncal insufficiency (2 patients < 2.5kg); 6 had aortic arch obstruction (2 patients < 2.5kg); and 4 had a coronary artery anomaly. Interestingly, when analysing neonates with respect to their week of operation, we found that neonates operated in the first and fourth week of life had significantly worse survival than those operated in weeks two or three. Neonates in the first week tended to present in a more critical state, often requiring admission to the intensive care unit for support, or had significant comorbidities including moderate to severe truncal valve insufficiency, aortic arch obstruction, coronary artery anomalies, or were low in weight. In fact, 92% - all but 2 of the 24 neonates – who were operated in the first week of life had significant concomitant anomaly, whereas significant concomitant anomalies were present in 62% (18/29) of neonates in the second week; 41% (11/27) in the third week; and 31% (4/13) in the fourth week. This is an interesting finding given that these concomitant anomalies taken in isolation were not found to be risk factors for mortality, however, when combined in the ‘neonatal’ sub-group of patients, neonatal surgery per se became a risk factor for mortality. Thus, neonatal surgery may be a surrogate risk factor for these previously reported higher risk patients. Clearly, neonates emergently requiring surgery in the first days of life are in a more critical state that places them at higher risk of a poor outcome. Furthermore, neonates who underwent repair during the fourth week of life had the highest proportion of patients who solely required admission to the intensive care unit for management of heart failure and did not have any significant concomitant anomalies. This suggests that those neonates who were operated in week four had over-circulation and worsening heart failure over time. The neonates operated during the fourth week of life had the highest mortality during the first year of life (**Figure 3.3B**). Importantly, there also appeared to be fewer admissions to the intensive care unit solely for the management of heart failure beyond the fourth week. Although the number of admissions to the intensive care

unit solely for heart failure management in weeks three and four did not reach statistical significance, likely due to the relatively small amount of patients, almost twice as many neonates were admitted to intensive care for heart failure management in week four as compared to week three. Collectively, this indicates that any neonate with signs of over circulation be operated on as soon as possible. Those who have survived beyond the neonatal period and have presented late in their clinical course, may have been 'naturally selected' to survive (in some cases up to 8 years).

Most deaths (14 of 23 late deaths) in our cohort occurred within the first year following repair, which is similar to previous studies (20, 30, 31, 69, 77, 94, 98). Rajasinghe and colleagues (30) reported that 57% (13/23) of their late deaths occurred within the first year after repair. Similarly, Tlaskal and colleagues (20) reported that 88% (7/8) of late deaths occurred within the first year. Unfortunately, there were no salient features in these patients that we have observed that may indicate risk of one-year mortality. Given the high proportion of deaths within the first year, truncus arteriosus patients should have more intensive follow-up during this time period. Survival beyond the first year is associated with excellent outcomes.

Of the 10 deaths in patients with a coronary artery anomaly, 4 occurred in patients with a major branch coronary artery crossing the right ventricular outflow tract which may have resulted from compression of the coronary artery. While the reason for these deaths cannot be definitively explored, it could potentially have results from compression of the branch coronary artery by the overlying conduit. The presence of a coronary artery anomaly has been reported to be a risk factor for mortality (13, 14, 31, 47, 49, 50, 96). Schreiber and colleagues (96) reported on 13 patients with a coronary artery anomaly and concluded that the presence of a coronary artery anomaly was associated with poorer surgical outcomes related to compression or distortion of the anomalous coronary artery. While coronary artery anomalies have been reported to be present in 5 – 20% of patients with truncus arteriosus it is difficult to ascertain the precise incidence of this anomaly. It is not uncommon for a coronary artery anomaly to be missed on preoperative echocardiogram in patients with truncus arteriosus. In fact, of the 27

patients in the current study with a coronary artery anomaly, only 12 were identified on preoperative echocardiogram. The remaining coronary artery anomalies were discovered intraoperatively. Thus, without clear delineation of both the coronary ostia, and epicardial course, many of these anomalies may well be missed entirely. Due to the importance of the coronary arteries, it is imperative that the coronary anatomy be clearly noted both with respect to its origin and epicardial course, as a major branch crossing the right ventricular outflow tract may become compromised at right ventriculotomy; due to compression by an overlying conduit; or distorted by a large truncal root (47, 49).

Truncal valve insufficiency was present in 43.9% of patients. Mild insufficiency is often well tolerated and not associated with mortality, while moderate or severe insufficiency has been reported to be a risk factor for death (15, 20, 71, 85, 90, 95). Neither the degree of insufficiency nor concomitant truncal valve surgery was risk factors for death in our cohort. Russell and colleagues (42), reported on 23 truncal valve operations in 572 patients operated between 2000 and 2009, concluding that failure to address significant truncal valve insufficiency was associated with poor outcomes. We report 30 patients with moderate insufficiency, and 6 with severe insufficiency, with a total of 33 patients undergoing concomitant truncal valve surgery. Of 6 patients with severe insufficiency, all underwent concomitant truncal valve surgery, with 4 deaths (2 early, 2 late), and 4 truncal valve reoperations at median time 50 days. Of the patients with moderate insufficiency, 17 underwent concomitant truncal valve surgery, with 2 deaths (early), and 8 truncal valve reoperations at median time 2.6 years. In the remaining 13 patients with moderate insufficiency who did not have concomitant truncal valve surgery, 5 have required late truncal valve surgery, while 5 have died before any intervention. Thus, only 3 patients with initial moderate insufficiency are currently alive without any intervention. Therefore, we would recommend that patients with moderate or greater insufficiency undergo truncal valve surgery at the time of truncus arteriosus repair. While the durability of repair remains questionable, it is preferable over replacement during the neonatal period.

Despite the high – albeit expected – reoperation rates, the long-term outcomes of truncus arteriosus patients are good for those who survived beyond 1 year after initial surgery. Importantly, all but one patient was in New York Heart Association Class I/II. The fate of the truncal valve is good in patients with mild insufficiency, while those with moderate or greater insufficiency often required valve repair, particularly those with a quadricuspid truncal valve.

Limitations

This study was limited by its retrospective nature. Perioperative techniques have varied during the study period. Some outcome variables contained a relatively small number of patients, thus limiting multivariate analysis. Syndrome diagnoses early in the study period were limited due to lack of definitive testing at the time. Coronary artery anomalies may be under-represented as many are only noted on intraoperative reports.

Conclusion

Truncus arteriosus repair in the neonatal period still presents significant surgical challenges. Neonates with signs of over-circulation should be operated on promptly. The presence of a coronary artery anomaly is a risk factor for late death. Survival beyond the first year following repair is associated with excellent outcomes.

Chapter 4: Rare association of an intramural coronary artery and truncus arteriosus

4.1 Introduction

In the previous Chapters, I have shown that coronary artery anomalies play an important role in the outcomes of truncus arteriosus. It was shown that an anomalous coronary artery – be it either abnormal origin, or epicardial course – can impact both early and late mortality. While it has been postulated that patients with an anomalous coronary artery crossing the right ventricular outflow tract are most at risk by compression of the overlying conduit, it is difficult to definitively attribute risk due to the small number of overall patients.

An often-overlooked coronary artery anomaly in patients with truncus arteriosus is an intramural coronary artery. The incidence of an intramural coronary artery has been reported to be up to 15% (99). However, many of these anomalies are initially missed on preoperative imaging and are often diagnosed intraoperatively. Taken in combination with the retrospective nature of many studies on truncus arteriosus, many intramural coronary arteries may in fact be missed entirely. Proper identification of this concomitant anomaly is important given the risk for myocardial ischaemia and death. The following Chapter aims to assess the documented incidence of truncus arteriosus and an intramural coronary artery at The Royal Children's Hospital, and review its surgical management.

Between 1996 and 2018, there were 99 patients with truncus arteriosus at The Royal Children's Hospital. Seven patients had a concomitant intramural coronary artery. Interestingly, only 3 patients had their intramural coronary artery identified on preoperative transthoracic echocardiogram, while the remaining 4 patients were identified intraoperatively.

Given the small number of patients and outcomes, no definitive recommendations can be drawn from this review. However, given the potential for

serious complications patients with truncus arteriosus and an intramural coronary artery may benefit from a coronary unroofing procedure.

4.2 Naimo PS, et al. Heart Lung Circ. 2020

The following study has been submitted to Heart, Lung & Circulation and is currently under review.

4.2.1 Background

Truncus arteriosus with an anomalous coronary artery has previously been shown to be a risk factor for death (13, 14, 31, 96). However, the true incidence of concomitant coronary artery anomalies is unknown. Rarely, patients with truncus arteriosus may have an intramural coronary artery, which may increase the risk of myocardial ischaemia. Herein, we describe our experience with truncus arteriosus and a concomitant intramural coronary artery.

4.2.2 Methods

The Human Research Ethics Committee at The Royal Children's Hospital approved the current study. Between 1996 and 2018 there were 99 patients with truncus arteriosus. Seven patients (7%, 7/99) had truncus arteriosus and an intramural coronary artery and are the focus of this report. Patient characteristics and outcomes are summarized in **Table 4.1**. Three patients had their intramural coronary artery identified on preoperative transthoracic echocardiogram. The remaining 4 patients were diagnosed intraoperatively.

4.2.3 Case Series

There were 4 patients who underwent concomitant unroofing of their intramural coronary artery. In 2015, a 39-day old female weighing 1.9kg underwent truncus arteriosus repair and concomitant left coronary artery (LCA) unroofing and truncal valve commissurotomy to facilitate the unroofing. On postoperative day (POD) 7, she suffered a cardiac arrest and was emergently

placed on ECMO. She subsequently underwent reoperation, and it was found that there was no flow in her left coronary artery (**Figure 4.1A and 4.1B**) and had redo unroofing and reimplantation of the LCA, as well as thrombectomy from the LCA neo-ostium (**Figure 4.2A and 4.2B**). She recovered well and was discharged from hospital. Unfortunately, she had persistent severe LV hypertrophy. Approximately 5 months later, she had a sudden cardiac arrest and died. In 2016, a 27-day old male weighing 3.1kg underwent truncus arteriosus repair and concomitant LCA unroofing. During the postoperative period he developed thrombus and subsequent obstruction of his SVC and innominate vein. He subsequently underwent replacement of his SVC and innominate vein 1 month after truncus repair. He is alive and well at 2.7 years. In 2017, a 12-day old male weighing 3.2kg underwent truncus arteriosus repair and concomitant LCA unroofing. The patient is alive and well at 1.3 years. In 2018, a 4-day old female weighing 3.0kg underwent truncus arteriosus repair and concomitant LCA unroofing and tricuspidization of a quadricuspid truncal valve with resection of a rudimentary cusp and reduction of the truncal annulus. She recovered well, was discharged from the hospital and is currently well at 1 year.

Three patients (in 1996, 1998, and 2012) with an intramural coronary artery underwent truncus arteriosus repair without any coronary intervention. In 2012, a 28-day old male weighing 3.7kg underwent truncus arteriosus repair. On POD 1 he suffered a cardiac arrest and was emergently placed on ECMO. He subsequently underwent reoperation for unroofing of his intramural coronary artery. He recovered well, was discharged from the hospital, and is currently well at 6.6 years. The remaining 2 patients are currently well, without requiring any coronary artery interventions at 17.9 and 20.1 years.

Table 4.1. Patient characteristics of patients with truncus arteriosus and an intramural coronary artery

Patient	Year	Age (days)	Weight (kg)	Intramural coronary	TV insufficiency	Concomitant surgery	Reoperation	Follow-up status
1	1996	164	5.6	LCA	None	PA reconstruction	RVOT conduit and TV replacement at 12.9 years	Alive at 18.9 years
2	1998	17	3.5	RCA	None	Nil	RVOT conduit at 4.5 years	Alive at 20.1 years
3	2012	28	3.7	LCA	None	Nil	Unroofing LCA at 1 day following cardiac arrest and ECMO	Alive at 6.7 years
4	2015	39	1.9	LCA	None	Unroofing LCA and TV commissurotomy to facilitate unroofing	Redo unroofing, removal of thrombus, and reimplantation of LCA at 7 days	Late death at 5 months
5	2016	27	3.1	LCA	None	Unroofing of LCA	Replacement of SVC and innominate vein due to obstruction at 1 month	Alive at 2.7 years
6	2017	12	3.2	LCA	Mild	Unroofing LCA	Nil	Alive at 1.3 years
7	2018	4	3.0	LCA	Moderate	Unroofing LCA and tricuspidization of quadricuspid TV	Nil	Alive at 1 year

ECMO, extracorporeal membrane oxygenation; LCA, left coronary artery; PA, pulmonary artery; RCA, right coronary artery; RVOT, right ventricular outflow tract; SVC, superior vena cava; TV, tricuspid valve

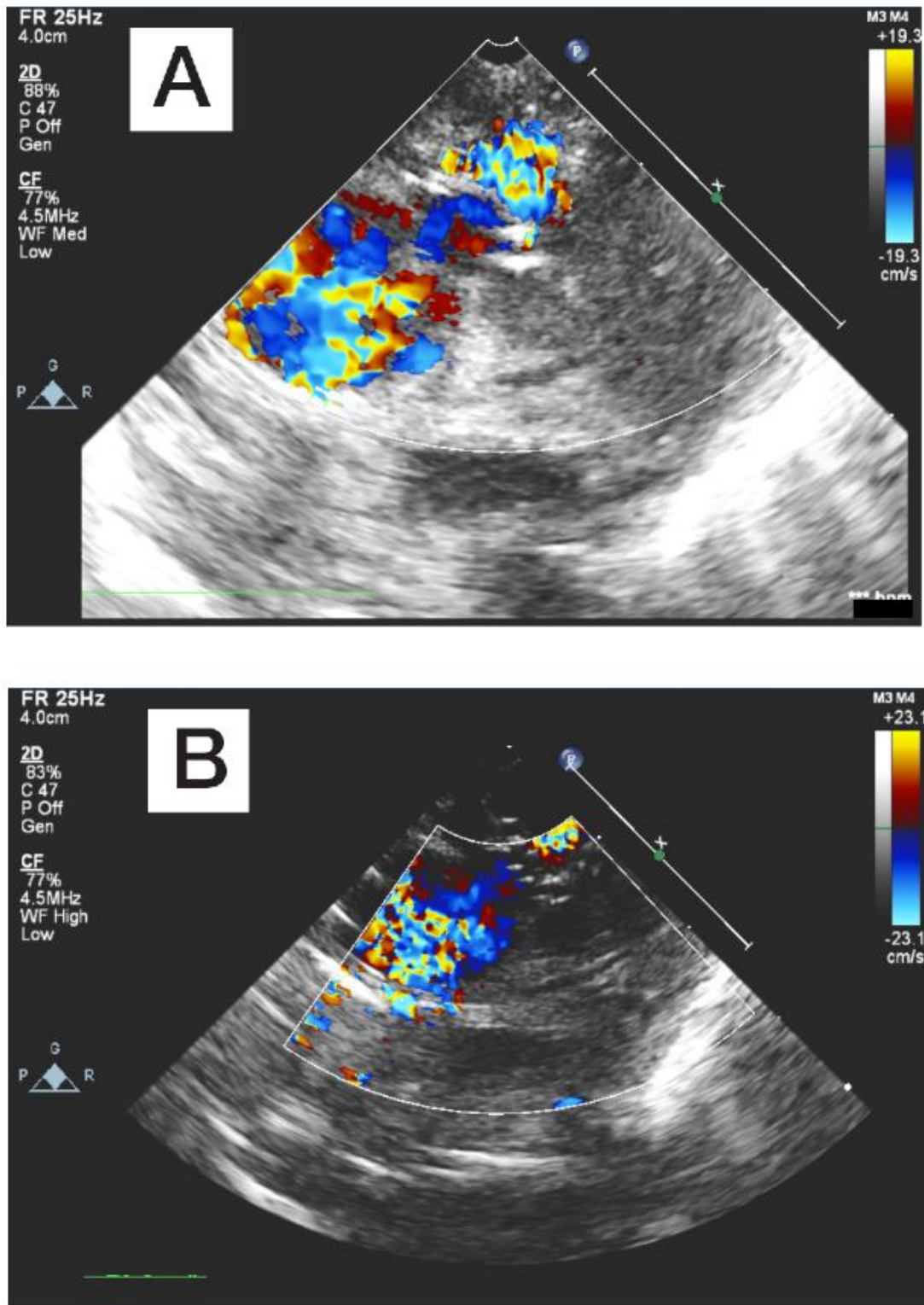


Figure 4.1. Epicardial echocardiogram of a 45-day old girl weighing 1.9kg with an intramural left coronary artery at reoperation before coronary artery unroofing following previous truncus arteriosus repair. A and B: occluded left coronary artery with no flow seen in the proximal left anterior descending artery.

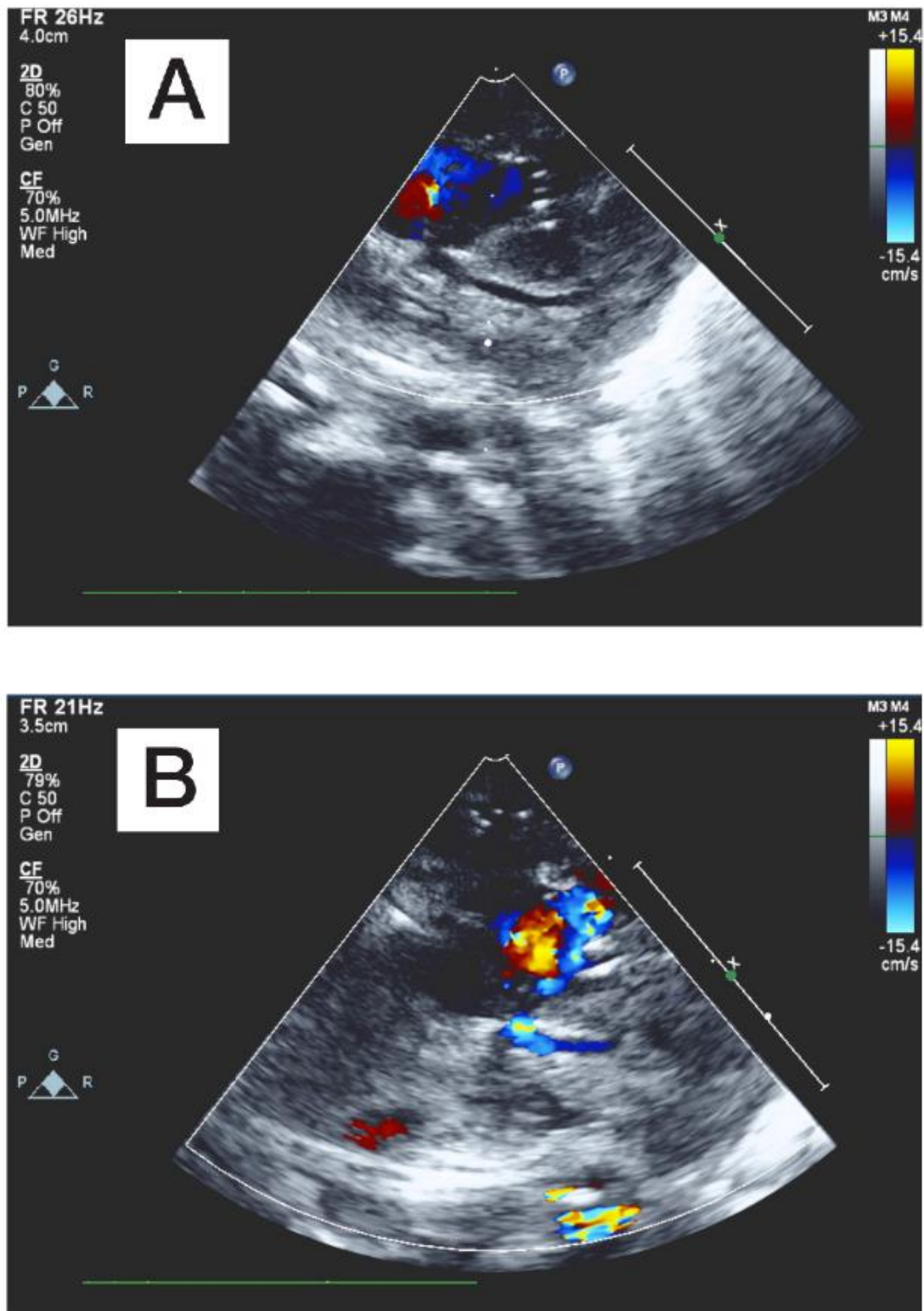


Figure 4.2. Epicardial echocardiogram of a 45-day old girl weighing 1.9kg with an intramural coronary artery at reoperation after coronary artery unroofing following previous truncus arteriosus repair. A: widely patent neo-ostium of the left main coronary artery following unroofing. B: excellent flow into the proximal left main coronary artery following large segment of unroofing and removal of thrombus.

4.2.4 Discussion

The true incidence of an intramural coronary artery in truncus arteriosus is unknown. Coronary artery anomalies in truncus arteriosus have been reported to range between 10 – 20% (13, 14, 31, 49, 50, 96, 99). A recent study by Patrick and colleagues (99) reported an intramural coronary artery was present in 15% of their patients. An abnormal coronary artery may not necessarily be visualised on preoperative echocardiography; thus, it is important for both coronary arteries to be visualized and inspected intraoperatively. Although rare, a truncus arteriosus with an intramural coronary artery may increase the risk of myocardial ischemia and sudden death. In neonates or infants, signs and symptoms of ischemia may be difficult to appreciate. Myocardial ischaemia may be caused by compression of the intramural segment; the acute angle of take-off, leaving it vulnerable to kinking; or the presence of an ostial ridge.

Surgical management of an intramural coronary artery in patients with truncus arteriosus involves unroofing of the intramural segment and forming a neo-ostium. However, the intramural segment may course behind the truncal valve commissure and thus may need to be reconstructed or resuspended to facilitate unroofing (100). One patient who did not undergo unroofing of the intramural segment suffered a cardiac arrest on postoperative day 1 and was emergently placed on ECMO and required reoperation for coronary unroofing.

Given the potential for serious postoperative complications, patients with truncus arteriosus and an intramural coronary artery may benefit from coronary unroofing with creation of a generous neo-ostium.

Chapter 5. Long-term outcomes following repair of truncus arteriosus and interrupted aortic arch

5.1 Introduction

Concomitant interrupted aortic arch has previously been reported to be a risk factor for death (32, 37, 70, 101). McCrindle and colleagues (43) reported that the outcomes of truncus arteriosus and concomitant interrupted aortic arch are worse than interrupted aortic arch alone. The largest multi-institutional study to date, which was published by the Congenital Heart Surgeons' Society (32), described 50 patients with truncus arteriosus and interrupted aortic arch between 1987 and 1997 with 34 deaths, and an overall survival in truncus arteriosus and interrupted aortic arch patients of 31% at 10 years (32). While concomitant interrupted aortic arch adds significant complexity, many single centre studies associating interrupted aortic arch and mortality have been from the 1990s. More contemporary studies may have mitigated the risk of mortality likely due to improved operative techniques and perioperative management of these complex patients.

To evaluate the surgical management and long-term outcomes of patients with truncus arteriosus and concomitant interrupted aortic arch, I conducted a review of all patients at The Royal Children's Hospital between 1979 and 2018. During this period, there were 24 patients with truncus arteriosus and concomitant interrupted aortic arch.

I found that despite the increased complexity of surgical repair, there was no increase in mortality. Most patients underwent end-to-side repair of their aortic arch via direct anastomosis without the use of a patch. Reoperation rates on the aortic arch are high, with 25% (6/24) of patients requiring reoperation. Freedom from aortic reoperation was 69% at 20 years.

5.2 Naimo PS, et al. Eur J Cardiothorac Surg. 2020;57(2):366-72

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Long-term outcomes following repair of truncus arteriosus and interrupted aortic arch

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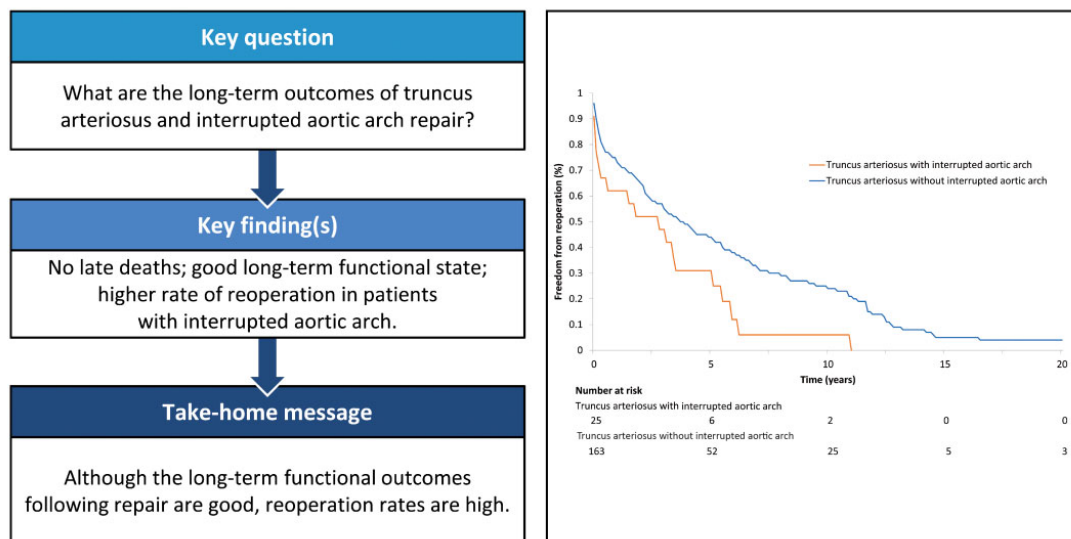
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Abstract

OBJECTIVES: We aim to evaluate the long-term outcomes following repair of truncus arteriosus with an interrupted aortic arch.

METHODS: We reviewed all children ($n=24$) who underwent repair of truncus arteriosus and an interrupted aortic arch between 1979 and 2018 in a single institution. The morphology of the interrupted aortic arch was type A in 5, type B in 18 and type C in 1.

RESULTS: The median age at repair was 10 days and the median weight was 3.1 kg. Direct end-to-side anastomosis of the ascending and descending aorta was performed in 16 patients (67%, 16/24), patch augmentation in 5 patients (21%, 5/24) and direct anastomosis with the use of an interposition graft to the descending aorta in 2 patients (8%, 2/24). One patient, the first in the series, underwent interrupted aortic arch repair via subclavian flap aortoplasty prior to truncus repair. A period of deep hypothermic circulatory arrest was used in 16

patients, and isolated cerebral perfusion was used in 8 patients. The early mortality rate was 17% (4 out of 24 patients). There were no late deaths and overall survival was $83 \pm 8\%$ [95% confidence interval (CI) 61–93] at 20 years. Freedom from any reoperation was $33 \pm 11\%$ (95% CI 14–54) at 5 years and $13 \pm 9\%$ (95% CI 2–34) at 10 years. Six patients underwent 10 aortic reoperations. Freedom from aortic arch reoperation was $69 \pm 11\%$ (95% CI 42–85) at 10 and 20 years. Follow-up was 95% complete (19/20), with a median follow-up time of 20 years. At last follow-up, no clinically significant aortic arch obstruction was identified in any patient, and all patients were in New York Heart Association Class I/II.

CONCLUSIONS: Repair of truncus arteriosus with an interrupted aortic arch with direct end-to-side anastomosis results in good survival beyond hospital discharge. Although the long-term functional state of patients is good, reoperation rates are high.

Keywords: Truncus arteriosus • Interrupted aortic arch • Surgery

INTRODUCTION

The combination of truncus arteriosus and an interrupted aortic arch is rare. There is limited cumulative experience regarding the management of this condition, the long-term outcomes [1–4]. However, many centres have reported truncus arteriosus with an interrupted aortic arch to be a risk factor for death [3, 5, 6]. We sought to review the long-term outcomes of patients with truncus arteriosus with an interrupted aortic arch at the Royal Children's Hospital. Outcomes were compared with children who underwent repair of truncus arteriosus without aortic arch obstruction ($n = 163$) during the same period.

PATIENTS AND METHODS

Definitions

Early mortality and reoperation were defined as death or reoperation occurring within 30 days of surgery or prior to hospital discharge. All other deaths and reoperations were considered late. A modified Van Praagh classification for truncus arteriosus was used [4]. Type 4 of the Van Praagh classification (truncus arteriosus with interrupted aortic arch) was reclassified into type 1–3, and the type of interrupted aortic arch specified. An interrupted aortic arch was defined as a complete discontinuity or a non-patent fibrous strand between the proximal and distal segments of the aortic arch. Interrupted aortic arch types were described using the Celoria and Patton classification [7]. Right ventricular outflow tract reoperation (i.e. conduit change) was performed when there was conduit obstruction or pulmonary valve insufficiency in association with either symptomatic right heart failure; right ventricular systolic pressure of at least 80% of systemic; right ventricular end-diastolic volume $\geq 160 \text{ ml/m}^2$; right ventricular end-systolic volume index $\geq 70 \text{ ml/m}^2$ and arrhythmia or QRS $> 180 \text{ ms}$ [8, 9]. Aortic arch reoperation was performed when there was an aortic arch obstruction in association with symptoms, systemic hypertension or a peak gradient of at least 30 mmHg, or when there was compression of adjacent structures from the reconstructed aortic arch (i.e. left bronchial compression).

Data analysis

Data were analysed using STATA version 14 (StataCorp LP, College Station, TX, USA). Continuous data are expressed as means $\pm$ standard deviations (range), whereas skewed continuous data are expressed as medians (interquartile range). Categorical data are summarized as frequencies and

percentages. Kaplan–Meier actuarial survival ($\pm$ standard error) curves were used to analyse and plot time-related end points. The log-rank test was used to compare the distribution of survival times between patients with and without an associated interrupted aortic arch. The statistical significance was set at P -value < 0.05 .

Patients

The Human Research Ethics Committee at the Royal Children's Hospital approved the study. Data were obtained by reviewing the medical records from initial admission until last cardiology follow-up. Between 1979 and 2018, 188 patients underwent repair of truncus arteriosus. A total of 25 patients (14%, 25/185) were identified with interrupted aortic arch (type A, $n = 5$; type B, $n = 19$; type C, $n = 1$). One patient had truncus arteriosus type 2 with intact ventricular septum, mitral atresia, hypoplastic left ventricle and type B interrupted aortic arch and underwent a uni-ventricular staged palliation that ultimately resulted in a Fontan procedure. This patient was excluded from the analysis. Patient characteristics are summarized in Table 1.

Table 1: Patient characteristics of patients with truncus arteriosus and interrupted aortic arch ($n = 24$)

Variables	Total patients (% , n)
Truncus arteriosus type	
Type 1	58 (14/24)
Type 2	25 (6/24)
Type 3	17 (4/24)
Interrupted aortic arch type	
Type A	21 (5/24)
Type B	75 (18/24)
Type C	4 (1/24)
Truncal valve insufficiency	
None	50 (12/24)
Mild	42 (10/24)
Moderate	4 (1/24)
Severe	4 (1/24)
Median age at repair	10 days (mean 28 days, range 2–164 days)
Median weight at repair	3.1 kg (mean 2.8 kg, range 1.2–4.1 kg)
Neonate at time of repair	83 (20/24)
Type of aortic arch reconstruction	
End-to-side anastomosis	67 (16/24)
Patch augmentation	21 (5/24)
Interposition graft	8 (2/24)
Subclavian artery flap	4 (1/24)

Table 2: Cause of death of patients with truncus arteriosus and interrupted aortic arch

Patient	Year	Age at repair (days)	Weight at repair (kg)	TA type	TV insufficiency	IAA type	Aortic arch repair	Cause of death	Age at death (days)
1	1998	10	3.0	2	Moderate	B	End-to-side	Required LVAD for 3 days postoperatively due to significantly reduced contractility. Extubated day 6. Developed <i>S. aureus</i> sepsis on day 11 and died the following day	22
2	2007	7	1.7	2	None	A	End-to-side	Severe cardiac failure postoperatively requiring ECMO. Could not be weaned from ECMO. Support was withdrawn on postoperative day 13	21
3	2013	6	1.3	1	Mild	A	End-to-side	Sudden cardiac arrest on postoperative day 5 and could not be resuscitated	11
4	2017	5	3.6	2	None	B	Patch augmentation	Unrelenting sepsis of unclear source. Unable to be weaned from ECMO	29

ECMO: extracorporeal membrane oxygenation; IAA: interrupted aortic arch; LVAD: left ventricular assist device; TA: truncus arteriosus; TV: tricuspid valve.

Operative technique

Surgery was undertaken through a midline sternotomy with cardiopulmonary bypass. The repair consisted of aortic arch reconstruction, ventricular septal defect closure and re-establishing right ventricle to pulmonary artery continuity. For aortic arch reconstruction, a period of deep hypothermic circulatory arrest was used in 16 patients, and isolated cerebral perfusion was used in 8 patients. The lowest temperature ranged from 13 to 25°C and was chosen at the discretion of the surgeon. Median cardiopulmonary bypass time was 198 min (108–225 min) and the median aortic cross-clamp time was 101 min (68–154 min). In patients who had deep hypothermic circulatory arrest, median circulatory arrest time was 38 min (32–54 min).

During cooling, the descending aorta was extensively dissected and mobilized. Once adequate cooling was established, the patent ductus arteriosus was ligated, a Castaneda clamp was placed onto the descending aorta and all ductal tissues were resected. Usually, 3 pairs of intercostal vessels were divided and cauterized to allow adequate mobilization of the descending aorta. Direct end-to-side anastomosis of the ascending and descending aorta was performed in 16 patients (67%, 16/24). When the descending aorta could not be adequately mobilized for the advancement procedure as described above, the aortic arch was repaired using patch augmentation or an interposition graft to the descending aorta. Patch augmentation was performed by posterior end-to-end anastomosis with augmentation of the inner curvature of the aortic arch with a patch. Five patients (21%, 5/24) underwent patch augmentation using autologous pericardium ($n=4$), or CardioCel patch (Admedus, Malaga, Australia) ($n=1$). Two patients underwent direct anastomosis of the aortic arch with the use of an interposition graft [12 mm aortic homograft, $n=1$; and 8 mm Gore-Tex tube (W.L. Gore and Associates, Flagstaff, AZ, USA), $n=1$] to the descending aorta, in 1 patient each. One patient, the first in the series, underwent interrupted aortic

arch repair via subclavian flap aortoplasty prior to truncus arteriosus repair.

The right ventricular outflow tract was reconstructed with the use of a valved conduit in 16 patients (67%, 16/24) and a non-valved conduit in 7 patients (29%, 7/24). In 1 patient (4%, 1/24), it was possible to establish direct right ventricular to pulmonary artery continuity with the placement of autologous pericardial tissue to act as a monocusp. The defect in the truncal wall was directly closed in all patients. The truncal valve was bicuspid in 3 patients, tricuspid in 15 patients and quadricuspid in 6 patients. Most patients had mild or less truncal valve insufficiency ($n=22$). One patient with a tricuspid truncal valve and moderate insufficiency underwent truncus arteriosus and interrupted aortic arch repair. This patient died on postoperative day 12 due to sepsis. One patient with a quadricuspid truncal valve and severe insufficiency underwent concomitant truncal valve repair with resection of the smallest truncal valve leaflet and annular plication. This patient is currently well with trivial insufficiency at 1 year.

RESULTS

Median age at repair was 10 days (mean 28 days, range 1–164 days). Median weight at repair was 3.1 kg (mean 2.8 kg, range 1.2–4.1 kg). There was 1 patient who did not receive a prostaglandin infusion preoperatively. Postoperatively, 2 patients required extracorporeal membrane oxygenation, and 1 patient required a left ventricular assist device—all 3 patients died (Table 2). Three patients were found to have a coronary artery anomaly with no deaths.

Mortality

Early mortality was 17% (4 out of 24 patients), and the cause of death is summarized in Table 2. Two early deaths occurred in

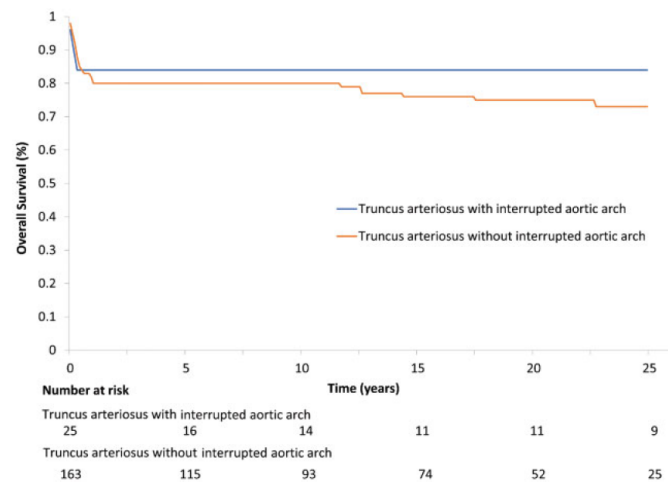


Figure 1: Kaplan-Meier overall survival of patients with truncus arteriosus with and without an interrupted aortic arch.

Table 3: Summary of reoperation procedures following truncus arteriosus and interrupted aortic arch repair

Reoperative procedure	Total patients (n)	Total reoperations (n)	Median time to reoperation
RV-PA conduit change	16	25	4.3 years
Aortic arch reoperation	6	10	26 days
Truncal valve replacement	2	2	5.6 years
PA reconstruction	10	15	3.8 years
Subaortic stenosis repair	2	2	4.3 years
Tricuspid annuloplasty	1	1	

PA: pulmonary artery; RV: right ventricle.

patients who weighed <2.0 kg. There were no late deaths. Overall survival in patients with an interrupted aortic arch was $83 \pm 8\%$ [95% confidence interval (CI) 61–93] at 20 years. For comparison, of the 163 remaining patients without an interrupted aortic arch, early mortality was 11% (18/163), and overall survival was $74 \pm 4\%$ (95% CI 66–81) at 20 years (Fig. 1). Characteristics of all truncus arteriosus patients from our hospital can be found in our previously published manuscript [1]. There was no difference in mortality between patients with an interrupted aortic arch and those without ($P = 0.74$).

Reoperations

There was a total of 39 reoperations in 18 patients, summarized in Table 3. Seven patients required 8 early reoperations (aortic arch, $n = 4$; right ventricular outflow tract, $n = 2$; pulmonary artery, $n = 1$). Freedom from any reoperation at 10 years (Fig. 2) was $23 \pm 4\%$ (95% CI 16–31) in patients without interrupted aortic arch and $13 \pm 9\%$ (95% CI 2–34) in patients with interrupted aortic arch ($P = 0.02$). Two patients required subaortic stenosis repair with septal myectomy due to left ventricular outflow tract obstruction.

Sixteen patients have undergone 25 right ventricular outflow tract reoperations. The median time to first right ventricular outflow tract reoperation was 3.6 years (3.0–6.3 years). Freedom from right ventricular outflow tract reoperation was $23 \pm 10\%$ (95% CI 7–44) at 10 years. Only 5 right ventricular outflow tract reoperations were done in conjunction with an aortic reoperation or truncal valve reoperation. Two patients required truncal valve replacement at 6 and 8 years following the initial procedure, respectively.

Six patients underwent 10 aortic reoperations (Table 3), most of whom had type B interrupted aortic arch (83%, 5 out of 6 patients). Aortic reoperations are summarized in Fig. 3. Freedom from aortic arch reoperation was $69 \pm 11\%$ (95% CI 42–85) at 10 and 20 years. Additionally, 3 patients underwent balloon aortic angioplasty. Three patients required aortic reoperations within 30 days of their initial operation. This included implantation of an 8-mm Gore-Tex interposition graft to the descending aorta through a left thoracotomy to relieve severe left bronchial compression by the reconstructed aortic arch in 2 patients on postoperative day 14 and 26, respectively. Additionally, 1 patient underwent pericardial patch enlargement of residual aortic arch obstruction on postoperative day 2. All 3 of these patients underwent end-to-side anastomosis of their aortic arch without the use of a patch. Of the 2 patients who underwent interposition graft to the descending aorta, the 8-mm Gore-Tex graft was replaced with a 16-mm Dacron graft at 11 years, whereas the 12-mm aortic homograft has not required replacement after 22 years.

Long-term outcomes

Follow-up was 95% complete (19 out of 20 patients), with a median follow-up time of 20 years (mean 18 years, range 1–30 years). At last follow-up, there was no clinically important (peak gradient >30 mmHg) aortic arch obstruction identified in any patient on echocardiography. All patients were in New York Heart Association Class I/II at last follow-up.

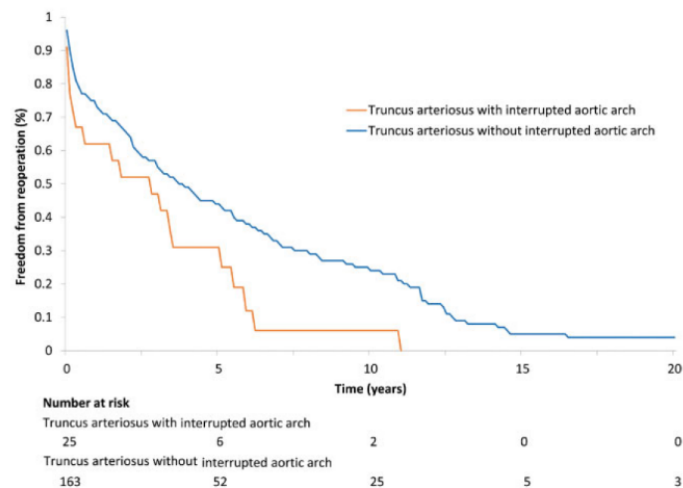


Figure 2: Kaplan–Meier freedom from reoperation in patients with truncus arteriosus with and without an interrupted aortic arch.

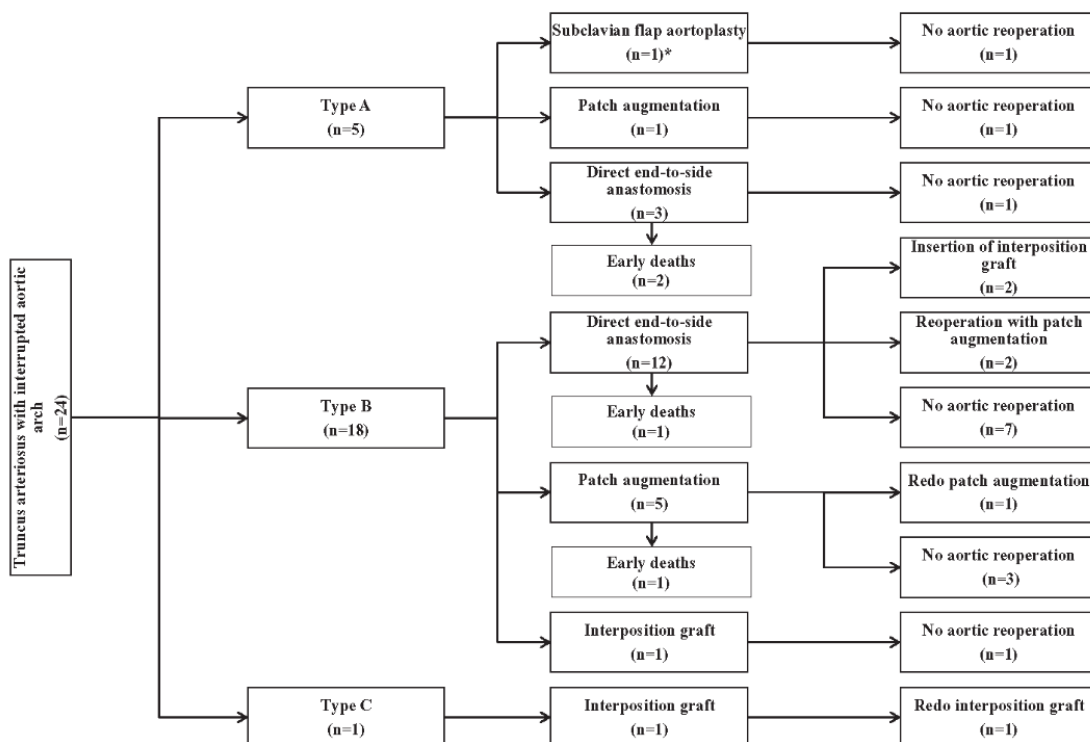


Figure 3: Flow chart of aortic arch reoperations. *Subclavian flap aortoplasty done prior to TA repair.

DISCUSSION

Truncus arteriosus with an interrupted aortic arch is a rare and complex condition, which often requires surgical repair in the

neonatal period. Since the initial description by Gomes and McGoon [10] in 1971, a number of surgical techniques have been described for repair of truncus arteriosus and interrupted aortic arch [2, 11–13], including a left carotid artery or left subclavian

Table 4: Outcomes of truncus arteriosus and interrupted aortic arch

Study	Study period	Patients (n)	Early deaths (%), % (n)	Late deaths (%), % (n)	Aortic arch reoperation, % (n)	Risk factor for death	Follow-up time (years)
Konstantinov <i>et al.</i> [2]	1987–1997	46	52 (24/46)	27 (6/22)	27 (6/22)	Yes	6
Jahangiri <i>et al.</i> [14]	1992–1998	9	0	0	0	No	1
Thompson <i>et al.</i> [15]	1992–1999	8	25 (2/8)	NR	NR	No	2.7
Brown <i>et al.</i> [6]	1978–2000	6	50 (3/6)	0	0	Yes	9.4
Danton <i>et al.</i> [16]	1988–2000	7	14 (1/7)	0	NR	No	4.2
Miyamoto <i>et al.</i> [17]	1987–2004	10	50 (5/10)	20 (1/5)	NR	NR	NR
Taskal <i>et al.</i> [3]	1981–2009	14	50 (7/14)	0	14 (1/7)	Yes	10.6
Current study	1979–2018	24	17 (4/24)	0	20 (4/20)	No	20

NR: not reported.

artery turn down, prosthetic conduit implantation and direct aortic arch anastomosis with or without patch augmentation. Data on the long-term outcomes of these complex patients is limited to a small series of patients. Therefore, it is difficult to ascertain how these patients fare in the long term. Herein, to our knowledge, we present the largest single institutional experience with repair of truncus arteriosus and an interrupted aortic arch with a median duration of follow-up of 20 years.

Repair of interrupted aortic arch in patients with truncus arteriosus has been reported as a risk factor for death (Table 4) [2, 3, 5, 6]. McCrindle *et al.* [5] reported that outcomes of truncus arteriosus with interrupted aortic arch were worse than interrupted aortic arch alone. Russell *et al.* [18] suggested that an interrupted aortic arch was the single greatest risk factor for mortality in patients with truncus arteriosus. The largest multi-institutional study to date, which was published by the Congenital Heart Surgeons' Society (CHSS), described 50 patients with truncus arteriosus and interrupted aortic arch between 1987 and 1997 with 34 deaths, including 28 early deaths, and overall survival of 31% at 10 years [2]. We have previously reported no association between mortality in truncus arteriosus with interrupted aortic arch and truncus arteriosus alone [1]. Herein, overall survival in patients with truncus arteriosus with interrupted aortic arch was $83 \pm 8\%$ at 20 years compared to $74 \pm 4\%$ at 20 years in patients with truncus arteriosus without interrupted aortic arch. The presence of an interrupted aortic arch was not associated with increased mortality, likely due to a small number of patients in this series.

Children with truncus arteriosus with an interrupted aortic arch and concomitant truncal valve insufficiency have very poor surgical outcomes. The CHSS study demonstrated that patients with associated truncal valve insufficiency had a mortality of 75% (18 out of 24 patients). Similarly, Russell *et al.* [2, 18] reported a mortality of 68% in patients with truncal valve insufficiency. We have previously reported that mild or less truncal valve insufficiency was well tolerated, whereas moderate or greater truncal valve insufficiency often necessitated truncal valve surgery [19]. Most patients (92%, 22 out of 24 patients) in this study had mild or less truncal valve insufficiency, whereas 2 patients had moderate or greater truncal valve insufficiency. One patient with moderate truncal valve insufficiency and type B interrupted aortic arch did not undergo truncal valve surgery and developed *S. aureus* sepsis and died. The other patient with a quadricuspid truncal valve and severe insufficiency underwent truncus arteriosus repair with aortic arch and truncal valve repair. This patient is currently well with trivial insufficiency at 1 year. There have been an

additional 2 patients who have required late truncal valve surgery due to progressive truncal valve regurgitation at 6 and 8 years. During the initial operation, all defects in the truncal wall were directly closed, and thus unlikely to contribute to progressive truncal valve regurgitation. Truncal valve repair in neonates could be challenging. We have recently described our techniques for neonatal truncal valve repair in detail [19, 20].

Most reoperations in patients with truncus arteriosus and an interrupted aortic arch are due to right ventricular to pulmonary artery conduit stenosis, which required surgery in 16 patients. There was no difference in right ventricular outflow tract reoperation between patients with or without an interrupted aortic arch. However, it is not uncommon that patients with truncus arteriosus and an interrupted aortic arch require reoperation for aortic arch reobstruction. The CHSS reported that only 28% of patients were alive at 5 years without aortic arch reoperation [2]. We report 6 patients who required 10 aortic reoperations, with 3 of these reoperations occurring within 30 days of initial repair and overall freedom from aortic reoperation of 69% at 10 years. McCrindle *et al.* [5] reported that aortic arch reoperation was more likely for those who had interrupted aortic arch repair by a method other than direct anastomosis with patch augmentation. Our centre has been using end-to-side repair for interrupted aortic arch since the early 1980s, and we aim for direct end-to-side anastomosis of the aortic arch without a patch when possible. A previous review of interrupted aortic arch repairs either in isolation or with truncus arteriosus repair at our centre demonstrated a low aortic arch reoperation rate using the end-to-side technique [12, 21, 22]. It is important to extensively mobilize the descending aorta [20]. However, if the descending aorta cannot be mobilized enough to approximate the aortic arch without overly distorting the anatomy of the arch, this may cause compression of the left pulmonary artery, or left main bronchus [23]. In these cases, a patch to the aortic arch should be used to augment the anastomosis. Of note, 5 out of the 6 patients in this series who required reoperation on the aortic arch had their initial interrupted aortic arch repaired without a patch. Two of these patients had compression of their left main bronchus. Bronchial compression is a rare complication of interrupted aortic arch repair, which may occur when the descending aorta is anastomosed more proximally on the ascending aorta. Interestingly, patients with type B interrupted aortic arch present a more challenging repair as their ascending aorta may be narrower and more likely to be complicated by left bronchial compression if repaired without a patch. Both patients in the current series with left bronchial compression had a type B interrupted aortic arch

and underwent direct end-to-side anastomosis without the use of a patch. These patients required reoperation within 30 days of initial repair and both patients underwent placement of an interposition graft to the descending aorta to relieve bronchial compression. Both patients remain asymptomatic at last follow-up, and each had subsequently required replacement of the interposition graft.

It is clear that patients with truncus arteriosus with an interrupted aortic arch present a significant challenge in both the short and the long-term. In the long-term, there are ongoing issues with recurrent aortic arch obstruction, and rarer occurrences of left bronchial compression.

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 the multivariable analysis.

CONCLUSION

Repair of truncus arteriosus with an interrupted aortic arch with direct end-to-side anastomosis has good survival beyond hospital discharge. Although the long-term functional state is good, reoperation rates are high.

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Chapter 6: Impact of truncal valve surgery on the outcomes of truncus arteriosus repair

6.1 Introduction

Truncal valve insufficiency occurs in approximately 25% of patients with truncus arteriosus (42, 81, 85). Some have suggested that truncal valve insufficiency was the most important factor influencing early outcomes (15, 20, 32, 42, 89, 90). However, the decision to operate on the truncal valve is often at the discretion of the surgeon as the indications for truncal valve repair remain contentious.

There is no uniform approach in managing truncal valve insufficiency. Various techniques for truncal valve repair have been described, including suturing partially developed commissures, suspension of leaflets, resection of the redundant portion of leaflets, annuloplasty of commissures and pericardial leaflet extension, tricuspidization of a quadricuspid valve, or repair of the bicuspid valve. Concomitant truncal valve surgery can have a mortality rate as high as 30% (42, 71), likely due to these – often neonates – presenting in a more critical state. Unsurprisingly, concomitant truncal valve surgery is more challenging due to it often being required in younger and critically ill patients. It is often prudent to intervene on the truncal valve at this stage, as not addressing severe truncal valve insufficiency has been associated with poor outcomes (30, 34, 35, 42, 71, 85, 91).

Though concomitant truncal valve surgery could be lifesaving, it has limited durability. Kaza and colleagues in 2010 showed that in 14 patients who underwent truncal valve repair, freedom from truncal valve reintervention was 70% at 5 years and 50% at 7 years (90).

To address these deficiencies in the literature, I focused on the surgical management of the truncal valve, and the progression of truncal valve insufficiency. Between 1979 and 2016, 180 patients underwent truncus arteriosus

repair at The Royal Children's Hospital. Of these 180 patients, 80 had some degree of truncal valve insufficiency.

I show that mild truncal valve insufficiency is often well tolerated and does not require intervention (71). However, most patients with moderate or greater truncal valve will require truncal valve surgery at some stage. Importantly, neither concomitant truncal valve surgery, nor the degree of truncal valve insufficiency was associated with mortality. In keeping with Kaza and colleagues (90), durability of truncal valve repair is poor with a freedom from reoperation of 19.2% at 20 years (71).

Additionally, I demonstrate that patients with a quadricuspid truncal valve and moderate or greater truncal insufficiency are more likely to require truncal valve surgery at some stage. Conversely, patients with a quadricuspid truncal valve and mild or less truncal insufficiency are unlikely to have progression of their truncal insufficiency.

6.2 Naimo PS, et al. Eur J Cardiothorac Surg. 2018;54:524-31

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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 $70.8 \pm 10.1\%$ 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 $62.3 \pm 15.0\%$ 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 $19.2 \pm 14.9\%$ at 20 years. In the remaining 159 patients, 14 required subsequent TV surgery, and the freedom from TV surgery was $84.0 \pm 4.6\%$ 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

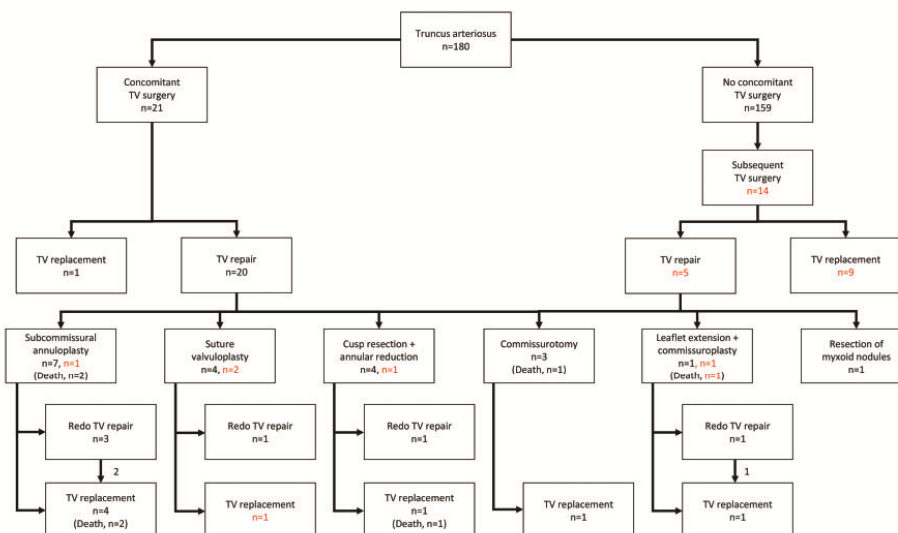


Figure 1: Flow chart of outcomes following TV surgery. Values in red indicate subsequent TV surgery. TV: truncal valve.

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 preoperative 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

Table 1: Outcomes of TA patients with TV insufficiency

Preoperative TV status	Overall (n = 180)	No TV insufficiency (n = 100)	Mild TV insufficiency (n = 61)	Moderate TV insufficiency (n = 17)	Severe TV insufficiency (n = 2)
Truncus arteriosus type					
Type 1, % (n/N)	64.5 (116/180)	59 (59/100)	70 (43/61)	70 (12/17)	100 (2/2)
Type 2, % (n/N)	24.4 (44/180)	29 (29/100)	20 (12/61)	18 (3/17)	0
Type 3, % (n/N)	11.1 (20/180)	12 (12/100)	10 (6/61)	12 (2/17)	0
TV anatomy					
Bicuspid, % (n/N)	12.2 (22/180)	11 (11/100)	18 (11/61)	0	0
Tricuspid, % (n/N)	57.8 (104/180)	72 (72/100)	46 (28/61)	24 (4/17)	0
Quadracuspid, % (n/N)	30 (54/180)	17 (17/100)	36 (22/61)	76 (13/17)	100 (2/2)
Median age at repair (days)	52	62	44	31	9
Median weight at repair (kg)	3.5	3.6	3.7	3.1	2.9
Neonate at time of repair, % (n/N)	33.3 (60/180)	27 (27/100)	38 (23/61)	47 (8/17)	100 (2/2)
Preoperative ICU admission, % (n/N)	28.9 (52/180)	28 (28/100)	25 (15/61)	47 (8/17)	50 (1/2)
Endotracheal intubation, % (n/N)	20.6 (37/180)	21 (21/100)	18 (11/61)	29 (5/17)	0
ECMO, % (n/N)	0.6 (1/180)	0	2 (1/61)	0	0
Aortic arch obstruction, % (n/N)	13.3 (24/180)	11 (11/100)	18 (11/61)	12 (2/17)	0
Interrupted aortic arch, % (n/N)	12.2 (22/180)	11 (11/100)	16 (10/61)	6 (1/17)	0
Coarctation of the aorta, % (n/N)	1.5 (2/180)	0	2 (1/61)	6 (1/17)	0
Chromosomal abnormality, % (n/N)	22.8 (41/180)	14 (14/100)	33 (20/61)	29 (5/17)	100 (2/2)
Concomitant TV surgery, % (n/N)					
Repair	11.1 (20/180)	2 (2/100)	12 (7/61)	53 (9/17)	100 (2/2)
Replacement	0.6 (1/180)	0	0	6 (1/17)	0
Reoperation					
Redo TV repair, % (n/N)	40 (8/20)	0	14 (1/7)	78 (7/9)	0
TV replacement, % (n/N)	23.8 (5/21)	50 (1/2)	14 (1/7)	10 (1/10)	100 (2/2)
Median time to surgery	2.0 years	11.8 years	8.5 years	2.4 years	35 days
Subsequent TV surgery					
Repair, % (n/N)	3.1 (5/159)	2 (2/98)	4 (2/54)	14 (1/7)	0
Replacement, % (n/N)	5.7 (9/159)	3 (3/98)	7 (4/54)	29 (2/7)	0
Median time to surgery (years)	7.9	12.9	5.5	0.6	
Mortality, % (n/N)					
Early	11.7 (21/180)	9 (9/100)	15 (9/61)	12 (2/17)	50 (1/2)
Late	11.1 (20/180)	11 (11/100)	10 (6/61)	12 (2/17)	50 (1/2)
Late TV outcomes ^a , % (n/N)					
No TV insufficiency ^a	79.5 (109/137)	81 (64/79)	78 (35/45)	77 (10/13)	0
Mild TV insufficiency ^a	18 (26/137)	18 (14/79)	20 (9/45)	23 (3/13)	0
Moderate TV insufficiency ^a	1.5 (2/137)	1 (1/79)	2 (1/45)	0	0
Severe TV insufficiency	0	0	0	0	0

^aLate outcomes are for surviving patients available for follow-up. Two patients were lost to follow-up and were not included.
ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; TA: truncus arteriosus; TV: tricuspid valve.

20 years was $79.1 \pm 4.5\%$ [95% confidence interval (CI) 68.5–86.4] and $73.8 \pm 6.5\%$ (95% CI 58.4–84.2) in patients with none/trivial and mild TV insufficiency, respectively (Fig. 2A). Eleven of the 152 (7.2%) patients with preoperative mild or less TV insufficiency required subsequent TV surgery due to worsening insufficiency during the follow-up period. This included 5 patients (TV repair, $n=2$; TV replacement, $n=3$) with none/trivial TV insufficiency at a median time of 12.9 years and 6 patients (TV repair, $n=2$; TV replacement, $n=4$) with mild TV insufficiency at a median time of 5.5 years. The long-term TV status in surviving patients with preoperative mild or less TV insufficiency who did not undergo concomitant TV surgery is excellent, with 98.3% (114/116) of patients having mild or less TV insufficiency at the last follow-up, while 2 patients had moderate TV insufficiency.

Moderate or greater tricuspid valve insufficiency

A total of 19 patients had moderate or greater TV insufficiency (moderate, $n=17$; severe, $n=2$) on preoperative TTE (Table 1).

The TV anatomy was tricuspid in 4 patients and quadracuspid in 15 patients. Both patients with severe TV insufficiency had a quadracuspid TV. As the degree of TV insufficiency increased, the age and weight of patients at the initial operation decreased (Table 1).

Twelve patients with moderate or greater TV insufficiency underwent concomitant TV surgery. Early mortality in this cohort was 25% (3/12; moderate, $n=2$; severe, $n=1$). There were 2 late deaths. Ten patients required TV reoperation (redo TV repair, $n=7$; TV replacement, $n=3$) during the follow-up period. Of the surviving patients, long-term TV status is good, with all patients having mild or less TV insufficiency at the last follow-up.

Seven patients with moderate TV insufficiency did not undergo concomitant TV surgery. These patients presented earlier in the study period when a more conservative approach to moderate TV insufficiency was undertaken, and these patients did not undergo concomitant TV surgery. Two of these patients died before any TV intervention, one of whom had a concomitant IAA and died after becoming septic. Three patients required subsequent TV surgery (TV replacement, $n=2$; TV repair, $n=1$) due to

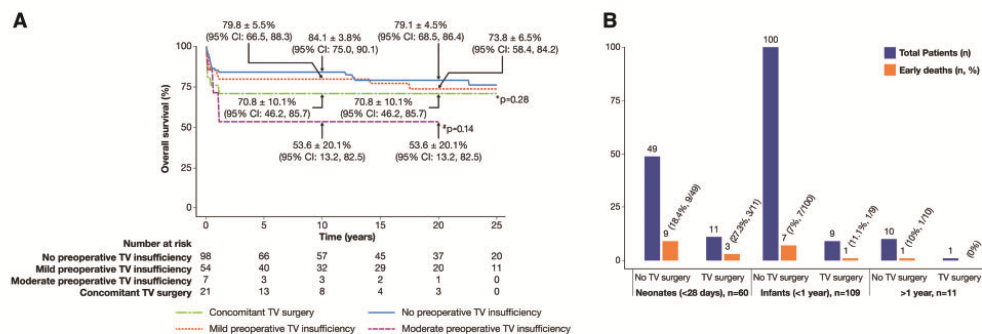


Figure 2: Mortality in patients with TV insufficiency and concomitant TV surgery. (A) Kaplan-Meier overall survival of TV insufficiency and concomitant TV surgery. *Log-rank mild or less TV insufficiency versus concomitant TV repair. *Log-rank mild or less TV insufficiency versus moderate TV insufficiency. (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 $70.8 \pm 10.1\%$ (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 $19.2 \pm 14.9\%$ (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 $84.0 \pm 4.6\%$ (95% CI 72.5–91.0) at 20 years. Surgical technique is summarized in Fig. 1. Seven of the 14 (50%) patients who underwent

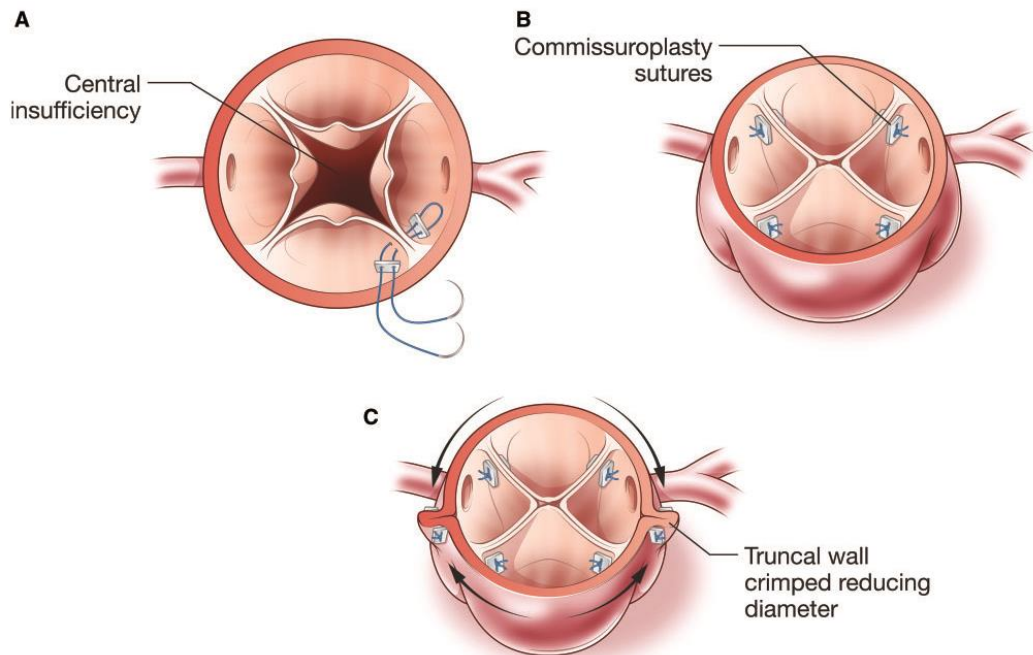


Figure 3: Subcommissural annuloplasty. Placement of 5-0 Ti-Cron (Medtronic, Minneapolis, MN, USA) sutures pledgeted with autologous pericardium to the sub-commissural region of the truncal valve. This aims to improve central coaptation in patients with a large truncal valve annulus and relatively normal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

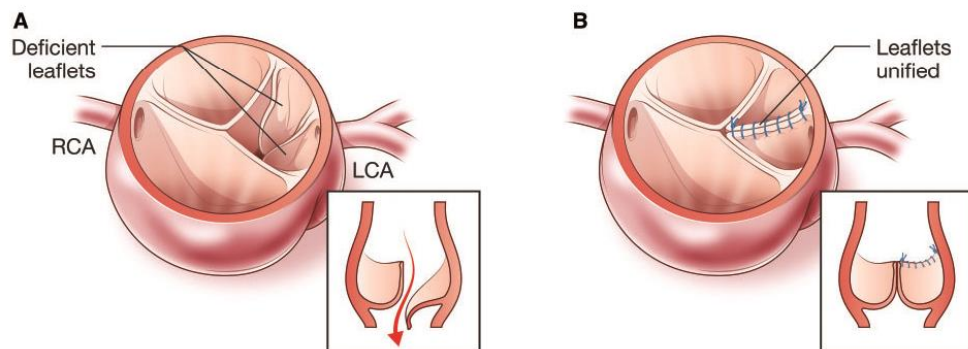


Figure 4: Suture valvuloplasty. Suture of a single prolapsing leaflet to the adjacent TV leaflet for support. LCA: left coronary artery; RCA: right coronary artery; TV: truncal valve.

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

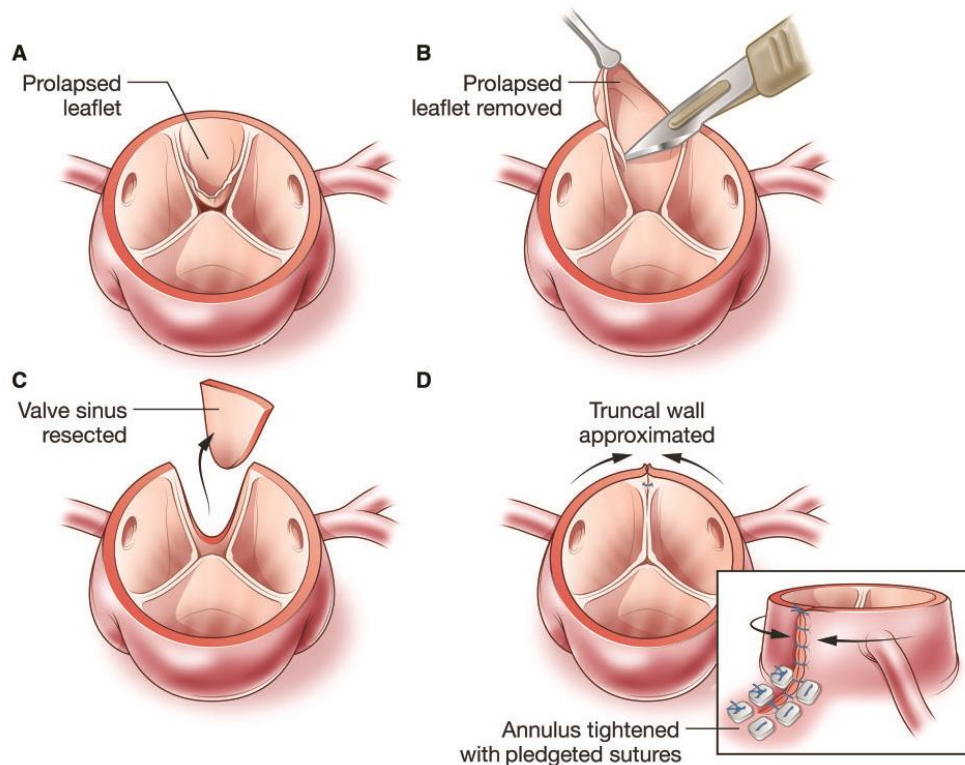


Figure 5: Cusp resection and annular reduction. First described by Imamura *et al.* [13] with tricuspidisation of a quadricuspid truncal valve. The smallest/incompetent leaflet is excised, along with the corresponding segment of the annulus. The remaining annular edges are sutured together to approximate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

univariable analysis for overall mortality ($P=0.38$). Overall survival in neonates was $72.8 \pm 5.8\%$ (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 $62.3 \pm 15.0\%$ (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 $53.0 \pm 17.6\%$ (95% CI 17.0–79.7) at 1 year and $39.8 \pm 17.5\%$ (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 $37.5 \pm 17.1\%$ (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

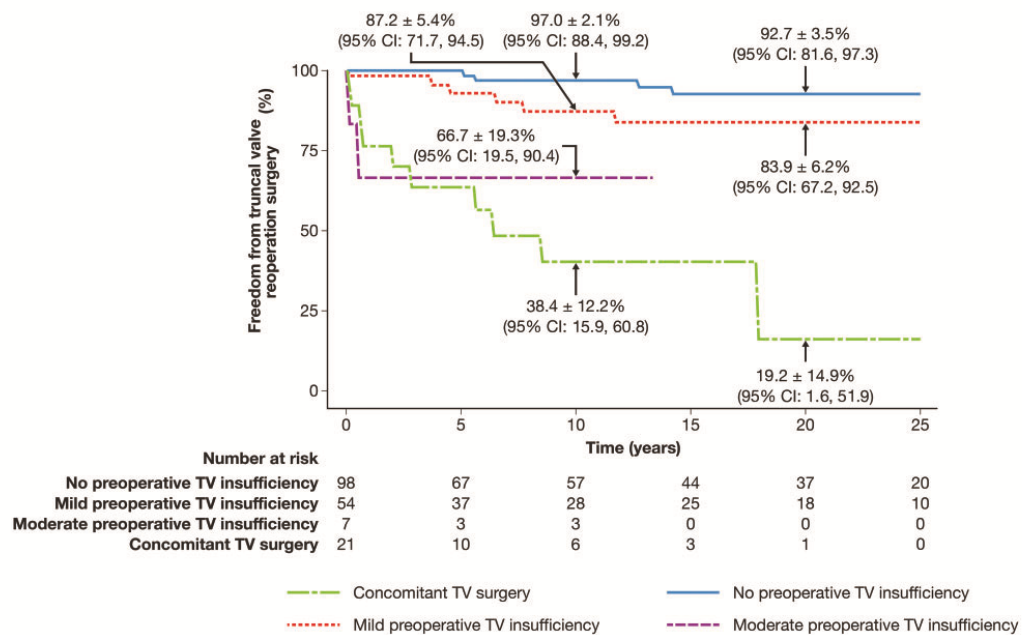


Figure 6: Freedom from TV reoperation surgery. Freedom from TV reoperation and subsequent TV surgery. TV: truncal valve.

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 <i>et al.</i> [4]	1987–1997	50	50	5	5	60 (3/5)	40 (2/5)	80 (4/5)	80 (4/5)	None	2.4
Henaine <i>et al.</i> [22]	1986–2003	153	134	9	NR	67 (6/9)	33 (3/9)	44 (4/9)	NR	2 × TV replacements	8.1
Kaza <i>et al.</i> [8]	1995–2008	17	NR	14	NR	100 (14/14)	0	0	NR	5 × redo TV repairs	2
Russell <i>et al.</i> [7]	2000–2009	572	NR	23	NR	96 (22/23)	4 (1/23)	26 (6/23)	NR	1 × TV replacement	NR
Russell <i>et al.</i> [23]	1979–2011	16	5	5	5	100 (5/5)	0	40 (2/5)	40 (2/5)	1 × redo TV repair	5.5
Myers <i>et al.</i> [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	18
										5 × TV replacements	

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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Chapter 7. The quadricuspid truncal valve: surgical management and outcomes

7.1 Introduction

There is little dispute about the importance of truncal valve competency. The previous Chapter illustrates that most patients with moderate or greater truncal valve insufficiency will require truncal valve surgery at some stage, particularly those with a quadricuspid truncal valve. Furthermore, most patients who required truncal valve surgery had a quadricuspid truncal valve. Likewise, Russell and colleagues (102) reported that most patients who underwent truncal valve surgery had a quadricuspid truncal valve.

While I have established that patients with moderate or greater truncal valve insufficiency should undergo truncal valve surgery, it is unclear which repair technique is the most durable. The following study addressed the durability of the various surgical techniques employed to repair the quadricuspid truncal valve. Between 1979 and 2018, there were 56 patients with truncus arteriosus and a quadricuspid truncal valve at The Royal Children's Hospital. Of these patients, 14 patients had concomitant truncal valve surgery, 8 of whom required truncal valve reoperation. Progression of truncal valve insufficiency requiring truncal valve surgery occurred in 7 patients.

The most common method of repair was tricuspidization of the truncal valve. Interestingly, I found that freedom from truncal valve reoperation was 64% at 10 years after tricuspidization compared to 0% at 6 years for any other repair method. These results signify two important findings. Firstly, tricuspidization appears to be the most durable repair method for the quadricuspid truncal valve. Secondly, in younger children, tricuspidization may avoid the need for mechanical prosthesis and necessitating life-long anti-coagulation.

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Naimo et al

Congenital

The quadricuspid truncal valve: Surgical management and outcomes

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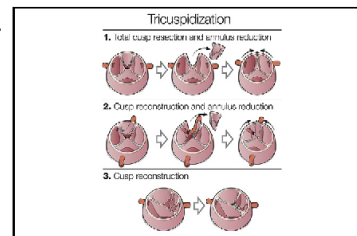
ABSTRACT

Objective: To determine the outcomes of patients with a quadricuspid truncal valve (TV) and durability of TV repair.

Method: We reviewed 56 patients with truncus arteriosus and a quadricuspid TV who underwent complete repair between 1979 and 2018.

Results: TV insufficiency was present in 39 patients (mild, $n = 22$; moderate, $n = 14$; and severe, $n = 3$). Fourteen patients had concomitant TV surgery. Early mortality in patients who had concomitant TV surgery was 14% (2 out of 14 patients) and overall survival was $77.1\% \pm 11.7\%$ at 15 years. Freedom from TV reoperation was $30.3\% \pm 14.6\%$ at 15 years. Early mortality in patients who did not undergo concomitant TV surgery was 9.5% (4 out of 42 patients) and overall survival was $74.9\% \pm 6.9\%$ at 15 years. Progression of TV insufficiency requiring TV surgery occurred in 16.7% (7 out of 42 patients). Freedom from TV reoperation was $77.1\% \pm 7.8\%$ at 15 years. The most common method of repair was tricuspidization of the TV. Freedom from TV reoperation was $64.3\% \pm 21.0\%$ at 10 years after tricuspidization and 0% at 6 years after other types of TV surgery. Overall follow-up was 97.6% (41 out of 42 patients) complete for survivors with median follow-up of 16.6 years. At last follow-up there was no TV insufficiency in 16 patients, mild insufficiency in 24 patients, and moderate insufficiency in 1 patient.

Conclusions: More than one-third of patients with a quadricuspid TV require TV surgery. Tricuspidization of the quadricuspid TV appears to be a durable repair option with good long-term outcomes. (J Thorac Cardiovasc Surg 2020; ■:1-9)



Techniques of tricuspidization of the truncal valve.

CENTRAL MESSAGE

More than one-third of children with a quadricuspid truncal valve will require truncal valve surgery. Tricuspidization is a durable repair option in young children.

PERSPECTIVE

Tricuspidization of the quadricuspid truncal valve has good long-term outcomes. In young children, tricuspidization of the quadricuspid valve is a durable repair option and may help to avoid the need for truncal valve replacement.

See Commentary on page XXX.

We recently reviewed the long-term outcomes of surgical repair of truncus arteriosus and the impact of truncal valve (TV) insufficiency.¹⁻³ Although there was no apparent association between TV surgery and mortality, concomitant TV surgery is a significant challenge during truncus arteriosus repair. We previously reported that most patients who have required TV surgery had a quadricuspid TV.¹⁻³ Furthermore, most patients with

moderate or severe TV insufficiency had a quadricuspid TV.¹⁻³ In contrast, mild insufficiency of the quadricuspid TV is rarely progressive.¹⁻³ Herein, we describe the outcomes of surgery in children with a quadricuspid TV.

PATIENTS AND METHODS

The Royal Children's Hospital Human and Research Ethics Committee approved the current study. All consecutive patients ($n = 56$) with truncus

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Abbreviations and Acronyms

TTE = transthoracic echocardiogram
TV = truncal valve

arteriosus and a quadricuspid TV who underwent operation at The Royal Children's Hospital between 1979 and 2018 were reviewed. Data were obtained by review of medical records from initial presentation until final cardiology follow-up. Patient characteristics are summarized in Table 1.

Definitions

Early mortality was defined as deaths occurring within 30 days of surgery or before hospital discharge. All other deaths were considered late. Subsequent TV surgery was defined as the first TV surgery done after initial truncus arteriosus repair. The presence of TV insufficiency was evaluated by preoperative transthoracic echocardiography (TTE) and color Doppler imaging using standard echocardiographic criteria,⁴⁻⁶ including M-mode assessment of left ventricular function, Doppler assessment of pressure half-time (mild [>500 ms], moderate [500-200 ms], and severe [<200 ms]), diastolic flow reversal in the descending aorta (mild [brief, early diastolic reversal], moderate [intermediate], and severe [holodiastolic flow reversal]), color flow regurgitant jet size (mild [small central jet $<25\%$ left ventricular outflow tract], moderate [intermediate jet greater than mild but no signs of severe], and severe [large central jet $>65\%$ left ventricular outflow tract]), and measurements of the truncal regurgitant jet width to annulus ratio (mild [<25], moderate [25-64], and severe [≥ 65]). TV insufficiency was graded qualitatively from none/trivial to severe. All patients underwent preoperative TTE. Generally, TV surgery was performed at truncus arteriosus repair when preoperative TV insufficiency was graded as moderate or severe. Lesser degrees of TV insufficiency were repaired only when intraoperative decision making dictated that TV repair was necessary.

Data Analysis

Data were analyzed using Stata version 14 (StataCorp LP, College Station, Tex). Descriptive statistics for continuous data are expressed as median (range). Mann-Whitney *U*-test and χ^2 test were used where appropriate. Categorical data were summarized as frequencies and percentages. Kaplan-Meier actuarial survival ($\pm$ standard error) was used to analyze and plot time-related end points. Log-rank test was used to compare survivor functions.

RESULTS

Median age at truncus arteriosus repair was 53 days (range, 1 day-3.1 years) and median weight was 3.6 kg (range, 1.7-12 kg). Median age decreased over time. Median age was 69.5 days between 1979 and 1988 ($n = 14$); 70 days between 1989 and 1998 ($n = 23$); 32 days between 1999 and 2008 ($n = 9$); and 8 days between 2009 and 2018 ($n = 10$). Concomitant anomalies were present in 27 patients (Table 1), including associated aortic arch obstruction in 7 patients. Preoperative TTE determined TV insufficiency in 39 patients. There were 17 patients with no TV insufficiency, 22 with mild insufficiency, 14 with moderate insufficiency, and 3 with severe insufficiency. Patient outcomes are summarized in Figure 1. Overall early mortality in patients with a quadricuspid TV was 10.7% (6 out of 56 patients) and there were 8 late deaths indicating an

overall survival of $75.4\% \pm 6.0\%$ (95% confidence interval [CI], 61.2%-85.1%) at 15 years. Overall survival in patients with mild or less TV insufficiency was $75.8\% \pm 7.1\%$ (95% CI, 58.5%-86.6%) at 15 years compared with $76.0\% \pm 10.5\%$ (95% CI, 48.0%-90.3%) at 15 years ($P = .93$) (Figure 2, A). Overall follow-up was 97.6% (41 out of 42 patients) complete for survivors with median follow-up of 16.6 years (range, 1-38 years). At final follow-up, all patients were found to be in New York Heart Association functional class I or II.

Concomitant TV Surgery

Concomitant TV surgery was undertaken in 14 patients (Figure 1). All but 1 patient had at least moderate TV insufficiency on preoperative TTE. One patient with mild TV insufficiency on initial preoperative imaging was deemed to have moderate insufficiency on follow-up imaging. Early mortality in patients who underwent concomitant TV surgery was 14% (2 out of 14 patients), both deaths occurred in neonates. The first early death was due to cardiac arrest, and the second early death was due to a persistently low cardiac output state in a patient who could not be weaned off extracorporeal membrane oxygenation. There was 1 late death due to acute-on-chronic respiratory failure secondary to bronchiolitis. Overall survival in patients who required concomitant TV surgery was $77.1\% \pm 11.7\%$ (95% CI, 44.2%-92.1%) at 15 years (Figure 2, B).

Surgery was performed via median sternotomy with the use of cardiopulmonary bypass in all patients. There were 3 surgeons (C.P.B., Y.D., I.E.K.) who performed TV surgery for quadricuspid valve during the study period. The truncus arteriosus was transected and the TV directly inspected. Characteristics and outcomes of patients who underwent concomitant TV repair are summarized in Table 2. As shown in Figure 3, A, tricuspidization was achieved by total cusp resection and annulus reduction, cusp reconstruction and annulus reduction, or cusp reconstruction. Often, the smallest or most dysplastic leaflet was identified and resected, along with the corresponding part of the arterial wall. The truncal wall was reconstructed by direct suture and this suture line continued to close the defect between the 2 adjacent valve leaflets (Figure 3, A-1). This method was used in 4 patients concomitantly at truncus repair. In 2 patients, the left coronary artery was arising from the sinus of the redundant valve leaflet, and the leaflet was partially resected and reconstructed in a similar fashion (Figure 3, A-2). In the remaining patient, the raphe between 2 rudimentary cusps was resected and both cusps were sutured together to form a single, good-quality cusp (Figure 3, A-3). Competence of the TV was achieved by nontricuspidization in 7 patients (Figure 3, B).

Eight patients underwent 11 TV reoperations (Figure 1). Median time to TV reoperation was 248 days (2.4 years;

TABLE 1. Patient characteristics

Characteristic	Overall (n = 56)	Concomitant TV surgery (n = 14)	No concomitant TV surgery (n = 42)
Age (d)	53 (1-1123)	12.5 (1-1123)	66 (4-682)
Weight (kg)	3.6 (1.7-12)	3.1 (1.7-12.0)	3.7 (2.0-8.2)
Neonate at time of repair	35.7 (20/56)	57.1 (8/14)	28.6 (12/42)
CPB time (min)	126 (60-241)	206 (87-241)	112 (60-227)
Crossclamp time (min)	63 (40-263)	120 (80-263)	59 (40-158)
Degree of TV insufficiency			
None	30.4 (17/56)	0	40.5 (17/42)
Mild	39.3 (22/56)	7.1 (1/14)	50.0 (21/42)
Moderate	25.0 (14/56)	71.4 (10/14)	9.5 (4/42)
Severe	5.4 (3/56)	21.4 (3/14)	0
Degree of TV stenosis			
None	82.1 (46/56)	64.3 (9/14)	88.1 (37/42)
Mild	12.5 (7/56)	21.4 (3/14)	9.5 (4/42)
Moderate	5.4 (3/56)	14.3 (2/14)	2.4 (1/42)
Severe TV stenosis	0	0	0
Concomitant anomalies			
Interrupted aortic arch	10.7 (6/56)	7.1 (1/14)	11.9 (5/42)
Coronary artery anomaly	7.1 (4/56)	14.3 (2/14)	4.8 (2/42)
MAPCA	7.1 (4/56)	14.3 (2/14)	4.8 (2/42)
Coarctation	1.8 (1/56)	7.1 (1/14)	0
DiGeorge syndrome	10.7 (6/56)	21.4 (3/14)	7.1 (3/42)
Scimitar syndrome	1.8 (1/56)	7.1 (1/14)	0

Values are presented as % (n/N) or median (range). TV, Truncal valve; CPB, cardiopulmonary bypass; MAPCA, major aortopulmonary collateral artery.

range, 12 hours-6.1 years). Four reoperations occurred within the first year following initial TV surgery. Overall freedom from TV reoperation was $30.3\% \pm 14.6\%$ (95% CI, 7.2%-58.2%) at 15 years. Freedom from reoperation in the 7 patients who underwent concomitant

tricuspidization of their TV was $64.3\% \pm 21.0\%$ (95% CI, 15.2%-90.2%) at 10 years compared with 0% at 6 years for any other repair method ($P = .04$). Two patients who underwent tricuspidization of their TV required TV reoperation at 2 months and 6 years. Of the remaining

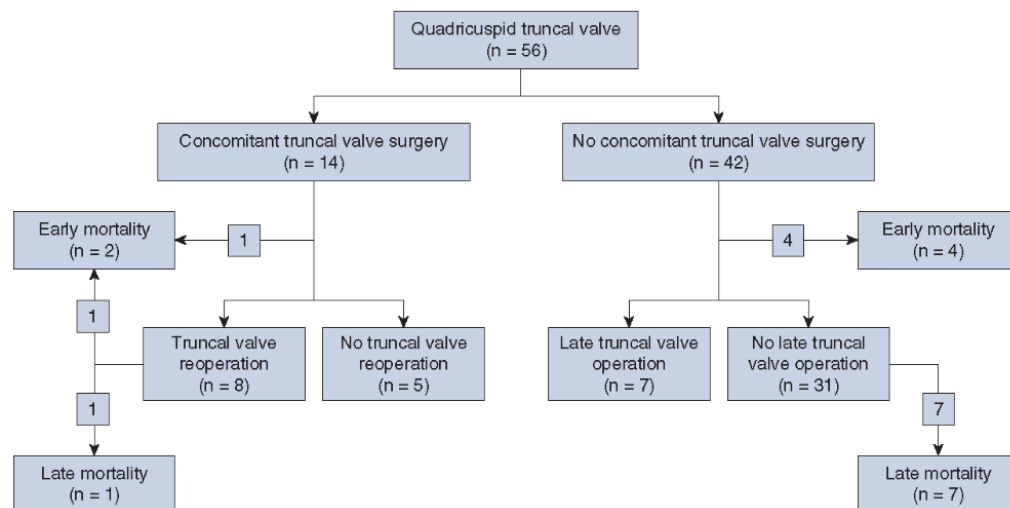


FIGURE 1. Diagram showing the timing and distribution of truncal valve surgery, mortality, and reoperation.

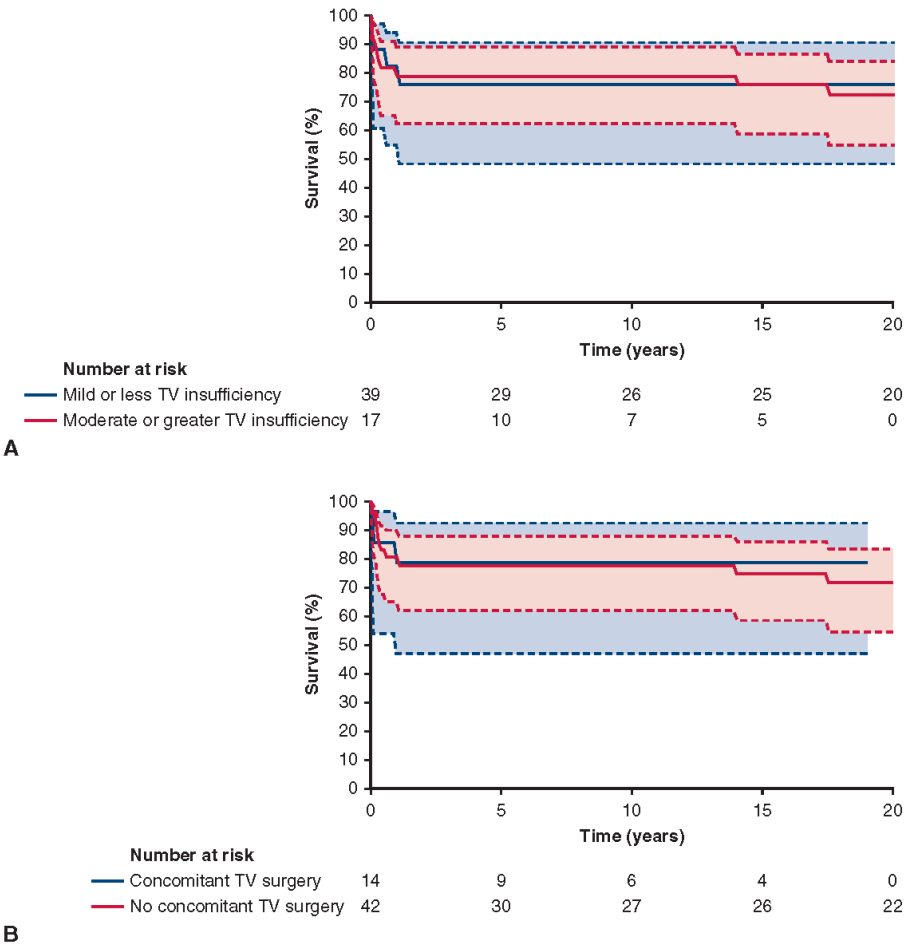


FIGURE 2. Survival in children with a quadricuspid truncal valve (TV). A, Mild or less TV insufficiency versus moderate or greater TV insufficiency. B, Concomitant TV surgery versus no concomitant TV surgery.

6 patients who required TV reoperation, 2 underwent tricuspidization of their previously repaired TV. The first patient initially underwent subcommissural annuloplasty and plication of the sinotubular junction, then underwent tricuspidization at 2.8 years, followed by replacement with a 24-mm aortic homograft 8 years later due to endocarditis with root abscess. The patient is currently well at 13 years. The second patient initially underwent resection of accessory tissue from the valve cusps, then underwent tricuspidization at 2.6 years. The patient is currently well at 2.7 years. After median follow-up time of 16.1 years (10.2 years; range, 1.2-19 years), there was TV insufficiency in 5 patients, and mild insufficiency in 6 patients after concomitant TV surgery.

No Concomitant TV Surgery

There were 42 patients who did not undergo concomitant TV surgery (Figure 1). Most patients who did not require concomitant TV surgery had mild ($n = 21$) or no ($n = 17$) TV insufficiency (90.5%; 38 out of 42). Early mortality in patients who did not require concomitant TV surgery was 9.5% (4 out of 42). Two early deaths were due to acute-on-chronic respiratory failure secondary to severe tracheobronchomalacia; 1 early death was due to cardiac arrest; and 1 early death was due to sepsis. There were 7 late deaths, 5 of which were within the first year following truncus repair and overall survival of $74.9\% \pm 6.9\%$ (95% CI, 58.3%-85.7%) at 15 years (Figure 2, B).

TABLE 2. Concomitant truncal valve (TV) surgery

	TV Pt insufficiency	Additional diagnoses	Age (d)	Weight (kg)	TV surgery type	Other surgery	Time to TV reoperation	TV reoperation	Follow-up time
1	Moderate	None	1	1.7	Commissurotomy and resection of accessory tissue	None	–	None	Death (early)
2	Mild	None	80	4.8	Tricuspidization (cusp reconstruction)	None	–	None	19.0 y
3	Moderate	Coronary anomaly	33	2.9	Tricuspidization (cusp reconstruction and annulus reduction)	None	–	None	19.0 y
4	Moderate	None	164	5.3	Tricuspidization (cusp resection and annulus reduction)	None	–	None	16.4 y
5	Moderate	DiGeorge syndrome	41	3.1	Subcommissural annuloplasty and STJ plication	None	2.8 y	Tricuspidization (cusp resection and annulus reduction)*	13.0 y
6	Severe	DiGeorge syndrome	10	2.8	Tricuspidization (cusp resection and annulus reduction)	None	0.2 y	Konno procedure and replacement with 19-mm Carbomedics aortic valve	Death (late)
7	Severe	Scimitar syndrome; MAPCA	7	3.0	Subcommissural annuloplasty	MAPCA ligation; right pneumonectomy	1 d	Replaced with 14-mm aortic homograft	Death (early)
8	Moderate	None	2	3.5	Replacement with 10-mm aortic homograft	None	0.6 y	Replaced with 17-mm St Jude aortic valve	11.7 y
9	Moderate	None	1123	12.0	Subcommissural annuloplasty	None	6.1 y	Subcommissural annuloplasty and STJ plication	9.8 y
10	Moderate	CoA	1	3.1	Commissurotomy and resection of accessory tissue	CoA repair	0.7 y	Commissuroplasty†	8.6 y
11	Moderate	DiGeorge syndrome	79	3.8	Tricuspidization (cusp resection and annulus reduction)	None	6.0 y	Commissuroplasty	8.2 y
12	Moderate	ASD	15	3.0	Resection of nodules from valve cusps	None	2.6 y	Tricuspidization (cusp resection and annulus reduction)	2.7 y
13	Moderate	Coronary anomaly	4	3.0	Tricuspidization (cusp reconstruction and annulus reduction)	Coronary unroofing	–	None	1.0 y
14	Severe	IAA	3	3.2	Tricuspidization (cusp resection and annulus reduction)	AA reconstruction	–	None	1.0 y

St Jude: St Jude Medical, St Paul, Minn; Carbomedics: LivaNova, London, UK; On-X: On-X Life Technologies, Austin, Tex. *Pt*, Patient; *TV*, truncal valve; *STJ*, sinotubular junction; *MAPCA*, major aortopulmonary collateral artery; *CoA*, coarctation; *ASD*, atrial septal defect; *IAA*, interrupted aortic arch; *AA*, aortic arch. *Replaced 8 years later with a 24-mm aortic homograft due to endocarditis with root abscess. †Replaced 4.2 years later with a 19-mm On-X aortic valve then again 1 year later with a 21-mm On-X aortic valve due to endocarditis.

Seven out of 42 patients (16.7%) required subsequent TV surgery (Figure 1). Median time to subsequent TV surgery was 5.2 years (range, 7 days–13.3 years). Of these patients, 1 initially had no TV insufficiency, 4 had mild insufficiency,

and 2 had moderate insufficiency. Freedom from subsequent TV surgery was $77.1\% \pm 7.8\%$ (95% CI, 57.3%–88.5%) at 15 years. Subsequent TV operations are summarized in Table 3. Five patients underwent TV

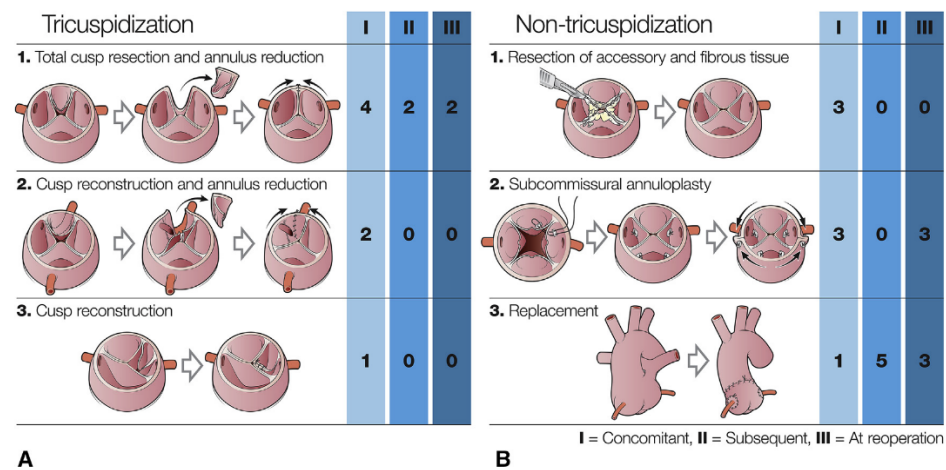


FIGURE 3. Truncal valve (TV) surgical techniques. A, Tricuspidization: 1 = cusp resection and annulus reduction, 2 = cusp reconstruction and annulus reduction, and 3 = cusp reconstruction. B, Nontricuspidization: 1 = resection of accessory and fibrous tissue, 2 = subcommissural annuloplasty, 3 = replacement. I, Concomitant TV surgery; II, subsequent TV surgery; III, procedure performed at reoperation.

replacement. Two patients underwent TV repair with tricuspidization of their TV at 7 days and 5.2 years. Of these 2 patients, the first required TV replacement at 15.6 years and is currently well at 21.7 years, whereas the second is free from TV reoperation and well at 15.3 years. At final follow-up, in patients who did not have concomitant TV surgery, there was no TV insufficiency in 11 patients, mild insufficiency in 17 patients, and moderate insufficiency in 1 patient. Furthermore, the TV status was unchanged in patients who had late deaths.

Tricuspidization

There was a total of 11 patients who underwent tricuspidization throughout the study period. The first concomitant tricuspidization was performed in 2000 (the second patient in this cohort to undergo concomitant TV surgery). There was no association between tricuspidization and era or surgery. Freedom from TV reoperation following tricuspidization was $64.9\% \pm 16.7\%$ (95% CI, 24.9%-87.4%) at 10 and 15 years (Figure 4, A and B). In comparison, freedom from TV reoperation following any

TABLE 3. Subsequent truncal valve (TV) surgery

Pt	TV insufficiency	Additional diagnoses	Age (d)	Weight (kg)	Late TV surgery type	Late TV surgery time	Time to TV reoperation	TV reoperation	Follow-up time
1	Mild	None	68	3.9	Replaced with 25-mm St Jude aortic valve	3.7 y	—	None	38.1 y
2	Mild	IAA	12	2.9	Replaced with 25-mm St Jude aortic valve	7.7 y	—	None	28.3 y
3	Moderate	DiGeorge syndrome	13	3.2	Replaced with 16-mm Carbomedics aortic valve	18 d	11.2 y	Replaced with 21-mm On-X aortic valve	25.1 y
4	Moderate	None	12	2.6	Replaced with 25-mm St Jude aortic valve	13.3 y	—	None	22.8 y
5	Mild	None	217	4.7	Tricuspidization (cusp resection and annulus reduction)	7 d	15.6 y	Replaced with 23-mm On-X aortic valve	21.7 y
6	None	None	32	4.0	Tricuspidization (cusp resection and annulus reduction)	5.2 y	—	None	15.3 y
7	Mild	None	17	3.3	Replaced with 21-mm On-X aortic valve	6.5 y	—	None	8.6 y

St Jude: St Jude Medical, St Paul, Minn; Carbomedics: LivaNova, London, UK; On X: On X Life Technologies, Austin, Tex. *Pt*, Patient; *TV*, truncal valve; *IAA*, interrupted aortic arch.

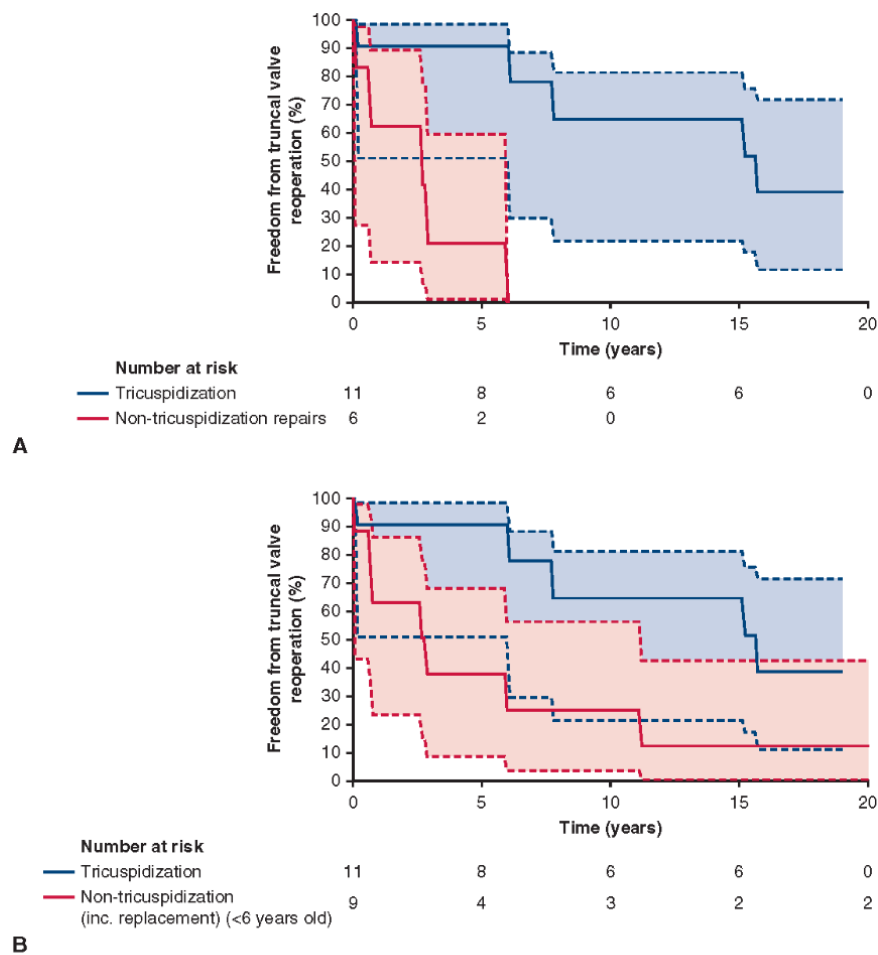


FIGURE 4. Freedom from truncal valve (TV) reoperation. A, Tricuspidization (blue) compared with other types of repair by nontricuspidization techniques (red) performed at any stage. B, Tricuspidization (blue) compared with other types of nontricuspidization, including TV replacement, in children younger than age 6 years (red).

other repair method was 0% at 6 years (Figure 4, A). When including patients younger than age 6 years who underwent any other TV surgery, including replacement, freedom from TV reoperation was $12.7\% \pm 11.9\%$ (95% CI, 0.7%-42.7%) at 15 years ($P = .05$) (Figure 4, B).

Neonates

Twenty neonates were included among the study population (35.7%; 20 out of 56). Overall early mortality in neonates was 15% and overall survival was $75.0\% \pm 9.7\%$ (95% CI, 50.0%-88.8%) at 15 years. Of the neonates, 8 underwent concomitant TV surgery (40%) with an early mortality of 25% and overall survival of

$62.5\% \pm 17.1\%$ (95% CI, 22.9%-86.1%) at 10 years. The outcomes of concomitant TV surgery in neonates can be seen in Table 2. Three neonates underwent tricuspidization. Of the remaining 12 neonates, early mortality was 8% (1 out of 12) and overall survival was $83.3\% \pm 10.8\%$ (95% CI, 48.2%-95.6%) at 10 years. Four neonates who did not have concomitant TV surgery required subsequent TV surgery (Table 3). Of these patients, 2 initially had mild insufficiency, and 2 had moderate insufficiency.

DISCUSSION

TV insufficiency is among the most important factors influencing outcomes of patients with truncus

arteriosus.^{1,2,7-10} We previously reported no apparent association between the degree of TV insufficiency or concomitant TV surgery with mortality.^{2,3} However, our previous analysis³ was limited by a small number of deaths. Despite the apparent lack of association with mortality, most surgeons would agree that severe TV insufficiency, particularly during the neonatal period, increases mortality.

The current study demonstrated that moderate or greater truncal insufficiency in the setting of quadricuspid morphology could be dealt with effectively by valve repair or replacement, so that overall survival was not different from those children with mild or less TV insufficiency (Figure 2, A). Additionally, concomitant TV surgery was effective, so that children who required concomitant TV surgery had similar survival to those who did not require concomitant TV surgery (Figure 2, B).

Previous studies have demonstrated that the most significant risk factors for death are moderate or greater TV insufficiency and an associated interrupted aortic arch.^{7,11,12} There were 6 patients in our cohort with an interrupted aortic arch, 5 of whom had mild TV insufficiency. There was 1 patient with an interrupted aortic arch and severe TV insufficiency who underwent concomitant TV and aortic arch repair. This patient is currently well at 1 year of follow-up.

We previously reported that patients with a quadricuspid TV and moderate or greater truncal insufficiency, were most likely to require TV surgery at some stage throughout their lives.² In contrast, most patients with a quadricuspid TV and mild or less TV insufficiency are free from long-term TV surgery. However, in the current study, 16% of patients with mild or less insufficiency had progressive TV insufficiency that required TV surgery. Furthermore, there were 4 patients with moderate TV insufficiency who did not undergo concomitant TV surgery, of whom 2 have required subsequent TV surgery, 1 has died, and 1 was lost to follow-up after 1 year.

We have used several techniques to concomitantly repair the TV. Our preferred method of repair, that appears to give best long-term results, is tricuspidization of the quadricuspid valve with reduction of the annulus. This can be achieved by either resection of a leaflet and annulus reduction, which was first described by Imamura and colleagues in 1999,¹³ cusp reconstruction and annulus reduction, or cusp reconstruction. We have used this technique concomitantly at truncus arteriosus repair in 7 patients; subsequently in an additional 2 patients who did not have initial TV surgery; and 2 patients who required reoperation following nontricuspidization. There were only 3 reoperations in 11 patients who underwent tricuspidization, compared with 4 reoperations in 6 patients who underwent repair by nontricuspidization. Freedom from reoperation in patients who underwent concomitant tricuspidization was 64% at 10 years compared with 0%

at 6 years in patients who underwent concomitant TV repair by nontricuspidization. Thus, tricuspidization appeared to provide superior results compared with other techniques of repair (Figure 4, A). Furthermore, tricuspidization provided better long-term outcomes even if the nontricuspidization group included younger children (younger than age 6 years), in whom TV replacement was performed (Figure 4, B). Clearly, in older children, TV replacement can be performed with an adult-sized mechanical prosthesis that may potentially last for life. In fact, 4 patients, aged 4 to 13 years, had TV replacement with an adult-sized mechanical prosthesis that has so far lasted without reoperation from 8.6 to 38 years (Table 3). However, such replacement with a large prosthesis may not be feasible in younger children. Besides, a mechanical prosthesis requires lifelong anticoagulation therapy. Thus, tricuspidization of the quadricuspid TV is desirable whenever possible. Although the current study is somewhat limited due to a small number of patients, it appears that tricuspidization of the TV is the most durable repair option in patients with a quadricuspid TV.

Limitations

This study is subject to the usual limitations of a retrospective study. Continuous echocardiographic data was not available, thus accurate timing for the progression of TV insufficiency was unable to be determined. Due to the overall limited sample size, some variables contained a relatively small number of patients, thus limiting statistical analysis.

CONCLUSIONS

More than one-third of patients with a quadricuspid TV require TV surgery. Tricuspidization of the quadricuspid TV appears to be a durable repair option with good long-term outcomes.

Conflict of Interest Statement

Dr d'Udekem has received personal fees from Actelion and Berlin Heart. All other authors have nothing to disclose with regard to commercial support.

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Key Words: truncal valve, truncus arteriosus, surgery

000 **The quadricuspid truncal valve: Surgical management and outcomes**
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More than one-third of children with a quadricuspid truncal valve will require truncal valve surgery. Tricuspidization is a durable repair option in young children.

CONG

Chapter 8: Long-term quality of life in adults following truncus arteriosus repair

8.1 Introduction

There are an increasing number of adults who underwent truncus arteriosus repair as children. Despite this, there is little known about their long-term quality of life. Most patients have undergone repair of truncus arteriosus with the use of a conduit, which invariably requires reoperation for replacement as the individual grows due to progressive stenosis and obstruction. Therefore, it is probable that progressive symptomology of the underlying stenosis, and awareness of eventual reoperation, may affect patient's quality of life.

The following study aimed to assess the long-term quality of life in adults who underwent truncus arteriosus repair at The Royal Children's Hospital using the Short Form 36 (SF-36) questionnaire. There were 42 patients who agreed to participate in the study.

It was found that while there were some discrepancies in the self-reported physical domains, the overall single measure of quality of life – the SF-6D score – was similar between patients with truncus arteriosus, and an age-matched Australian population. There were only 2 patients with DiGeorge syndrome who participated in the study who were independent. This limited comparative analysis between those with and without DiGeorge syndrome.

Furthermore, patients with truncus arteriosus, a condition with a typically high reoperation rate, had similar quality of life to patients who underwent the arterial switch operation, a condition with a typically low reoperation rate.

8.2 Tay H, Naimo PS, et al. *Interact J Cardiovasc Surg.* 2019;29(6):950-54

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Long-term quality of life in adults following truncus arteriosus repair

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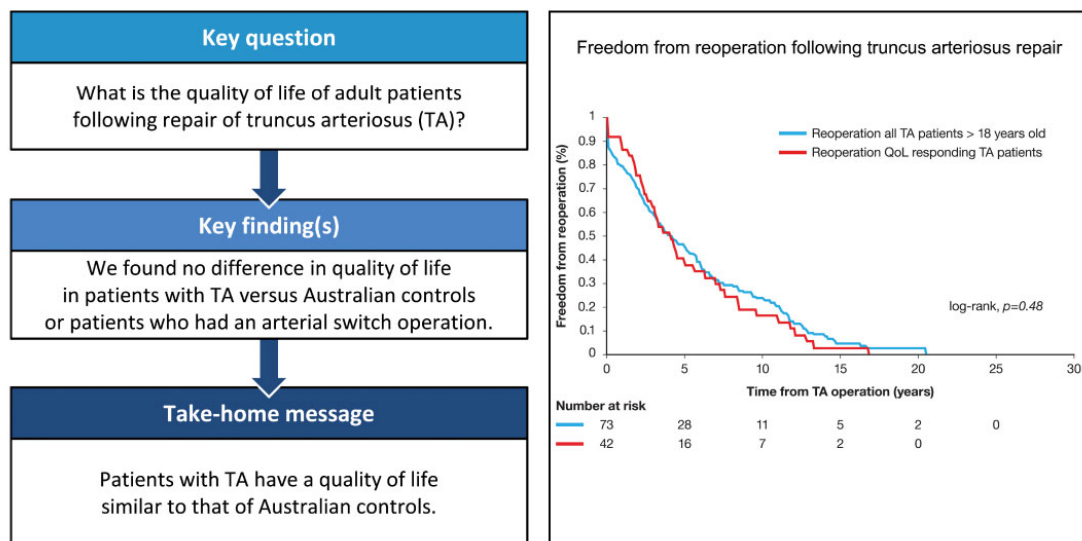
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Abstract

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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[†]The first two authors contributed equally to this study and share co-first authorship.

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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].

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

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.

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
RUPH	80.8 ± 34.1 (60.2–101.4)	88.8 ± 26.4 (87.5–90.0)	0.28	88.0 ± 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.

^aAll 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; RUPH: 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 $3 \pm 2\%$ (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 $85 \pm 2\%$ (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 $82 \pm 4\%$ (95% CI 73–89) at 20 years. There was

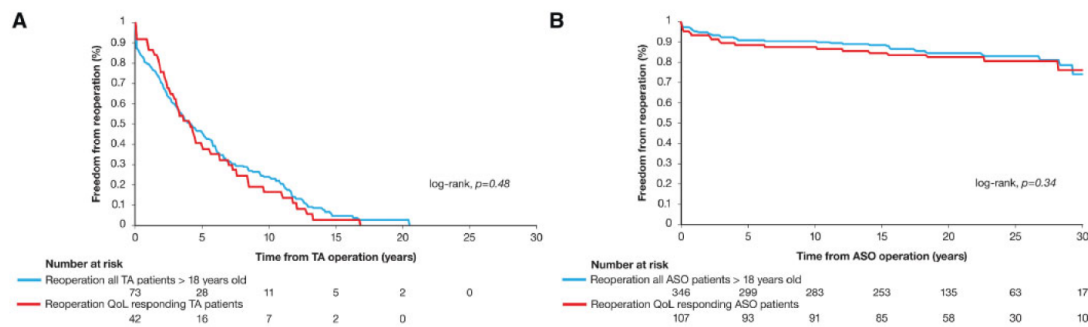


Figure 1: Freedom from reoperation. (A) Freedom from reoperation in all TA patients (blue) and TA patients who participated in quality of life survey (red). (B) Freedom from reoperation in all ASO patients (blue) and ASO patients who participated in quality of life survey (red). ASO: arterial switch 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.

^aAll 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 ± 0.102 , 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 $75\% \pm 3\%$ 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.

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 over estimation 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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Chapter 9: Conclusions

9.1 Overview

In order to improve the lives of children with truncus arteriosus, it is imperative to understand our current management strategies and risk factors associated with poor outcomes. This Doctor of Philosophy has focused on the short and long-term outcomes of truncus arteriosus repair, with particular attention to risk factors for poor outcomes and long-term quality of life. Many previous studies on truncus arteriosus have either focused on the immediate outcomes of surgery or have lacked patient numbers and sufficient follow-up time to allow for adequate assessment in the long-term.

9.2 Findings

The early outcomes of truncus arteriosus repair have been thoroughly documented. However, these reports contain conflicting results, likely due to the low overall number of patients in the studies, and a small number of events of interest. Thus, the true impact of important anatomical and surgical factors is debatable. Furthermore, many previous reports have limited long-term follow-up of truncus arteriosus patients beyond childhood. Little is known about this ever-growing adult population of repaired truncus arteriosus.

In Chapter 2 I reported the largest single institutional experience with truncus arteriosus repair with the longest median follow-up time of 19 years. I found that following truncus arteriosus repair, patients had a good long-term functional status, but had a high rate of reoperation owing to the right ventricular outflow tract. Importantly, neither truncal valve insufficiency nor the presence of an interrupted aortic arch were found to be risk factors for mortality. However, as further discussed in Chapters 3 and 4, the presence of a coronary artery anomaly was found to be a risk factor for mortality. Furthermore, those with DiGeorge syndrome warrant ongoing follow-up due to the risk of late death, most commonly

from infection, which may be a consequence of the lymphopaenia associated with DiGeorge syndrome.

In Chapter 3 I combined results from The Royal Children's Hospital with two centres in Queensland – The Prince Charles Hospital and the Queensland Children's Hospital (formerly Lady Cilento Children's Hospital). Despite differences in the volume of truncus arteriosus cases, there was little variability in surgical technique and outcomes. This series of patients provided the largest multi-centre study on truncus arteriosus assessing long-term outcomes. Firstly, I found that most deaths – over 80% in fact – occurred within the first year following truncus arteriosus repair. If a patient was to survive to one year following repair, their overall survival would be 93.5% at 20 years. Secondly, I also found that neonatal surgery and low operative weight were risk factors for early mortality. Most truncus arteriosus repair is now performed during the neonatal period. Delving into the neonatal deaths, most were of low operative weight with significant concomitant anomalies. Thus, neonatal surgery per se may not be a true risk factor for mortality, rather it comprised several traditionally higher risk groups and those who were in more of a critical state at the time of surgery. Lastly, coronary artery anomalies were found to be a risk factor for overall mortality. The need to correctly identify the coronary artery ostia and epicardial course cannot be overstated.

Having shown in both Chapters 2 and 3 that coronary artery anomalies were a risk factor for death, I explored truncus arteriosus patients with an intramural coronary artery in Chapter 4. Herein, I observed again that many intramural coronary artery diagnoses are in fact made intraoperatively. Thus, the true incidence of an intramural coronary artery in the truncus arteriosus population is unknown. Of our patients with an intramural coronary artery, 4 had undergone concomitant coronary artery unroofing procedures. Of the remaining 3 patients, 1 suffered a cardiac arrest on postoperative day 1 and required emergency coronary artery unroofing. While the patient numbers are low, given the potential for serious postoperative complications, patients with truncus arteriosus and an intramural coronary artery may benefit from coronary artery unroofing with creation of a generous neo-ostium. As previously stated, the

coronary anatomy should be clearly visualised and documented, both with respect to the coronary ostia and epicardial course. Further research into the coronary ostia is required to elucidate the true incidence and impact of an intramural coronary artery in patients with truncus arteriosus.

As discovered in Chapters 2 and 3, the presence of an interrupted aortic arch was not found to be a risk factor for mortality. This is in contrast to many previous reports in the literature. In Chapter 5, I therefore aimed to assess our outcomes with truncus arteriosus and interrupted aortic arch to determine the long-term results and methods of repair. I found that truncus arteriosus and concomitant interrupted aortic arch repair with direct end-to-side anastomosis results in good survival beyond hospital discharge. Although this is the preferred method of aortic arch repair at The Royal Children's Hospital, if the descending aorta cannot be adequately mobilised for advancement to the ascending aorta, a patch should be used to augment the anastomosis. As I discovered, patients who underwent direct end-to-side repair of their aortic arch had a higher rate of left bronchial compression resulting in reoperation for placement of either a pericardial patch to augment the aortic arch anastomosis, or placement of an interposition graft to the descending aorta. The long-term outcomes of patients with truncus arteriosus and an interrupted aortic arch are good, although reoperation rates are high.

In Chapters 6 and 7 I assessed the impact of the truncal valve on the outcomes of truncus arteriosus. It had previously been suggested that truncal valve competence is the single most important factor in determining the successful outcome of truncus arteriosus repair. When first examining the impact of truncal valve insufficiency, I found that most patients with mild truncal valve insufficiency are free from truncal valve surgery up to 25 years, despite their truncal valve anatomy. In contrast, most patients with moderate or greater truncal valve insufficiency – particularly those with a quadricuspid truncal valve – will require truncal valve surgery at some stage in their lives. Of note, concomitant truncal valve surgery was not associated with mortality, however, those who underwent truncal valve surgery were at higher risk of truncal valve reoperation later in life. The durability of truncal valve repair was found to be poor. In Chapter

6, I suggested that all patients with moderate or greater truncal valve insufficiency may benefit from concomitant truncal valve surgery.

Upon closer investigation of patients with a quadricuspid truncal valve in Chapter 7, I determined that over one-third of these patients require truncal valve surgery throughout their lives. Of the various repair methods used on a quadricuspid truncal valve, it seems that tricuspidization of the quadricuspid valve appears to be the most durable repair option with good long-term outcomes. In fact, only 3 of 11 patients who underwent tricuspidization required reoperation, compared to 4 of 6 patients who underwent non-tricuspidization techniques. Additionally, tricuspidization provided better long-term outcomes even if the non-tricuspidization group included younger children (less than 6 years of age), in whom truncal valve replacement was performed. This is an important finding as it suggests that younger children may benefit from truncal valve repair rather than a replacement with a smaller (non-adult sized) mechanical prosthesis which may require repeat replacement. Additionally, avoiding a mechanical prosthesis also avoids life-long anti-coagulation and the associated risks. Thus, I suggest that tricuspidization of the quadricuspid truncal valve is a desirable option, whenever possible.

Lastly, in Chapter 8 I explored the quality of life in adult survivors of childhood truncus arteriosus repair. There are no studies currently in the literature exploring the quality of life in adults with truncus arteriosus. Using the SF-36 questionnaire I discovered that adults with truncus arteriosus had a similar quality of life compared with age-matched Australian controls. Furthermore, as we know from Chapters 2 and 3, patients with truncus arteriosus can expect several reoperations throughout their lifetime. It is unknown what impact multiple reoperations would have on one's quality of life. I therefore compared the quality of life in patients with truncus arteriosus, to a patient cohort of similar complexity, but traditionally low reoperation rates – patients who had the arterial switch operation. Despite a higher reoperation rate in truncus arteriosus patients, they have a similar quality of life to patients who underwent the arterial switch. There were 2 patients who had DiGeorge syndrome who participated in the study who were both independent. This clearly limited comparison between those with

and without DiGeorge syndrome. Larger cohort studies of those with truncus arteriosus and DiGeorge syndrome are required to fully elucidate its long-term impact. Interestingly, when assessing each of the domains of the SF-36 questionnaire, physical function was consistently lower than age-matched controls in all age groups. While the SF-36 questionnaire does not assess one's level of physical function, it is difficult to ascertain if there are limitations due to a sedentary lifestyle, or whether despite physical activity, adults with truncus arteriosus have physical limitations. Further quantitative assessment of physical functioning through exercise testing is required to elucidate potential underlying cardiac limitations of physical activity.

9.3 Future directions

While the long-term outcomes of truncus arteriosus repair have been explored, high risk sub-groups of patients require additional large multi-centre studies. Firstly, there is ongoing concern with respect to the incidence and optimal management of coronary artery anomalies in truncus arteriosus. Secondly, the optimal management of the truncal valve has not yet been established. While this Doctor of Philosophy suggests that (i) moderate or greater truncal valve insufficiency should undergo truncal valve surgery; and (ii) tricuspidization of the quadricuspid truncal valve is the most desirable outcome, there are a limited number of patients to draw statistically meaningful conclusions. Lastly, quantitative measures of physical limitations would be beneficial to completely characterise the long-term state of adults with truncus arteriosus. This could be accomplished through exercise testing and determining maximal oxygen uptake. It has previously been shown that exercise post congenital heart surgery can be incredibly beneficial. If an exercise program can be prescribed, we may see further improvements in quality of life, and potentially, improvement in long-term cardiac function.

9.4 Conclusions

Repair of truncus arteriosus is associated with excellent survival following the first year of repair. However, reoperation rates remain high due to the use of a conduit for the right ventricular outflow tract. Neonatal surgery, coronary artery anomalies, and DiGeorge syndrome are associated with mortality. The long-term functional state of survivors is excellent, and their quality of life similar to the age-matched control.

Patients with mild truncal valve insufficiency are free from truncal valve surgery up to 25 years. Patients with moderate or greater truncal valve insufficiency, particularly those with a quadricuspid truncal valve, will likely require truncal valve surgery throughout their lifetime. Tricuspidization of the quadricuspid truncal valve appears to be the most durable method of repair and may avoid the need for life-long anti-coagulation in younger children.

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Appendix A: Additional manuscripts authored during candidature

A.1 Naimo PS, Konstantinov IE. Ann Thorac Surg. 2020; In Press

Surgery for truncus arteriosus: contemporary practice.

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Abstract

Surgery for truncus arteriosus has an early mortality of 3 to 20% with a long-term survival of approximately 75% at 20 years. Nowadays, truncus arteriosus repair is mostly done in the neonatal period together with a single-staged repair of concomitant cardiovascular anomalies. There are many challenging subgroups of patients with truncus arteriosus including those with clinically significant truncal valve insufficiency, an interrupted aortic arch, or a coronary artery anomaly. In fact, truncal valve competency appears to be the most important factor influencing the outcomes after the truncus arteriosus repair. The use of a conduit during the neonatal period invariably requires reoperation on the right ventricular outflow tract. Through improvements in perioperative techniques over time, many children are now living well into adulthood following

repair of truncus arteriosus, albeit with a high rate of reoperation. Despite this, the long-term outcomes of truncus arteriosus repair are good, with many patients being asymptomatic and with a quality of life comparable to the general population.

Introduction

Truncus arteriosus (TA) was first reported in an autopsy case by Wilson (1) in 1798, and later the anatomical details were described by Buchanan (2) in a six-month-old infant. Although TA has an incidence of 3 to 10 per 100,000 live births, it accounts for 4% of all critical congenital cardiac anomalies (3, 4). Although there has been improvement in perioperative management of TA, the reported operative mortality during the last decade remains between 3 and 20% (5-16). The challenging patients with TA are those with truncal valve insufficiency, concomitant interrupted aortic arch (IAA), or anomalous coronary anatomy. The optimal methods of reconstruction of the right ventricular-to-pulmonary artery connection that could minimize the operation rate is yet to be found. We reviewed current outcomes of TA repair focusing on evolving strategies to decrease mortality and reoperation rate.

Methods

A structured review of the literature was performed using PubMed and MEDLINE databases. The search strategy involved the terms “truncus arteriosus” or “common arterial trunk” or “truncal valve” in the title or keywords. We mostly selected publications from the last 20 years; however, we did not exclude commonly referenced and highly regarded older publications. We also searched the reference list of articles identified by this search strategy and selected those we judged relevant. The last search was conducted in January 2020.

Current outcomes of truncus arteriosus repair

Early mortality for TA is 3–20%, depending on the perioperative status and the presence of concomitant anomalies (5-16). Long-term survival after TA repair has been reported to be approximately 75% at 20 years (5-18). Most deaths appear to occur within the first year following repair (13, 16, 19-23). Rajasinghe and colleagues (21) reported that 57% (13/23) of their late deaths occurred within the first year after repair. Similarly, Tlaskal and colleagues (13) reported that 88% (7/8) of late deaths occurred within the first year. We have recently demonstrated that patients who survive to one year following TA repair have excellent outcomes with 92.5% survival at 20 years. The mortality following TA repair is summarized in **Table A.1.1** (5-16, 20-22, 24-28). Nowadays it is well accepted that complete surgical repair of TA is done within the first weeks of life (5, 13, 15, 16, 29-31). While it is not uncommon to operate within the first days of life, these neonates may be at higher individual risk as they may require emergent surgery due to clinically significant truncal valve (TV) insufficiency or concomitant anomalies and thus being in a critical state.

Most patients require reoperation throughout their lives as a conduit is often used to reconstruct their right ventricular outflow tract (RVOT). We have previously a freedom from reoperation of 3% at 20 years (16). Of our 171 patients, 62% (106/171) have required at least 1 RVOT reoperation. The optimal method of RVOT reconstruction has yet to be found, as is discussed in more detail below.

Despite a high rate of reoperation, the long-term functional state of patients following TA repair is good. Most patients are in NYHA Class I/II, and most patients are reported to have mild or less TV insufficiency.

Table A.1.1. Outcomes of truncus arteriosus repair

Study	Year	Study Period	Patients (n)	Age at Repair (median, days)	Early Mortality	Overall survival	Follow-up (mean, years)
Jahangiri et al (6)	2000	1992-1998	50	14	4.0% (2/50)	96% at 3 years	1.9 [#]
Schrieber et al (27)	2000	1976-1998	106	134	17.9% (19/106)	61% at 10 years	6.0
Alexiou et al (7)	2001	1974-1994	23	51	17.4% (4/23)	79% at 10 years	14.8
Brown et al (43)	2001	1978-2000	60	76*	16.7% (10/60)	82% at 10 years	9.4
Danton et al (9)	2001	1988-2000	61	34	13.1% (8/61)	73% at 5 years	4.2
Thompson et al (10)	2001	1992-1999	65	10	4.6% (3/65)	92% at 3 years	2.7 [#]
Kalavrouziotis et al (17)	2006	1993-2005	29	28	3.4% (1/29)	93% at 6 years	6.2
Henaine et al (11)	2008	1986-2003	153	35	17.0% (26/153)	79% at 10 years	8.1
Raisky et al (12)	2009	2000-2006	32	74*	15.6% (5/32)	76% at 5 years	3.3
Hawkins et al (18)	2010	1999-2008	42	31	9.5% (4/42)	82% at 5 years	5.0
Taskal et al (13)	2010	1981-2009	83	54	22.9% (19/83)	75% at 10 years	10.9
Vohra et al (28)	2010	1964-2008	32	14	9.4% (3/32)	91% at 20 years	24.5 [#]
Xu et al (14)	2010	2000-2006	23	350	8.7% (2/23)	91% at 5 years	4.1
Buckley et al (20)	2019	2009-2016	216	10	6.9% (15/216)	87% at 5 years	2.9 [#]
Ivanov et al (25)	2019	1997-2017	97	32	17.5% (17/97)	68% at 10 years	2.5 [#]

* denotes mean age at repair; # denotes median follow-up time.

Truncal valve surgery

TV insufficiency is one of the most important factors influencing outcomes of patients with TA (11, 15, 32-34). Mild TV insufficiency is often well tolerated and often does not require surgical intervention at the time of TA repair. However, a small proportion of patients with mild TV insufficiency may progress to moderate or greater insufficiency, requiring surgical intervention on the valve. We have previously reported 7.2% (11/159) of patients with mild or less TV insufficiency who have progressed to moderate or greater insufficiency with a freedom from TV surgery of 85% at 20 years (15).

One of the most challenge patient cohorts are neonates with clinically significant TV insufficiency. Unfortunately, the proportion of neonates with TV insufficiency and their associated outcomes are seldom reported in the literature. Neonates with a higher degree of TV insufficiency often present earlier, with more overt signs of heart failure necessitating urgent surgical intervention. Clearly, operating on neonates in this critical state would increase the risk of early mortality. We have previously reported on 11 neonates who underwent concomitant TV surgery, with an early mortality of 27% (3/11), compared to 10% (1/10) in older patients. Similarly, Russell and colleagues (33) 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. However, given the poor quality of the TV and overt signs of heart failure, there is often no choice but to operate on the TV.

Several studies have shown that moderate or greater TV insufficiency was a risk factor for early reoperation for TV replacement (13), early mortality, and generally poorer long-term outcomes if not adequately addressed during the initial operation (21, 32, 35-38). However, Tlaskal and colleagues (13) determined that persistent moderate insufficiency is usually well tolerated and does not lead to an increase in early mortality, although was associated with the need for eventual TV replacement. Despite a number of different techniques in a surgeon's armamentarium, it is often difficult to decide when to address TV insufficiency. When there is severe TV insufficiency, the decision is obvious. However,

contention arises when discussing moderate TV insufficiency. At The Royal Children's Hospital Melbourne, we routinely aim to repair the TV in the setting of moderate or greater insufficiency. Furthermore, we have previously reported no apparent association between the degree of TV insufficiency or concomitant TV surgery and mortality (15, 16), perhaps owing to our approach to the TV. We have previously reported in 17 patients with moderate TV insufficiency, of whom 13 underwent TV surgery. In the remaining 4 patients, 2 have died, and only 2 are alive without TV intervention (15).

Unfortunately, though concomitant TV surgery may be necessary, it has limited long term durability. We have previously reported that freedom from TV reoperation was 19.2% at 20 years following concomitant TV surgery (15). Kaza and colleagues (34) reported 29% (5/14) of patients who concomitant TV repair required TV reoperation with a freedom from TV reoperation of 50% at 7 years. Like others, we employed several surgical techniques to for TV repair (**Figure A.1.1 A to D**). These include suturing partially developed commissures, resuspension of leaflets, resection of redundant portion of leaflets, pericardial leaflet extension, tricuspidization of a quadricuspid valve (**Figure A.1.1A and B**), or reduction of the annulus (**Figure A.1.1C and D**). The outcomes of these methods are varied with early mortality as high as 30% (32). There is now an evolving appreciation for the need of reduction of the diameter of the truncal annulus that may be a key for successful repair.

The quadricuspid truncal valve

Interestingly, it appears that the most common subgroup of patients requiring TV surgery were those with a quadricuspid TV. Russell and colleagues (33) reported that most patients who underwent TV surgery had a quadricuspid TV. Of our patient cohort who required TV surgery 57% (12/21) had a quadricuspid TV. Furthermore, most patients with moderate or greater insufficiency had a quadricuspid TV (79%, 15/19) (15, 39). In contrast, most patients with a quadricuspid TV and mild or less insufficiency did not require TV surgery. In fact, only 16.7% (7/42) of patients who had a quadricuspid TV had progression of insufficiency requiring surgery, of whom 5 had mild or less TV insufficiency (15, 40).

Our preferred method of TV repair, that appears to give best long-term results, is tricuspidization with reduction of the annulus (**Figure A.1.1 A and B**) (40). This can be achieved by either resection of a leaflet and annulus reduction, which was first described by Imamura and colleagues in 1999 (41), cusp reconstruction and annulus reduction, or cusp reconstruction. Interestingly, we have shown durability of tricuspidization to be superior to non-tricuspidization techniques. In our recent study, there were only 3 reoperations in 11 patients who underwent tricuspidization, compared to 4 reoperations in 6 patients who underwent repair by non-tricuspidization (40). Freedom from reoperation in patients who underwent concomitant tricuspidization was 64% at 10 years compared to 0% at 6 years in patients who underwent concomitant TV repair by non-tricuspidization (40). Furthermore, tricuspidization provided better long-term outcomes even if the non-tricuspidization group included younger children (less than 6 years of age), in whom TV replacement was performed (40). Similarly, Myers and colleagues reported tricuspidization methods of TV repair tended to improve freedom from reoperation on the TV (42).

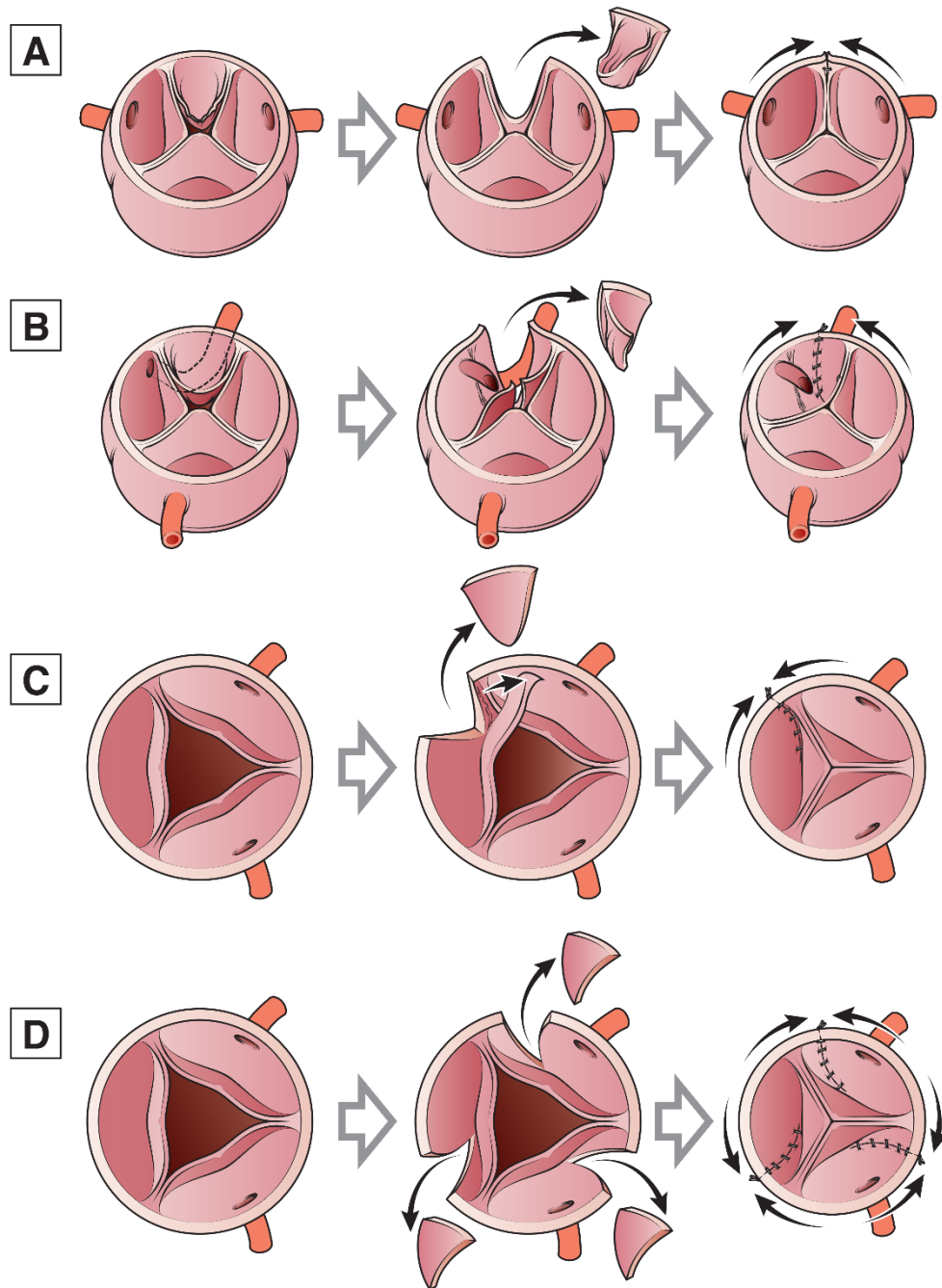


Figure A.1.1. Surgical approaches to addressing significant tricuspid valve insufficiency in patients with truncus arteriosus. A. Tricuspidization of the TV with resection of the smallest or most redundant leaflet and reduction of the annulus. **B.** In the case of an intramural coronary artery crossing underneath the commissure, the redundant leaflet is resected along with the commissure and the remaining valve leaflet reconstructed and coronary artery unroofed. **C** and **D.** A large tricuspid TV can be addressed through reduction of the annulus allowing for a larger surface for coaptation.

Interrupted aortic arch

Another significant issue in patients with TA is an interrupted aortic arch. An IAA occurs in approximately 10 – 20% of patients with TA, and is commonly type B (8, 29, 31, 43-46). Several previous studies have shown an IAA to be a risk factor for mortality (6, 8, 13, 21, 29, 32, 47), however, many of these studies were assessing patients who underwent surgery in the 1980s and 1990s. McCrindle and colleagues reported that outcomes of TA with IAA were worse than IAA alone (47). More contemporary studies have mitigated the risk of mortality likely due to improved surgical techniques and perioperative management of these complex patients. However, many of these patients present early in the neonatal period and still pose a significant surgical challenge. We have previously reported no association between mortality in TA with IAA and TA alone (16). In fact, overall survival in patients with TA with IAA was 83% at 20 years compared to 74% at 20 years in patients with TA without IAA. Thus, it would appear that IAA per se does no longer increase risk of mortality in patients with TA operated in the modern era (48). Rather, the competence of the TV may be the most important factor influencing outcomes.

Our centre has been using end-to-side repair since the early 1980s, and we aim for end-to-side anastomosis of the aortic arch when possible (23, 48, 49). Repair can be undertaken with the use of deep hypothermic circulatory arrest or isolated cerebral perfusion. Anastomosis of the ascending and descending aorta is then performed with or without the use of a patch or interposition graft. If, after mobilisation and approximation there appears to be undue distortion of the aortic arch, or potential for compression of the left pulmonary artery (**Figure A.1.2**), a patch can be used to augment the anastomosis (23, 48, 50).

It is not uncommon that patients with concomitant IAA require reoperation for aortic arch obstruction. The Congenital Heart Surgeon's Society (29) reported an aortic arch reoperation rate of 13.2% (5/38), with a Kaplan Meier survival of only 28% at 5 years without reoperation. McCrindle and associates (47) reported that aortic arch reoperation was more likely for those who had IAA repair by a method other than direct anastomosis with patch augmentation. A previous review of IAA repairs either in isolation, or with TA repair at our centre

demonstrated a low aortic arch reoperation rate using the end-to-side technique (23, 43, 49). Of note however, 5 out of 6 patients who required aortic arch reoperation in our series on TA and IAA had initial repair without the use of a patch (48). In those patients with TA and an IAA, we reported an overall freedom from aortic reoperation of 68% at 10 years, with 3 patients requiring reoperation within 30 days of initial repair (48).

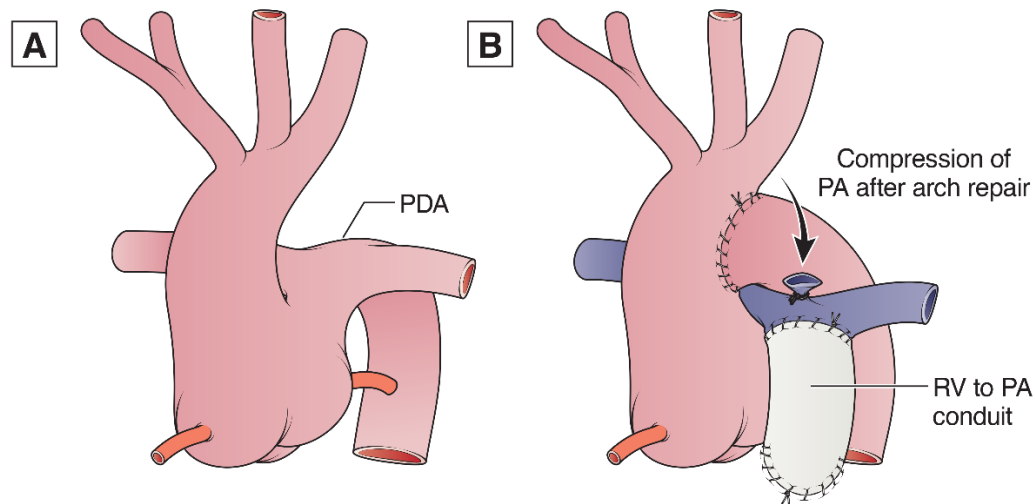


Figure A.1.2. Surgical repair of truncus arteriosus and interrupted aortic arch. A.

Schematic of TA with IAA. **B.** Surgical repair of TA with IAA. The descending aorta is extensively dissected and mobilized, advanced, and directly anastomosed end-to-side to the ascending aorta. The PDA is ligated and all ductal tissues resected. When the descending aorta cannot be adequately mobilized for the advancement procedure as described above, the aortic arch can be repaired using patch augmentation of the arch or interposition graft to the descending aorta. Care should be taken to avoid compression of the right pulmonary artery.

Coronary artery anomalies

The concomitant coronary artery anomaly has been reported to be a risk factor for mortality (8, 9, 16, 27, 51-53). Schreiber and colleagues (27) reported on 13 patients with a coronary artery anomaly and concluded that the coronary artery anomaly was associated with poorer surgical outcomes related to compression or distortion of the anomalous coronary artery. While coronary

artery anomalies have been reported in 5 – 20% of patients with TA it is difficult to ascertain the precise incidence of this anomaly. It is not uncommon for a coronary artery anomaly to be missed on preoperative echocardiogram in patients with TA and, subsequently, diagnosed intraoperatively. Abnormalities of the coronary arteries mostly consist of abnormal origin of a coronary artery with or without intramural course, a single coronary artery giving rise to the entire coronary circulation, or variable epicardial courses of these arteries (54).

While there is a limited cumulative experience with coronary artery anomalies and TA, it appears that many deaths occurred in patients with a major branch coronary artery was crossing the RVOT (16). While the reason for these deaths cannot be definitively explored, it could potentially have resulted from compression of the branch coronary artery by the overlying conduit. This is a difficult predicament as the overlying conduit would require sufficient spacing from the underlying coronary artery to avoid compression as well as compact enough to avoid kinking or distortion when the sternum is closed.

Rarely, patients with TA may have an intramural coronary artery (Figure 3A), which may increase the risk of myocardial ischemia. A recent study by Patrick and colleagues (55) reported that an intramural coronary artery occurred in 15% of their patients. Myocardial ischaemia may be caused by compression of the intramural segment, kinking due to an acute take-off angle, or the compression by an ostial ridge. Surgical management of TA and an intramural coronary artery involves unroofing the intramural segment and formation of an unobstructed neo-ostium (Figure 3B and 3C). The intramural segment may course behind the truncal valve commissure and may need to be reconstructed or resuspended to facilitate unroofing (39). We have previously described our technique for coronary artery unroofing in detail and provided a video of the unroofing technique (39).

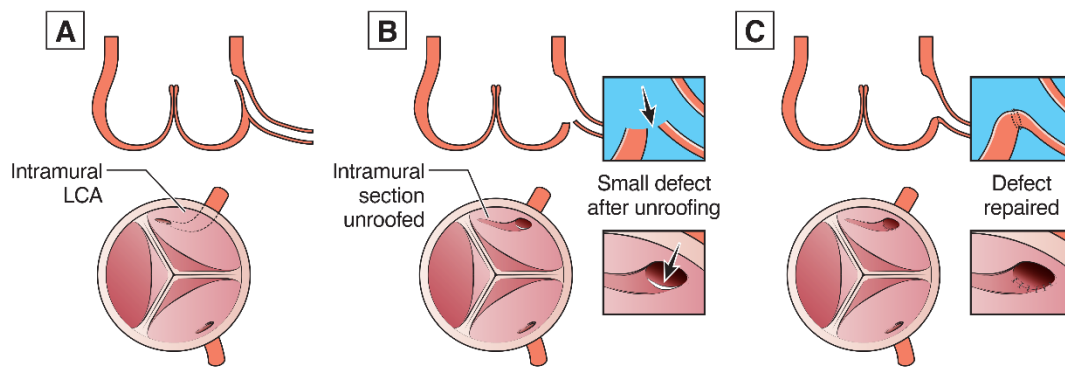


Figure A.1.3. Truncus arteriosus with concomitant intramural coronary artery. A. TA with an intramural coronary artery, often with an acute angle and ridge of tissue. **B.** The coronary artery should be unroofed with the creation of a generous neo-ostium. **C.** If a small defect occurs after the unroofing procedure the vascular wall is re-approximated by running suture.

Right ventricular outflow tract reconstruction

Reconstruction of the RVOT can be established with a conduit or direct anastomosis of the pulmonary artery to the right ventricle. The best method of RVOT reconstruction is yet to be determined. The use of a conduit to reconstruct the RVOT is the most common method. However, conduits have limited durability as they cannot grow or regenerate, and therefore inevitably require reoperation (56-58). Additionally, like any foreign material, they are prone to infection and thrombosis (57).

Bioprosthetic conduits

The choice of conduit depends on several factors including but not limited to availability, patient size and haemodynamics, and surgeon preference. The Contegra (Medtronic, Minneapolis, MN) bovine jugular vein conduit is predictable in performance and lacks immunogenic properties (59). Herrmann and colleagues (60) reported on 100 TA patients between 1981 and 2018 with a median follow-up time of 15.6 years. They demonstrated longer freedom from reoperation with the bovine jugular vein conduit compared to an aortic homograft, but no

difference to a pulmonary homograft (60). Furthermore, they showed that larger conduit size was associated with longer freedom from reoperation. Interestingly, Vitanova and colleagues (61) reported on RVOT reconstruction in 145 patients and found that the overall durability of homograft, bovine jugular vein conduits, and porcine-valved conduits to be similar, however, the bovine jugular vein conduit appeared to develop insufficiency and stenosis earlier than other types. In contrast to these more favourable results, Buckley and colleagues (20) reported on 216 neonates which showed a two-fold increase risk of reintervention when the Contegra conduit was used compared to a homograft, regardless of size. Furthermore, several studies have reported an increased rate of endocarditis in patients with a Contegra conduit (60, 62, 63).

Homografts

An alternative to the bioprosthetic conduits above are the pulmonary and aortic homografts. Homografts have been the conduit of choice in recent decades, but have been limited due to smaller sizes, availability, and potential for obstruction. Homografts reportedly have better haemodynamic properties and increased longevity (64). Vohra and colleagues (28) in 2010 reported on 32 patients who underwent TA repair with 24 aortic homograft and 8 pulmonary homograft reconstructions, resulting in a freedom from reoperation of 68% at 10 years, and 37% at 20 years. As with bioprosthetic conduits, larger homograft sizes increase longevity and improve freedom from reoperation. Several studies have suggested homografts less than 12mm in diameter fail earlier, requiring earlier replacement (13, 16, 21, 65, 66). Vohra and colleagues (28) showed that oversizing the homograft increased longevity of the graft for up to 12 years. However, care must be taken to not excessively oversize the conduit. Mastropietro and colleagues (67) reported on 216 neonates in a multicentre study and showed that conduit type did not impact reoperation rates, while a conduit size >50mm/m² had a five-fold increase in mortality. Furthermore, larger sized conduits appear to have an increased risk for coronary artery compression, TV or pulmonary artery distortion, and they require a larger ventriculotomy (22).

Polytetrafluoroethylene conduit

More recently, polytetrafluoroethylene (PTFE) conduits have become increasingly used due to their availability, ease of construction, lower cost, being immunologically inert, and having comparable results to other conduits (68, 69). Seese and colleagues (68) reported on 28 neonates between 2004 and 2016 who underwent RVOT reconstruction with either a homograft (n=7) or a PTFE conduit (n=18). They reported that the rates of reintervention and time to reintervention on the RVOT were similar between PTFE conduits and homografts. Interestingly, Seese and colleagues reported that at both 5 and 10 year follow-up, patients who had a PTFE conduit had better survival than those who had a homograft. Similarly, Mercer and colleagues (69) reported on RVOT reconstruction in 55 patients less than 2 years old between 2004 and 2015, and found that reintervention rates and time to reintervention were similar between patients who received a homograft and those who had a PTFE conduit. Furthermore, as with other conduits, larger conduit size resulted in longer freedom from reintervention on the RVOT. Interestingly, it appears that the primary mode of failure with the PTFE conduits may be fibrosis or narrowing at the distal anastomosis over time rather than fibrous tissue formation within the conduit (69).

Direct right ventricle to pulmonary artery anastomosis

The biggest hindrance to long-term freedom from conduit reoperation is the lack of living material with the capacity for growth or regeneration. Any child who requires a conduit as part of their truncus arteriosus repair will invariably require reoperation. In an attempt to circumvent this issue, direct anastomosis of the pulmonary artery to the right ventricle, with or without the use of autologous tissues, has been explored (9, 12, 14, 26). In the case of TA type 1, the main pulmonary artery can be sutured to the right ventriculotomy with the anterior portion of the RVOT being reconstructed with a pericardial patch and a monocusp valve created of autologous pericardium. Danton and colleagues (9) reported a freedom from right ventricular outflow tract reoperation of 89% at 4 years in patients who underwent direct anastomosis of the main pulmonary artery to the right ventricle compared to 58% at 4 years in patients who underwent conduit repair. An issue with direct anastomosis of the RVOT is that without favourable anatomy, it often leads to pulmonary artery distortion which necessitates early

reoperation (70). Another draw-back to this method is the potential for severe pulmonary regurgitation, which has not yet been observed likely due to short follow-up (9, 12, 14, 26). Augmentation of the anastomosis with a patch anteriorly has been suggested to avoid pulmonary artery distortion, which would also allow for interval growth and avoid or delay obstruction to the RVOT or the branch pulmonary arteries (9). While early mortality is similar between direct anastomosis and using a conduit, there is limited long-term data (9, 12, 14).

Long-term Quality of Life after Truncus Arteriosus Repair

There is an ever-growing population of TA patients reaching adulthood, yet there is little information about their quality of life. As most patients who undergo TA repair require reoperation throughout their lifetime, it is unclear whether this negatively impacts their quality of life. O'Bryne and colleagues (71) reported on 25 patients with a median age of 11.8 years who underwent TA repair and assessed their health status. Factors such as exercise tolerance, VO2 max, maximal work, and forced vital capacity were all lower than normal for age and sex (71). Additionally, health-related quality of life was diminished and comparable with that of children with severe heart disease, represented by the Fontan population (71). However, psychosocial functional status was not significantly diminished. These findings collectively represent moderate morbidity and disability (71). By understanding the health-related quality of life following TA repair, we may be able to assess the overall impact of this condition on the individual, and potentially provide a reference for management to address physical or psychosocial issues that may arise.

We have recently reported on the quality of life in adult survivors of childhood TA repair (72). Using the SF-36 questionnaire we observed that adults with TA had a similar quality of life compared with age-matched controls. Furthermore, we compared the quality of life in patients with TA, to a patient's who underwent the arterial switch operation, neonatal procedure with traditionally low reoperation rates. Despite a higher reoperation rate in TA patients, they have a similar quality of life to patients who underwent the arterial

switch. Interestingly, when assessing each of the domains of the SF-36 questionnaire, physical function was consistently lower than age-matched controls in all age groups. While the SF-36 questionnaire does not assess one's level of physical function, it is difficult to ascertain if there are limitations due to a sedentary lifestyle, or whether despite physical activity, adults with TA have physical limitations. Further quantitative assessment of physical functioning through exercise testing is required to elucidate potential underlying cardiac limitations of physical activity.

Conclusion

Repair of TA is associated with excellent survival beyond the first year after repair. However, reoperation rates remain high due to the use of a conduit for the RVOT. The long-term functional state of survivors is excellent, and their quality of life similar to the age-matched control.

The competence of the TV appears to be the most important factor influencing early outcomes. Children with mild TV insufficiency are free from TV surgery up to 25 years. However, children with moderate or greater TV insufficiency, particularly those with a quadricuspid TV, will likely require TV surgery throughout their lifetime.

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Commentary

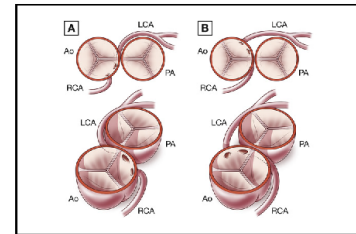
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Commentary: Surgery for an anomalous aortic origin of a coronary artery: To do, or not to do? That is the question

Phillip S. Naimo, MD,^{a,b,c}
Edward Buratto, MBBS, PhD,^{a,b,c,d} and
Igor E. Konstantinov, MD, PhD, FRACS^{a,b,c,d}

Management of asymptomatic patients with anomalous aortic origin of a coronary artery (AAOCA) (Figure 1) is a dilemma that has been tormenting surgeons and physicians alike for decades. Does the risk of surgery in asymptomatic patients outweigh the risk of sudden death? What is the risk of sudden death? Will we ever know the true risk of sudden death in the general population with unknown incidence of AAOCA? Despite feverish discussions of the topic at multiple meetings, the research addressing these questions is limited. Will these questions ever be answered?

Clearly, the true incidence of sudden death is difficult, perhaps even impossible, to establish. It has been reported that AAOCA is the second most common cause of sudden death,¹⁻³ with a rate of 0.6 deaths/100,000 people, albeit in competitive young athletes. Although AAOCA of a right coronary artery is 6 to 10 times more common than AAOCA of a left coronary artery, it appears that AAOCA of the left coronary artery has a slightly higher risk of sudden death.^{4,5} Brothers and colleagues¹ calculated a cumulative risk of death over a 20-year period in people aged 15 to 35 years with AAOCA participating in competitive sports to be 6.3% for AAOCA of the left coronary artery and 0.2% for right coronary artery. One would expect that the



Anomalous aortic origin of the left (A) or right (B) coronary artery with an interarterial course.

CENTRAL MESSAGE

The role of surgery, despite its low risk, in asymptomatic patients with AAOCA is unclear.

incidence of such events should be lower in the general population compared with competitive athletes.

Given that these studies of AAOCA have been performed in competitive athletes, the true incidence of sudden death in the general population due to AAOCA is unknown. Even less is known about the incidence of sudden death in asymptomatic patients with AAOCA. For decades, physicians and surgeons have attempted to risk-stratify patients. Nowadays, observation appears to be reasonable for asymptomatic patients with an AAOCA without ischemia, or physiological evaluation suggesting potential for coronary compromise.⁶

Unfortunately, surgery is not without its risks. Jegatheeswaran and colleagues⁷ report a small (10%), but not insignificant risk of developing new aortic regurgitation, particularly in patients who underwent commissural manipulation. Furthermore, 2% of patients developed a new decrease in ejection fraction following surgery.⁷ Of particular importance, 20% of patients had ongoing symptoms of ischemic chest pain.⁷ Thus, if a patient did not have any inducible symptoms on exercise testing, is it reasonable to observe these patients rather than to expose them to the risk of surgery, albeit small?

Patients presenting after hemodynamic collapse, with ischemic chest pain, or with a positive stress test should be offered surgery. It is clear what to do with these patients. It is not clear what to do with asymptomatic patients. Lifelong observation does not seem unreasonable. Or, do we offer surgery to address the lesion and potentially introduce new cardiac complications? To do surgery, or not to do surgery? That is the question.

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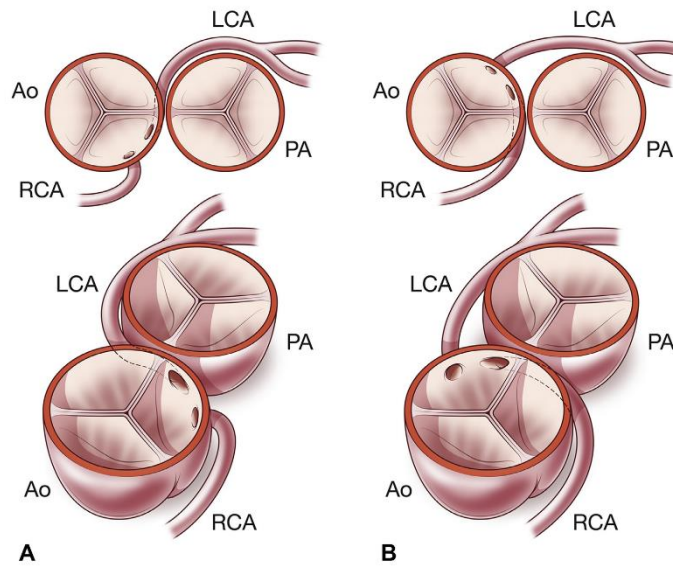


FIGURE 1. Anomalous aortic origin of the left (A) or right (B) coronary artery with an interarterial course. Ao, Aorta; LCA, left coronary artery; PA, pulmonary artery; RCA, right coronary artery.

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Commentary

See Article page XXX.

Commentary: The road map for collaterals—A scenic route from the Abbey Road to the operating theater?

Phillip S. Naimo, MD,^{a,b,c} and
Igor E. Konstantinov, MD, PhD, FRACS^{a,b,c,d}

In the early 1960s, the Beatles had their first recording session with Electric and Musical Industries (EMI) at the Abbey Road Studios (formerly EMI Recording Studios). Their momentous rise in popularity changed the face of modern music at the time. It has since been surmised—albeit unverified—that this led to one of the biggest radiologic advances in modern medicine. In the late 1960s, Godfrey Hounsfield, an electrical and computer engineer with no formal qualifications working for a scientific arm of the profitable EMI, began experimenting on whether images could be produced with differential x-ray attenuation values, leading ultimately to the first computed tomography (CT, initially known as *computer axial tomography*, or CAT) scan.^{1,2} It was in 1967 that the first experimental CT scan (of a mouse) was done, which took 9 days to complete.³ Unbeknownst to Hounsfield, Allan Cormack, a particle physicist, had also shown that multiple measures of x-ray attenuation around a target enable one to compute an image of that target. Both Cormack and Hounsfield received the Nobel Prize in Physics and Medicine in 1979.

Since its humble beginnings of 4 minutes per slice and 7 minutes per reconstruction,³ CT scanning has evolved to a rapid diagnostic and investigative tool for physicians

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Igor E. Konstantinov, MD, PhD, FRACS (left), and
Phillip S. Naimo, MD (right)

CENTRAL MESSAGE

A 3-dimensional interactive imaging reconstruction can be helpful in patients with pulmonary atresia and major aortopulmonary collateral arteries.

and surgeons alike. With such disparate uses as diagnosing an acute abdomen in the emergency department or in staging pulmonary malignancies, CT has revolutionized many areas of medicine and is continuing to do so. In the current issue of the *Journal*, Ghosh and colleagues⁴ have adopted CT angiography with digital 3-dimensional reconstruction for detailed and accurate assessment of the major aortopulmonary collateral arteries (MAPCAs) in patients with tetralogy of Fallot with pulmonary atresia. MAPCAs are often tortuous and complex, which may limit such traditional imaging modalities as echocardiography and angiography. The 3-dimensional reconstruction allows an interactive and comprehensive assessment of each patient's anatomy. This would certainly benefit surgical planning. Additional 3-dimensional imaging in the interactive format could be helpful, particularly for those patients in whom the ratio of native branch pulmonary arteries to MAPCAs would sway decision making from “Let It Be” to “Come Together.”^{5,6}

It has been a long journey from the Abbey Road to the cardiac operating theater for CT imaging. Just when it seems that CT imaging reached the limits of its usefulness, a new scenic interactive modality appears.

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Commentary

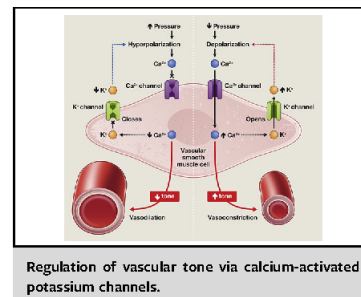
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Commentary: Ions from eons: A hidden therapeutic potential of the resting potential?

Phillip S. Naimo, MD,^{a,b,c} and
Igor E. Konstantinov, MD, PhD, FRACS^{a,b,c,d}

Calcium-activated potassium channels, particularly, large conductance potassium channels (BK_{Ca}), have been identified in virtually every type of smooth muscle. In blood vessels, they are involved in vascular tone regulation. In the uterus, BK_{Ca} channels participate in the control of myometrial cell membrane potentials.¹ In the airway, BK_{Ca} channels regulate the tone and contractility of bronchioles.¹ In gastrointestinal tract, BK_{Ca} channels are involved in the regulation of colonic motility.¹

Potassium is one of the most common ions in living cells, and potassium channels are ubiquitous to all domains of life. The ion-channel superfamilies are thought to be as ancient as the last common ancestor of all organisms on earth.² Because of their wide distribution, potassium channels are thought to be one of the first ion channels to have evolved. The evolution of potassium channels has been traced back to the prokaryotic world.³ Furthermore, small potassium channels have been found in viruses, which are some of the simplest potassium channels, and this has been suggested to predate the more complex channels seen in early bacteria. There have been both major (gene fusion and gene duplications) and minor (single-base mutations and deletions) genetic events that have led to the fascinating diversity of potassium channels that we see today.³ Amazingly, the general molecular characteristics of the BK_{Ca} channels are evolutionarily conserved from worms to mammals.^{1,4} A single mammalian gene



CENTRAL MESSAGE

Large calcium-activated potassium channels may play an important role in vasodilation of the internal thoracic artery.

may generate many variants of BK_{Ca} channels that may explain the variation in calcium sensitivity in blood vessels.

BK_{Ca} channels appear to play a crucial role in arterial smooth muscle tone by providing a negative feedback loop to regulate the degree of depolarization and hyperpolarization.⁵ Small arteries exist in a partially contracted state from which they can either constrict further or dilate depending on the end-organ demand for blood.⁵ Although several pathways are responsible for the contraction or relaxation of vascular smooth muscle, increases in intracellular calcium that occur during cell depolarization increase vascular tone and open the BK_{Ca} channels to restore the cell's resting potential (Figure 1).⁵ Conversely, a reduction in intracellular calcium that occurs during cell hyperpolarization decreases vascular tone and closes BK_{Ca} channels to, again, restore the cell's resting potential.⁵

The study by Sun and colleagues⁶ in this issue of the *Journal* has demonstrated a remarkable difference in the BK_{Ca} subtypes within the internal thoracic artery and saphenous vein, pointing at a potential therapeutic target to treat internal thoracic artery spasm. They demonstrated a greater proportion of BK_{Ca} channels within the internal thoracic artery, which may explain the greater variability in vasodilatory properties of the vessel.⁶ Although systemic therapy may wreak havoc on the whole body, given the widespread distribution of these channels, a targeted therapy at the time of surgery may prove to be potentially beneficial.

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Commentary

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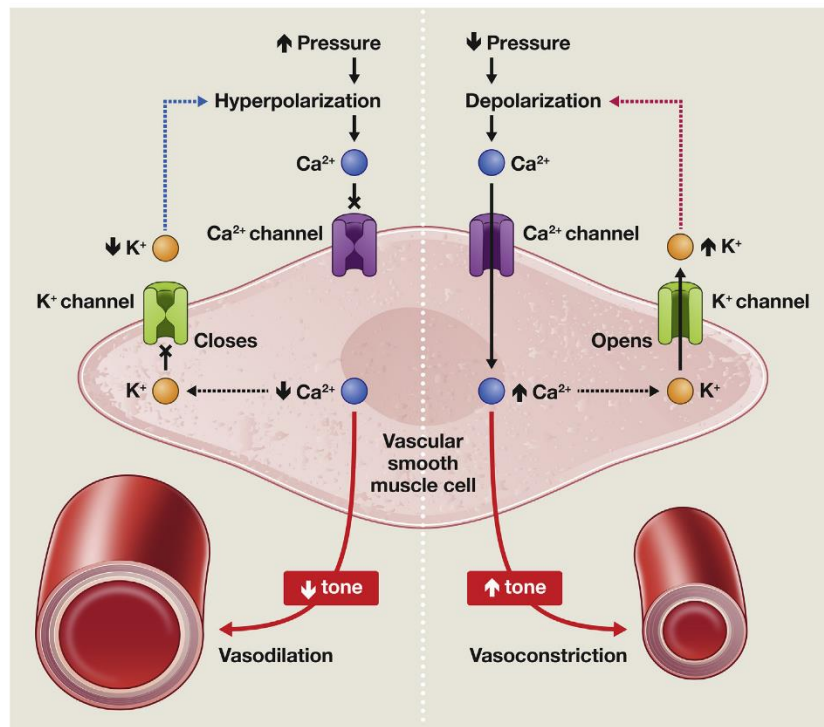


FIGURE 1. Regulation of vascular tone and restoration of cellular resting potential via calcium-activated potassium channels. A decrease in blood pressure causes the cell to depolarize. This opens calcium channels flow into the smooth muscle cell. The increase in intracellular calcium causes vasoconstriction and activates potassium channels, which opens and allows potassium to leave the smooth muscle cell. The potassium efflux has a negative effect on depolarization and restores the cell's resting potential. An increase in blood pressure causes the cell to hyperpolarize. This closes calcium channels and, thus, lowers intracellular calcium. A reduction in intracellular calcium causes vasodilation and closure of potassium channels. Keeping potassium inside the cell causes the hyperpolarized cell to return to it resting potential.

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Commentary

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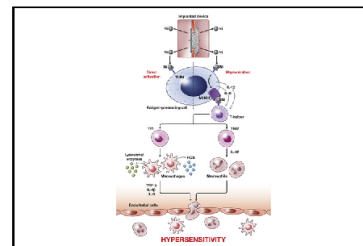
Commentary: A nickel for your thoughts: An overlooked allergen in implantable devices?

Phillip S. Naimo, MD,^{a,b,c} and
Igor E. Konstantinov, MD, PhD, FRACS^{a,b,c,d}

Nickel is a ubiquitous metal with a vast array of uses, ranging from household products to aerospace, military, and implanted medical devices. Its wide use is due to its corrosion resistance, durability, and ease at which it alloys with other metals. Currently, nickel allergy is the most common cause of contact dermatitis in the industrial world, affecting up to 20% of the population, particularly women.^{1,2} Many of these allergies manifest as dermatitis, but a subset of these patients may experience systemic symptoms.³ It is a growing health concern, so much so that nickel earned itself the title of “allergen of the year” in 2008.¹ Until now, nickel may have been overlooked as a potential health problem causing systemic hypersensitivity.

The article by Sharma and colleagues⁴ in the current issue of the *Journal* describes the removal of nickel-containing atrial septal defect (ASD) closure devices in patients with nickel allergy and refractory symptoms. After device removal, patients experienced a resolution of symptoms and improved quality of life. This interesting study provides insight into a likely allergic process to occluder devices that contain higher proportions of nickel.⁴ A few comments seem appropriate to give some perspective to this article.

The possibility of nickel toxicity has been raised with the use of ASD closure devices, intracoronary stents, and pacemaker devices.⁵ Implantable devices are not uniform in



Interaction of nickel-containing devices with the immune system.

CENTRAL MESSAGE

Nickel allergy may present a significant problem with some implantable devices.

their composition, and there is a wide inter-device variability of nickel composition. Many devices contain nitinol, which is an alloy composed of 45% titanium and 55% nickel. Nickel in these devices has been shown to be released into the body, causing an increase in systemic nickel.^{6,7} In fact, during the first 6 weeks after device closure, serum nickel levels may increase up to 5-fold.⁸ Patients with a nickel allergy may experience dyspnea, headache, fatigue, and chest pain,⁶ which has been coined “device syndrome.” Rigatelli and colleagues⁶ observed “device syndrome” within 2 weeks of ASD device closure and suggested that a low-level immunologic reaction was the cause of the phenomena, likely related to the nickel substance in the device, and this produced a mild leukocytosis.

However, implanted devices may have titanium alloy, platinum, and iridium, but also epoxy resins, polymethyl-metacrylates, and isocyanates, all of which may be immunogenic in some patients.⁹ Furthermore, the metal strut in coronary artery stents is made from 316L stainless steel, which contains nickel, as well as other endovascular prostheses and prosthetic valves. For example, the Edwards Magna Ease bioprosthetic aortic valve (Edwards Lifesciences, Irvine, Calif) and the Sapien transcatheter aortic valve (Edwards Lifesciences) have, among other alloys, approximately 15% nickel, in comparison with the pure nitinol frames of the Amplatzer device (St Jude, St Paul, Mo), in which the nickel concentration is approximately 55%.⁴ It may well be that the higher proportion of nickel in occluder devices provides a greater substrate for reactivity with the host immune system. It is interesting to note that clips

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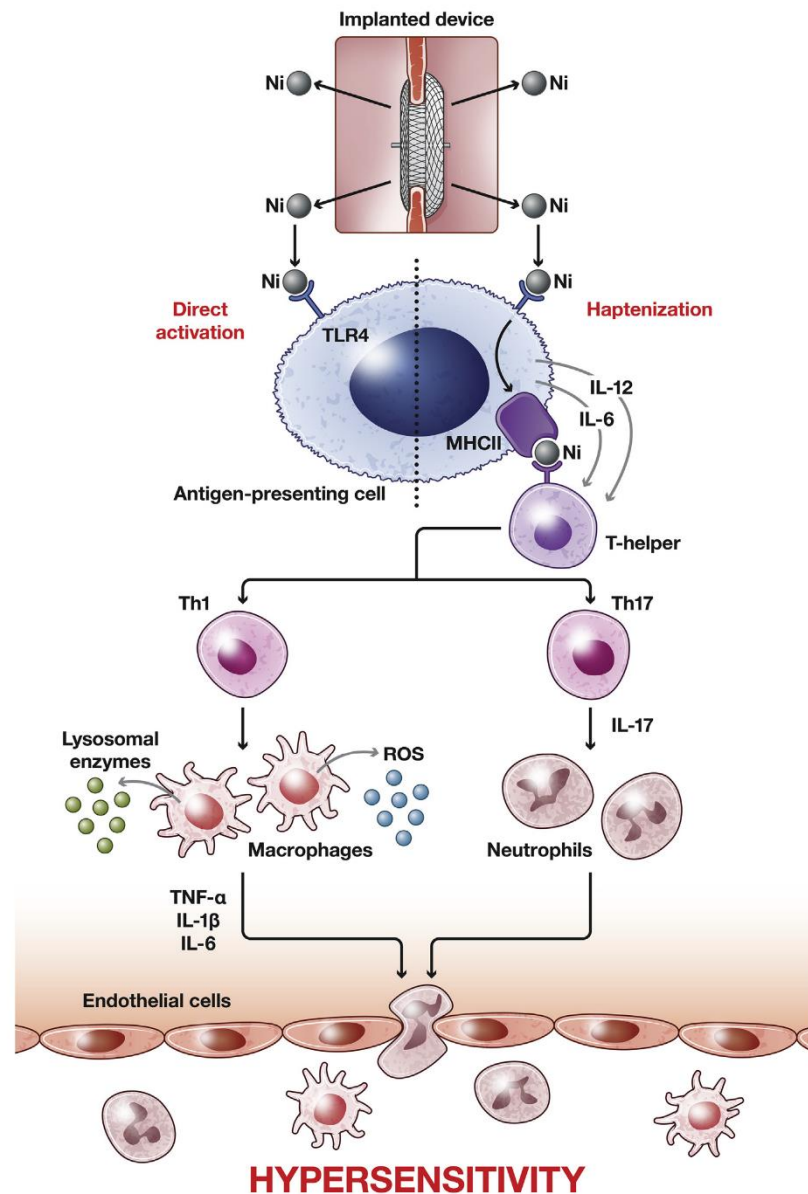


FIGURE 1. Interaction of nickel-containing devices with the immune system. Nickel ions are suggested to bind to toll-like receptor (*TLR*) 4 directly or are haptenized and interact with major histocompatibility complex (*MHC*) class 2 receptors, both of which can activate antigen-presenting cells (APCs). These activated APCs will subsequently present that immunogen to naïve T-helper (Th) cells¹² and release cytokines (interleukin [*IL*]-12) that will cause the naïve Th cell to differentiate into type 1 T cells, Th1 cells. The Th1 cell will release several cytokines, including interferon- γ , which activates macrophages. The activated macrophages will release *IL*-1 β , *IL*-6, and tumor necrosis factor- α , which cause expression of receptors on endothelial cells to recruit more leucocytes to the area. Activated macrophages release reactive oxygen species (*ROS*) and toxic lysosomal enzymes; this causes tissue damage that can manifest itself in a variety of ways. The APCs may also release *IL*-6 and other cytokines that cause naïve Th cells to differentiate into Th17 cells. The Th17 cells release *IL*-17, which activates neutrophils in the area. Re-exposure to the same allergen would lead to the activation of specific T cells, which subsequently enter the bloodstream and produce visible signs of hypersensitivity at 48 to 72 hours after allergen exposure.¹³ *IL*, Interleukin; *Th*, T helper; *TNF*, tumor necrosis factor.

containing nickel, chromium, molybdenum, cobalt, and titanium can also induce allergic reactions and may be a cause of delayed wound healing.¹⁰

The underlying mechanism of a systemic nickel allergy is unclear. However, because nickel leaks into the bloodstream, it has been suggested that this may result in a type IV hypersensitivity reaction^{4,7} (Figure 1). Patients may have been previously sensitized to the allergen or this may occur de novo. The strength of this foreign body reaction is variable, and research continues into the question of why some patients have a more excessive response than others. Much of our understanding of nickel allergy comes from skin exposure to nickel in which the nickel ions penetrate the skin and activate epithelial cells that produce various cytokines, such as interleukin-1 β , interleukin-6, and tumor necrosis factor- α .¹¹⁻¹³

Although the best management of allergies is to limit exposure, this may not always be possible with some medical devices. In some cases, different devices may be used that contain a lower concentration of the offending metal ion. In other cases, the side effects can be managed with low doses of prednisolone and antiplatelet therapy.⁶ Yet, the best approach to any allergen is to remove the exposure to it. No device, no problem.

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Naimo and Konstantinov

Commentary

Commentary: White matter injury and heart surgery—Will we get to the heart of the matter?

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Igor E. Konstantinov, MD, PhD, FRACS (left), and Phillip S. Naimo, MD, BSc (right)

Central Message

There is no direct correlation between cerebral oxygenation or autoregulation and white matter injury after congenital cardiac surgery.

See Article page XXX.

It appears that the understanding of cerebral blood circulation has been evolving for centuries. Physicians have been aware of blood flow to the brain since approximately 2800 BCE; however, it was not until 1762 CE that investigation into the physiology of cerebral blood flow commenced.¹ Finally, in the mid-1900s, Kety and Schmidt² reported the first quantitative measure of cerebral blood flow. Since then, there has been a dramatic increase in research on cerebral blood physiology, and a number of noninvasive measurement techniques have been developed. Of particular interest in recent years has been the mechanism of white matter injury during neonatal and infantile cardiac surgery.

In a thought-provoking and thorough study published in the current issue of the *Journal*, Claessens and colleagues³ report that there was no correlation between cerebral oxygenation or cerebral autoregulation and postoperative white matter injury. There have been several methods used as a proxy to measure cerebral autoregulation. In the study of Claessens and colleagues,³ cerebral oxygenation was measured by near-infrared spectroscopy and correlated with mean arterial blood pressure to give an estimation of cerebral autoregulation. Although near-infrared spectroscopy appears to be a useful tool in measuring cerebral oxygenation, care must be taken in interpreting results, because several factors may affect measurements. First, near-infrared spectroscopy will represent a mixed oxygen saturation, of which 75% is determined by venous saturation,³ and thus it may be affected in cyanotic heart conditions. In addition, factors as simple as sensor placement or fluid retention may also alter results.⁴ Although no direct correlation has been demonstrated in this prospective study, it is an important step in our understanding of perioperative white matter injury.

It appears that neonatal cerebral vasculature and autoregulatory systems are underdeveloped, and even more so in neonates with congenital heart defects.^{5,6} In some

patients, autoregulatory systems may not be functioning, and passive cerebral perfusion is not uncommon.⁷ Although studies have shown new white matter injury in 30% to 60% of neonates undergoing cardiac surgery,⁵ it is important to recognize that 20% to 40% of injury may occur preoperatively.^{5,8,9} The direct correlation of white matter injury with cardiac surgery thus remains elusive.

Although this prospective study of Claessens and colleagues³ failed to find any correlation, it did not fail in its purpose. We would like to sum up with a famous statement that often is attributed to Thomas A. Edison, “I have not failed. I have just found 10,000 ways that won’t work.” Indeed, once again we see no clear correlation between cerebral oxygenation or cerebral autoregulation and white matter damage after cardiac surgery.

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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 $98.3 \pm 1.2\%$ (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 $88.6 \pm 4.0\%$ (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

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 $\pm$ standard deviations (range), whilst skewed continuous data are expressed as medians (interquartile range).

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.

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 $P < 0.05$.

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

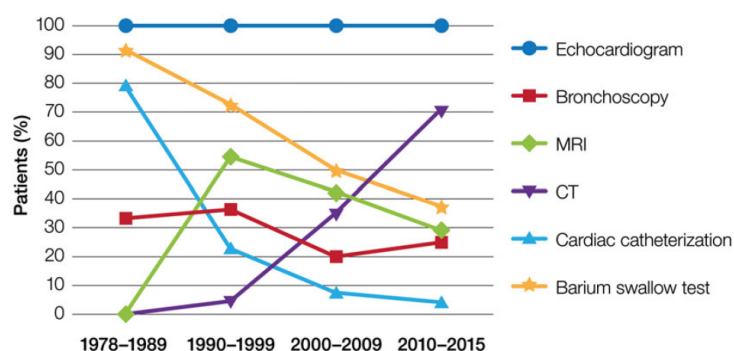


Figure 1: Frequency of imaging modalities over the 4 decades.

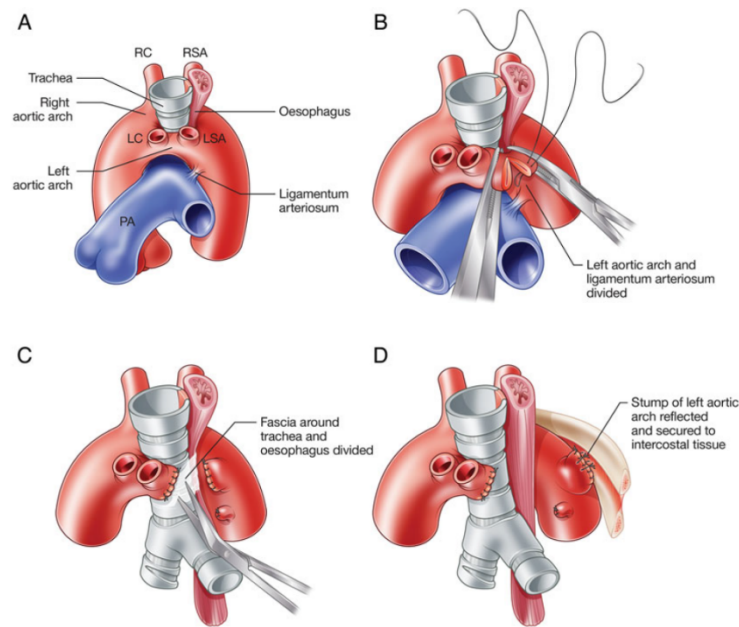


Figure 2: Double aortic arch repair. Double aortic arch (A). Repair of the double aortic arch is undertaken through division of the smaller arch and division of the ligamentum arteriosum (B and C). The distal remnant of the divided arch or diverticulum of Kommerell is oversutured. The oversutured stump 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 arterioplexy 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 arterioplexy 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. Arterioplexy (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 $98.3 \pm 1.2\%$ (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

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 $96.9 \pm 1.8\%$ (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 $88.6 \pm 4.0\%$ (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.

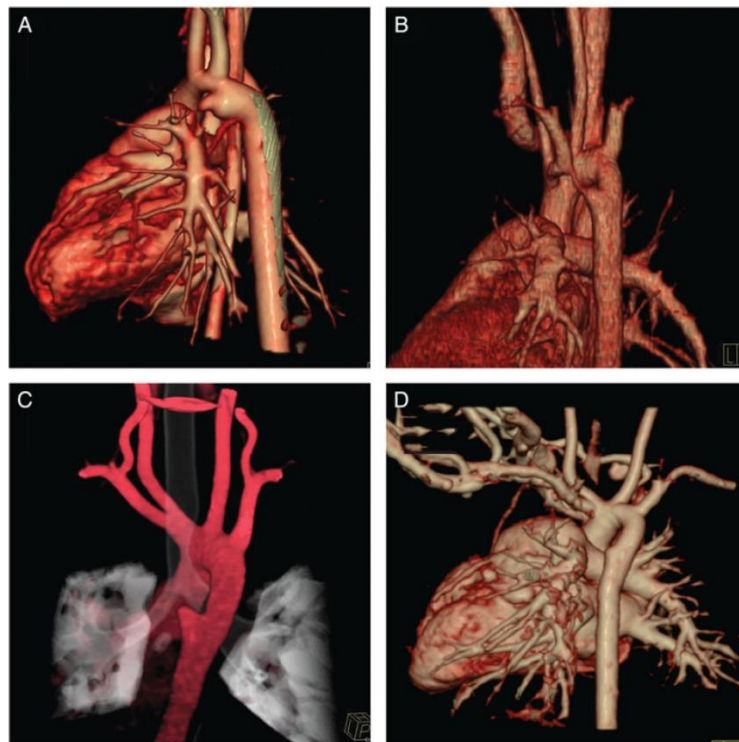


Figure 3: Spectrum of complete vascular ring anomalies on computed tomography. (A) Double aortic arch with two patent arches. (B) Double aortic arch with severely hypoplastic, yet patent, left aortic arch. (C) Double aortic arch with an atretic left aortic arch—this anomaly may be misinterpreted as a 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, arteriopathy 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

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.

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A.8 Naimo PS, et al. J Thorac Cardiovasc Surg. 2017;153:654-5

A curious course of an intramural anomalous left coronary artery from the pulmonary artery



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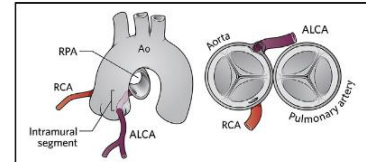
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Anomalous origins of the left coronary artery from the right pulmonary artery.

Central Message

Coronary transfer and unroofing are important techniques for managing rare cases of intramural anomalous left coronary artery from the right pulmonary artery.

See Article page 648.

Anomalous left coronary artery from the pulmonary artery (ALCAPA) is a rare congenital cardiac malformation accounting for approximately 1 in 300,000 live births.¹ The first reported child with ALCAPA was described by Russian pathologist Alexei Ivanovich Abrikosov in 1911, when he described postmortem “a left ventricular aneurysm with anomalous origin of the left coronary artery from pulmonary artery in a 5-month old child.”² A comprehensive clinical description was given in 1933 by American physicians Edward Bland, Paul Dudley White, and Joseph Garland.³

Thus, a typical clinical presentation is often referred to today as Bland-White-Garland syndrome.

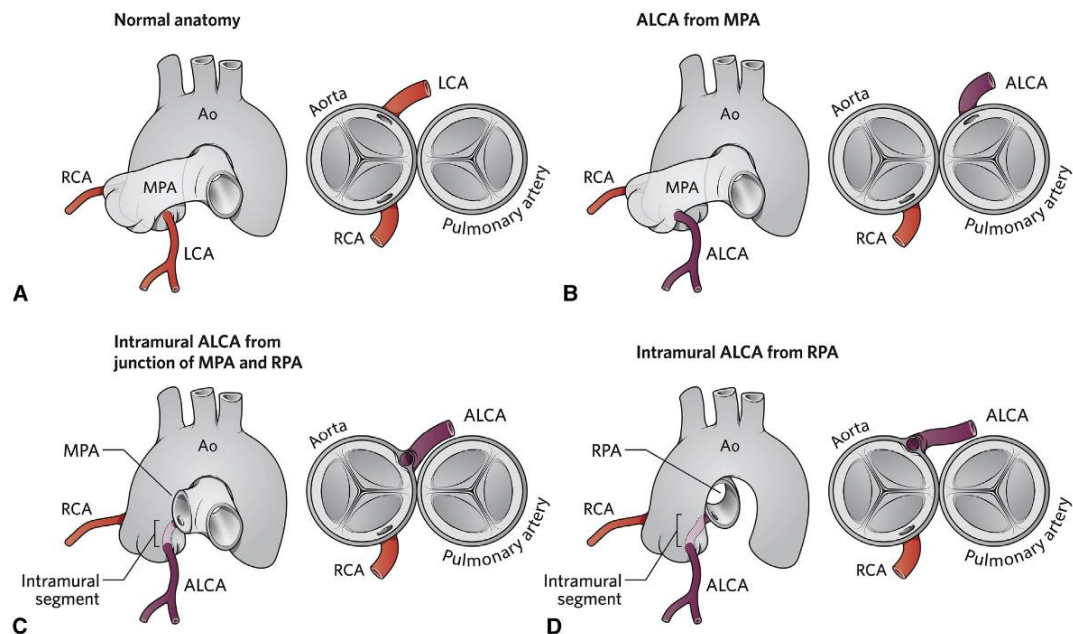


FIGURE 1. Anomalous left coronary artery origin from the pulmonary artery and its relation to normal anatomy of the great arteries. A, Normal anatomy. B, ALCA from MPA. C, Intramural ALCA from the junction of MPA and RPA. D, Intramural ALCA from RPA. Ao, Aorta; RCA, right coronary artery; MPA, main pulmonary artery; LCA, left coronary artery; ALCA, anomalous left coronary artery; RPA, right pulmonary artery.

To understand the pathologic anatomy of this rare anomaly, one should appreciate that the normal ascending aorta and main pulmonary artery (PA) are almost perpendicular to one another (Figure 1, A). In ALCAPA, the left coronary artery (LCA) most commonly originates from the posterior facing sinus of the PA (Figure 1, B) in close proximity to where the normal origin of the LCA would be. Nonetheless, the LCA can come from any part of the main PA or its branches, albeit rarely. If the LCA comes from the junction of the main PA and right PA (Figure 1, C) or the right PA (Figure 1, D), it may have an intramural aortic course. This is an exceedingly rare association. The literature is limited to a few case reports and small series.⁴⁻⁹ A remarkable article by Zhang and colleagues¹⁰ describes 10 children with intramural course of the ALCAPA arising from the right PA. It is fascinating that 10 children with such rare anomaly had surgery over a relatively short period of 7 years, likely owing to the fact that the report comes from one of the largest volume institutions from Beijing, China. Consider that in our institution only 1 of 42 children undergoing operation for ALCAPA over a 35-year period had intramural course of an anomalous coronary artery.¹¹ Furthermore, our experience was similar to that of others.⁴⁻⁸

The patients studied by Zhang and colleagues¹⁰ were older at the time of repair compared with most modern reports, which likely explains a higher proportion of children with left ventricular aneurysms and relatively high mortality. The surgical technique of coronary artery transfer and unroofing appears to provide reliable reperfusion of the myocardium and resulted in improvement of the left ventricular function. Coronary unroofing is, indeed, a simple and reliable technique and could be safely used even in neonates with intramural coronary arteries.¹² Due to the close resemblance to normal anatomy, the intramural course of the coronary artery commonly remains undiagnosed on pre-operative imaging. The intramural course should be suspected in all children with ALCAPA originating from the right PA⁶ to avoid damage to the intramural segment. The

value of opening the main PA first to identify the origin of the LCA cannot be overemphasized. As long as the coronary artery is not allowed to kink during reimplantation, the unroofing is easy and likely to be the best option.⁴ The technique described by Zhang and colleagues¹⁰ is a valuable addition to armamentarium of any cardiothoracic surgeon who deals with congenital coronary anomalies.

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A.9 Naimo PS, et al. Ann Thorac Surg. 2016;101:1842-9.

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 $\pm$ 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

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% $\pm$ 15.4%
Fractional shortening	17.0% $\pm$ 10.0%
LVEDD	4.0 $\pm$ 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.

(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

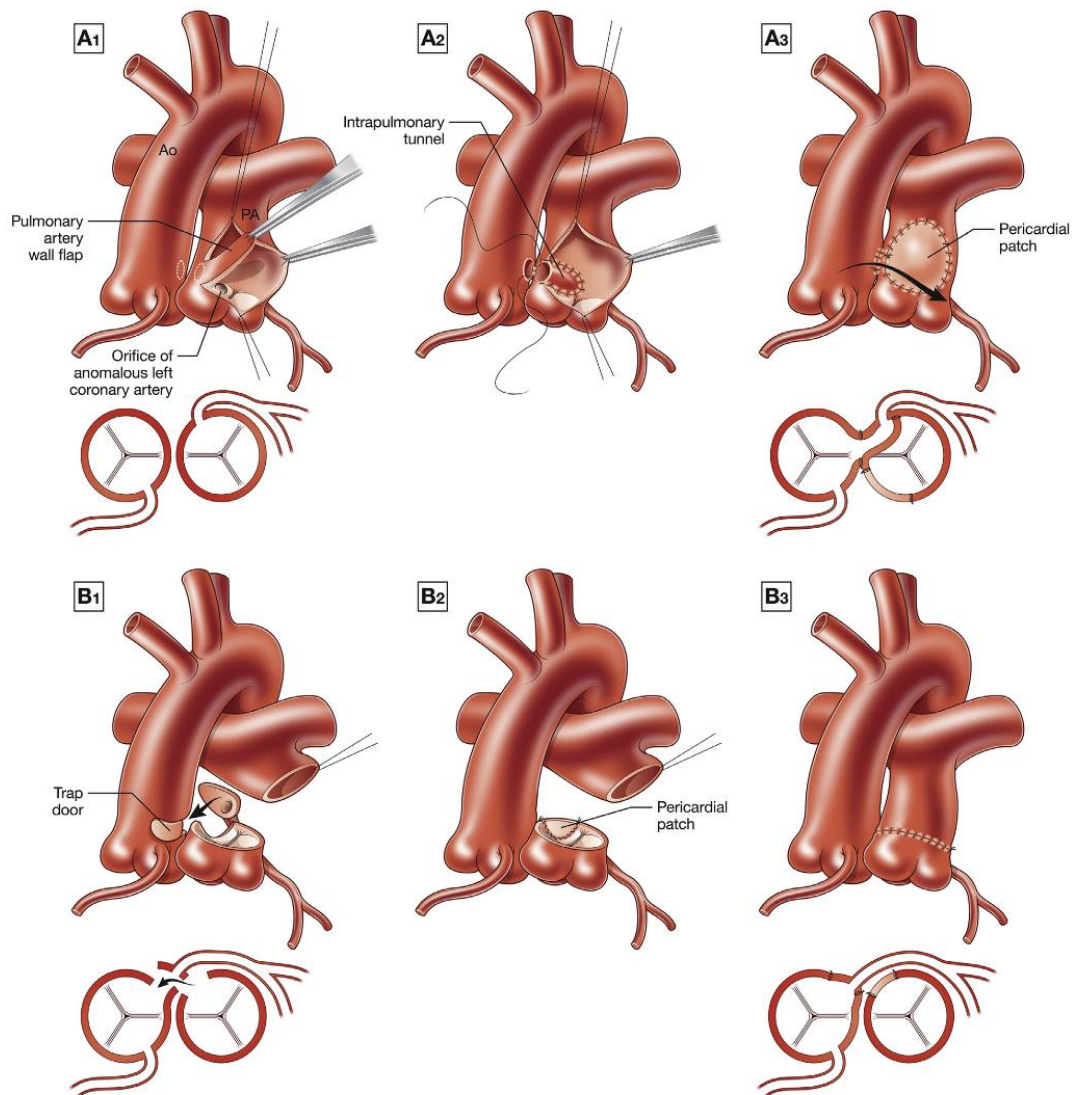


Fig 1. Repair of anomalous left coronary artery from pulmonary artery (PA). (A1–A3) Takeuchi repair. (A1) Opening of main pulmonary artery (MPA) with creation of flap of anterior PA wall. (A2) Creation of aortopulmonary window and baffling of anomalous coronary artery with flap of anterior PA wall. (A3) 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 $98\% \pm 2\%$ (95% confidence interval [CI], 86–100) at 5, 10, and 20 years.

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 $71\% \pm 18\%$ (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 $86\% \pm 6\%$ (95% CI, 71–94) at 5 and 10

years and $81\% \pm 8\%$ (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 $88\% \pm 7\%$ (95% CI, 74–96) at 5 and 10 years and $76\% \pm 8\%$ (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.

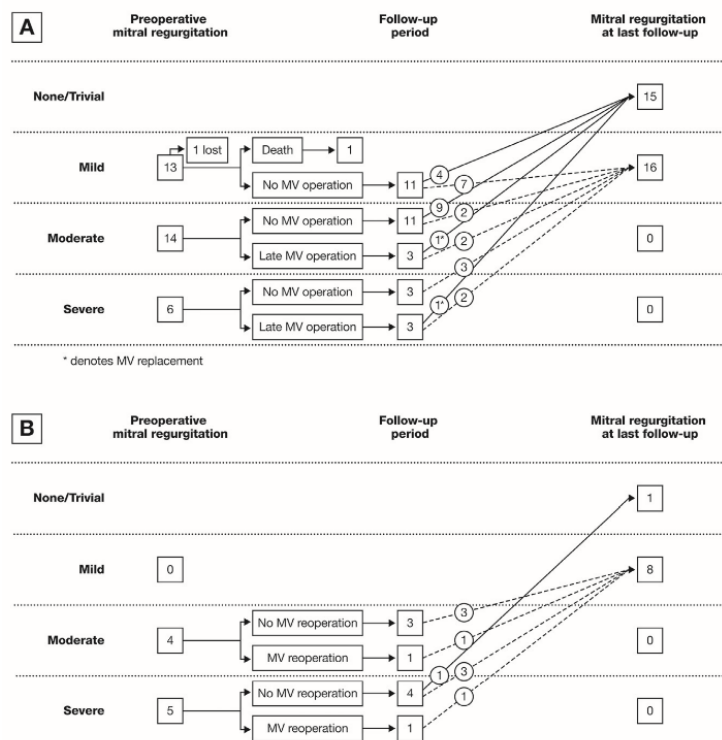


Fig 2. Outcomes of mitral valve (MV) (A) without and (B) with concomitant MV repair at anomalous left coronary artery from the pulmonary artery (ALCAPA) repair.

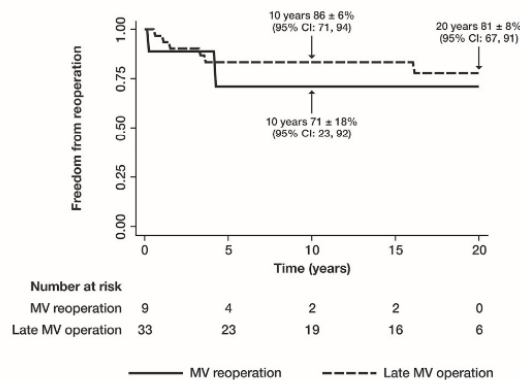


Fig 3. Freedom from mitral valve (MV) reoperation and late mitral valve operation. Freedom from MV reoperation in patients who underwent concomitant MV repair versus late MV operation in patients who did not undergo concomitant MV repair.

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 supraventricular 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

Table 2. Mortality of ALCAPA Repair

Study	Study Period	Patients (n)	Early Deaths (%)	Late Deaths (%)	Concomitant MV Operation (n)	Early Deaths (%)	Late Deaths (%)	Follow-Up (mean, years)
Schwartz et al [18]	1977–1995	42	14 (6 of 42)	0 (0 of 36)	1	0 (0 of 1)	0 (0 of 1)	3.7
Huddleston et al [23]	1980–1996	16	6 (1 of 16)	0 (0 of 15)	1	0 (0 of 1)	0 (0 of 1)	6.9
Isomatsu et al [7]	1982–2000	29	7 (2 of 29)	0 (0 of 27)	24	8 (2 of 24)	0 (0 of 22)	8.3
Azaki et al [9]	1952–2000	47	9 (4 of 47)	0 (0 of 43)	1	0 (0 of 1)	0 (0 of 1)	4.7
Caspi et al [20]	1992–2005	23	0 (0 of 23)	0 (0 of 23)	0	NA	NA	6.5
Lange et al [11]	1977–2002	56	14 (8 of 56)	4 (2 of 48)	1	0 (0 of 1)	0 (0 of 1)	11.0
Brown et al [17]	1975–2005	25	8 (2 of 25)	4 (1 of 23)	0	NA	NA	10.1
Ali et al [19]	1986–2007	62	10 (6 of 62)	4 (2 of 56)	3	0 (0 of 3)	0 (0 of 3)	9.7
Nasseri et al [25]	1992–2007	14	0 (0 of 14)	0 (0 of 14)	3	0 (0 of 3)	0 (0 of 3)	10.4
Alexi-Meskishvili et al [14]	1986–2010	27	0 (0 of 27)	0 (0 of 27)	9	0 (0 of 9)	0 (0 of 9)	11.5
Bakhtiar et al [26]	1999–2009	18	0 (0 of 18)	0 (0 of 18)	0	NA	NA	5.0
Kudumula et al [8]	1990–2011	25	0 (0 of 25)	0 (0 of 25)	4	0 (0 of 4)	0 (0 of 4)	7.8
Total		384	8 (29 of 384)	1 (5 of 355)	47	4 (2 of 47)	0 (0 of 45)	8.0

ALCAPA = anomalous left coronary artery from the pulmonary artery; MV = mitral valve.

underwent MV repair at ALCAPA repair, this had no effect on the normalization of LV function or other postoperative outcomes. Some surgeons advocate no intervention on the MV at ALCAPA repair, regardless of its severity [6, 14, 23, 24] on the basis that MR often improves postoperatively once coronary blood flow is restored. Kudumula and colleagues [8] described their experience with 25 children who underwent ALCAPA repair between 1990 and 2011 with a policy of addressing only structurally defective MVs. Nineteen patients had preoperative moderate or severe MR, and only 4 patients underwent MV repair at ALCAPA repair because of a structural problem with the MV [8]. They reported no deaths after a median follow-up of 7.8 years, with 4 patients having moderate MR after a median follow-up of 8 years. Conversely, Isomatsu and colleagues [7] described their experience with 29 patients between 1982 and 2000 with a policy of MV repair in all patients with MR. Twenty-four patients underwent MV annuloplasty. They reported 2 early deaths in patients with severe MR, and no late deaths after a mean follow-up of 8.3 years, with an overall survival of 93.1% at 10 years [7]. Additionally, only 1 of the 24 patients who underwent initial MV repair required late MV reoperation. Other centers operate on the MV only if ischemic lesions of the papillary muscles are evident intraoperatively [19], in patients with severe MR particularly in older children [14], or in older children with moderate to severe or severe MR [17].

Despite these various approaches, there are no clearly defined indications for concomitant MV repair at the time of ALCAPA procedures. Of the 11 patients in our study who had severe MR, 5 patients had concomitant MV repair. One of those 5 patients underwent MV reoperation. Of the 6 patients who had severe MR and did not have the concomitant MV repair, 3 required MV repair or replacement during the follow-up period. Therefore 50% (3 of 6) of those patients with untreated severe MR at the time of repair did not require late intervention. Thus overall, 8 of 11 (73%) patients with severe preoperative MR underwent MV repair. Although a definitive recommendation on MV repair cannot be ascertained in this study, if MV repair is deemed to be required at ALCAPA repair, it can be undertaken safely and with good results. Because we did not have adverse outcomes from concomitant MV repair and because 50% of patients with severe MR who did not undergo concomitant MV repair had late MV operation, it seems reasonable to perform concomitant MV repair in those presenting with severe MR. In patients with other degrees of MR, the MR decreases as the ventricular function improves; therefore intervening in these patients does not seem justified. However, because of relatively small numbers, we do not have statistical data to support or refute this opinion.

Limitations

This study is subject to the usual limitations of a retrospective study. Perioperative techniques may have varied during the study period. Statistical analysis of risk factors for mortality was limited because of a relatively small number of patients and outcomes.

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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INVITED COMMENTARY

Although not the first to describe this lesion, Edward Bland, Paul White, and Joseph Garland described an infant who died at 3 months of age as a result of this coronary anomaly [1]. For many years this condition was referred to as Bland-Garland-White syndrome before it took on the acronymous term ALCAPA (Anomalous Left Coronary Artery from the Pulmonary Artery). The typical infantile presentation of ALCAPA is characterized by heart failure,

a left ventricular ejection fraction of less than 20%, and at least moderate mitral valve regurgitation—certainly not an ideal circumstance to consider any sort of cardiac surgical procedure. Despite this, the results with surgical repair of this lesion are outstanding, and the subsequent recovery of left ventricular function is one of the most remarkable findings in congenital heart surgical practice. Several controversies regarding the specifics of treatment

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Operative Techniques in
Thoracic and
Cardiovascular Surgery

Aortopulmonary Window Repair in Children



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An aortopulmonary window (APW) is a rare congenital cardiac anomaly, which involves communication between the ascending aorta and the main pulmonary artery. It may be an isolated anomaly (simple APW) or associated with concomitant cardiovascular anomalies (complex APW). Contemporary repair of simple APW has a mortality approaching zero. Mortality is almost always due to concomitant cardiovascular anomalies. One of the most common concomitant cardiovascular anomalies is an interrupted aortic arch. Rarely, an APW may have a concomitant anomalous coronary artery. Herein we describe the surgical technique to repair APW with associated interrupted aortic arch.

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KEYWORDS aortopulmonary window, interrupted aortic arch, congenital heart disease, surgery, neonates

Introduction

An aortopulmonary window (APW) is a communication between the ascending aorta and the main pulmonary artery (PA) in the presence of 2 separately formed semilunar valves. It may be located just above the semilunar valves, or more distal, incorporating part of the right PA. It is a rare congenital cardiac anomaly accounting for 0.1%-0.2% of all cardiac malformations.¹⁻³ The natural history of an unrepaired APW has approximately 40% mortality within the first year of life, that often results from sequelae of congestive cardiac failure.⁴ Small defects may not manifest clinically. However, APWs do not close or contract over time, therefore, progression of disease is likely.⁵ For most patients, repair should be undertaken early in infancy to prevent development of cardiac failure or irreversible pulmonary hypertension. Closure of APW is indicated for all patients less than 6 months of age. Patients who present later than 6 month of age should undergo cardiac catheterization to assess the degree of pulmonary hypertension and reversibility.⁶

An APW may be an isolated anomaly (simple APW) or, in up to 80% of cases, patients with APW have a concomitant cardiovascular anomaly (complex APW).^{5,7-9} Surgical repair of simple APW is straight forward and has mortality of 0% in

most institutions.^{5,7-9} Mortality is almost always due to concomitant cardiovascular anomalies rather than surgical repair of the APW itself. One of the most common concomitant cardiovascular anomalies found in association with an APW is an interrupted aortic arch (IAA), which has a reported incidence of approximately 20%,⁷ and is often type A IAA.¹⁰ Some studies have shown that an APW with concomitant IAA is an independent risk factor for mortality.^{5,9,10} Occasionally, an APW may have a concomitant anomalous coronary artery.⁷ Although this is a rare anomaly, delineation of the coronary anatomy is vital for successful correction of APW. The anomalous coronary artery is often the right coronary artery that can arise from the main PA or the APW itself. During surgery, therefore, both coronary ostia must be identified and included on the aortic side of repair.

Currently, at the Royal Children's Hospital, we separate the great vessels, and perform either a direct closure or patch closure of the aorta and PA, taking care to preserve normal anatomy. The transaortic approach, or incision through the APW itself, allows the best visualization of the defect, as well as the coronary ostia. We currently perform a single-staged repair of APW and all concomitant cardiovascular anomalies via sternotomy (Figs. 1-10).

Although surgery for simple APW is not difficult, repair of APW associated with IAA is much more complex and is worth detailed technical discussion below. The technique described should avoid surgical pitfalls in these rare patients, particularly, those with associated anomalous origin of the coronary artery. A thorough understanding of the anatomical classification of the APW in association with IAA is helpful in individualizing a surgical approach in each of these patients.

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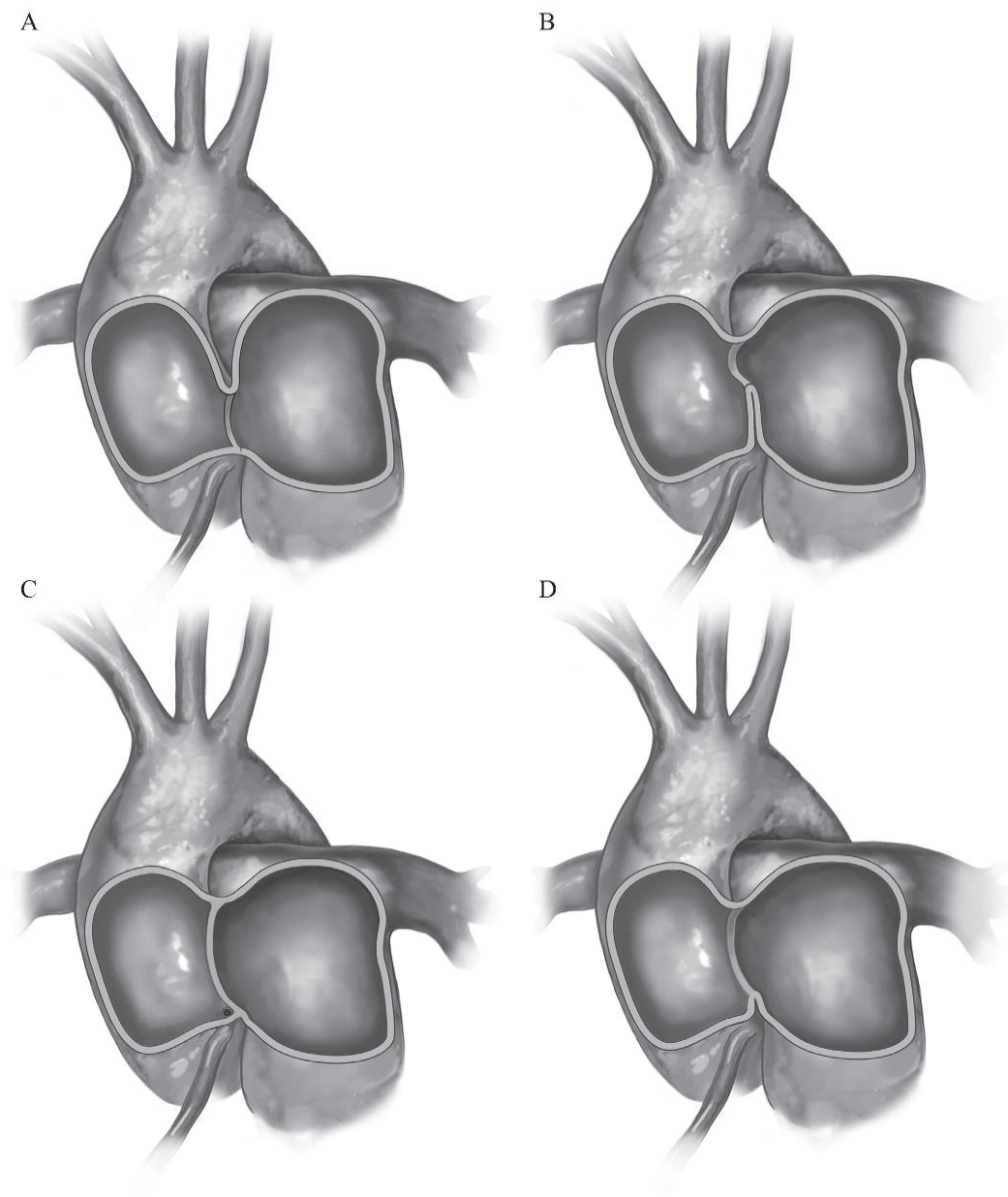


Figure 1 Classification of aortopulmonary window used by the Society of Thoracic Surgeons² adapted with permission from Mori et al¹¹ (A) Type I—proximal defect; (B) Type II—distal defect; (C) Type III—total defect; and modified with permission from Ho et al⁵ by adding (D) Type IV—intermediate defect. In proximal extension of the aortopulmonary window, the ostium of the right coronary artery may come from the aortopulmonary window or originate in close proximity to it.

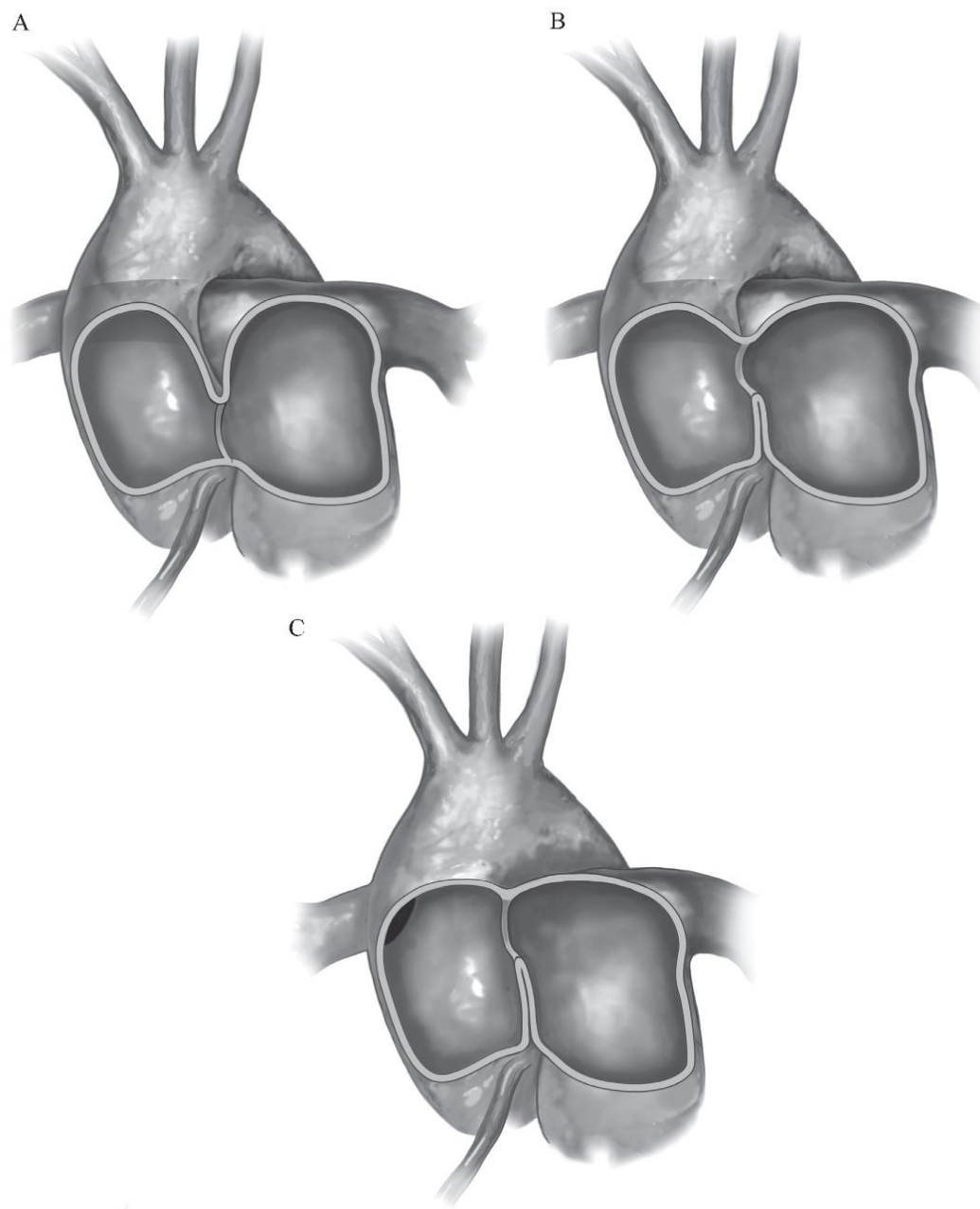


Figure 2 Classification of aortopulmonary window as proposed by Richardson et al³ (A) Type I is a “typical” aortopulmonary window between the posteromedial wall of the ascending aorta and the main pulmonary artery. (B) Type II located between the posterior wall of the ascending aorta and the origin of the right pulmonary artery. (C) Type III defects are defined as an anomalous origin of the right pulmonary artery from the posterolateral wall of the ascending aorta. For all practical reasons, we believe that Type III should only be classified as aortopulmonary window, if there is a distinct communication between aorta and main pulmonary artery in addition to the anomalous origin of the right pulmonary artery from aorta. If anomalous origin of the right pulmonary artery from aorta is an isolated anomaly, it should not be classified as an aortopulmonary window.

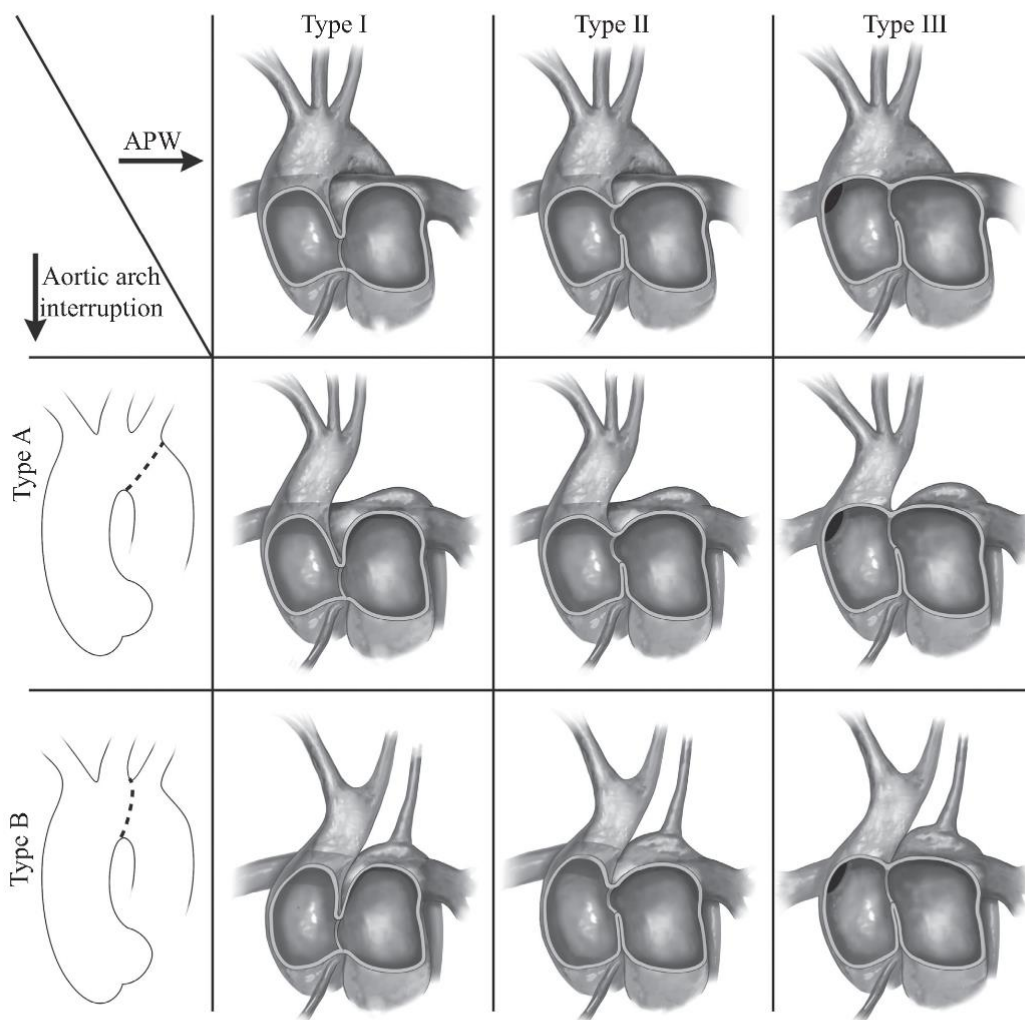


Figure 3 Aortopulmonary window with concomitant interrupted aortic arch. Appearance of aortopulmonary window (using Richardson's classification) with concomitant types A or B interrupted aortic arch. Of our 9 patients with aortopulmonary window and interrupted aortic arch, 8 neonates had type A, and 1 neonate had type B. Of those 8 neonates with type A, 4 had aortopulmonary window type I. In the remaining 4 neonates, aortopulmonary window was type II, involving the origin of the right pulmonary artery as in distal defect ($n = 3$) or total defect ($n = 1$) by the Society of Thoracic Surgeons classification earlier. The neonate with interrupted aortic arch type B had concomitant aortopulmonary window type I.

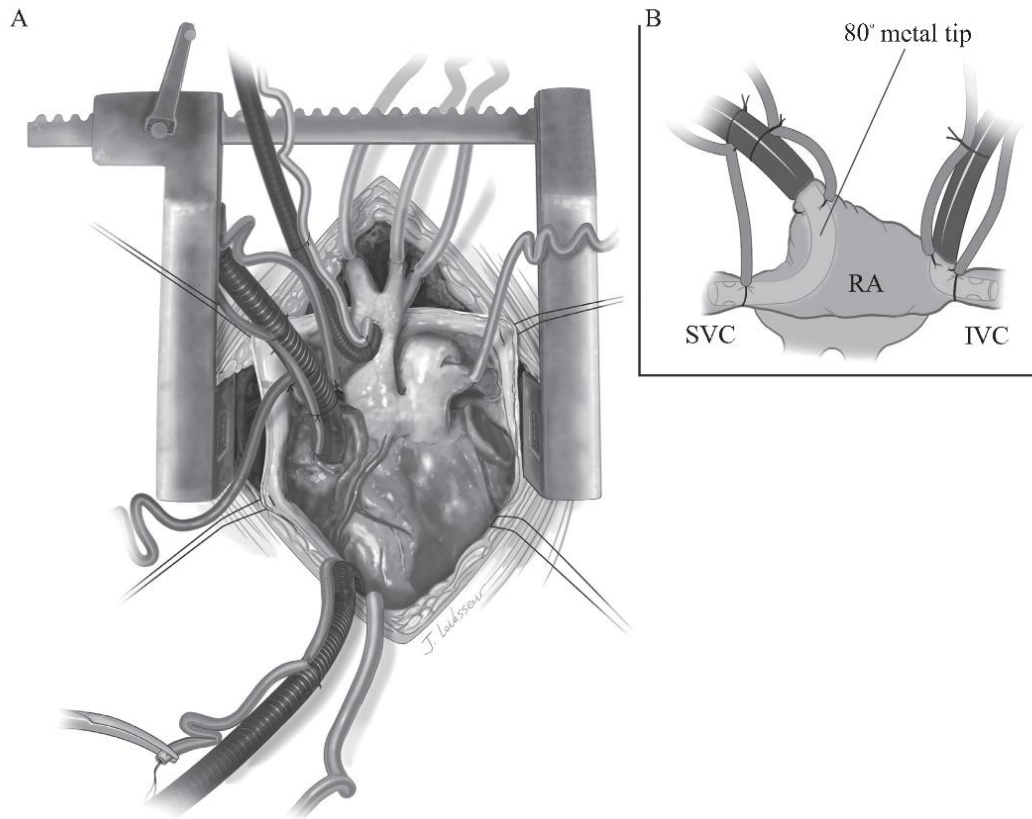


Figure 4 (A) Following heparinization, the aorta is cannulated just below the origin of the innominate artery and slightly to the right lateral wall of the aorta, so that this cannula could be introduced into the innominate artery for subsequent cerebral perfusion. Tourniquets around the branch pulmonary arteries and the aortic arch branches are placed. Bicaval cannulation is performed, if concomitant repair of intracardiac defects is required. (B) As these children are often small, we avoid direct cannulation of the superior vena cava, and rather place an 80° cannula via the appendage of the right atrium into the superior vena cava. Tourniquets are placed around the venae cavae. In those without intracardiac defects, a single venous cannula is placed into the right atrium.

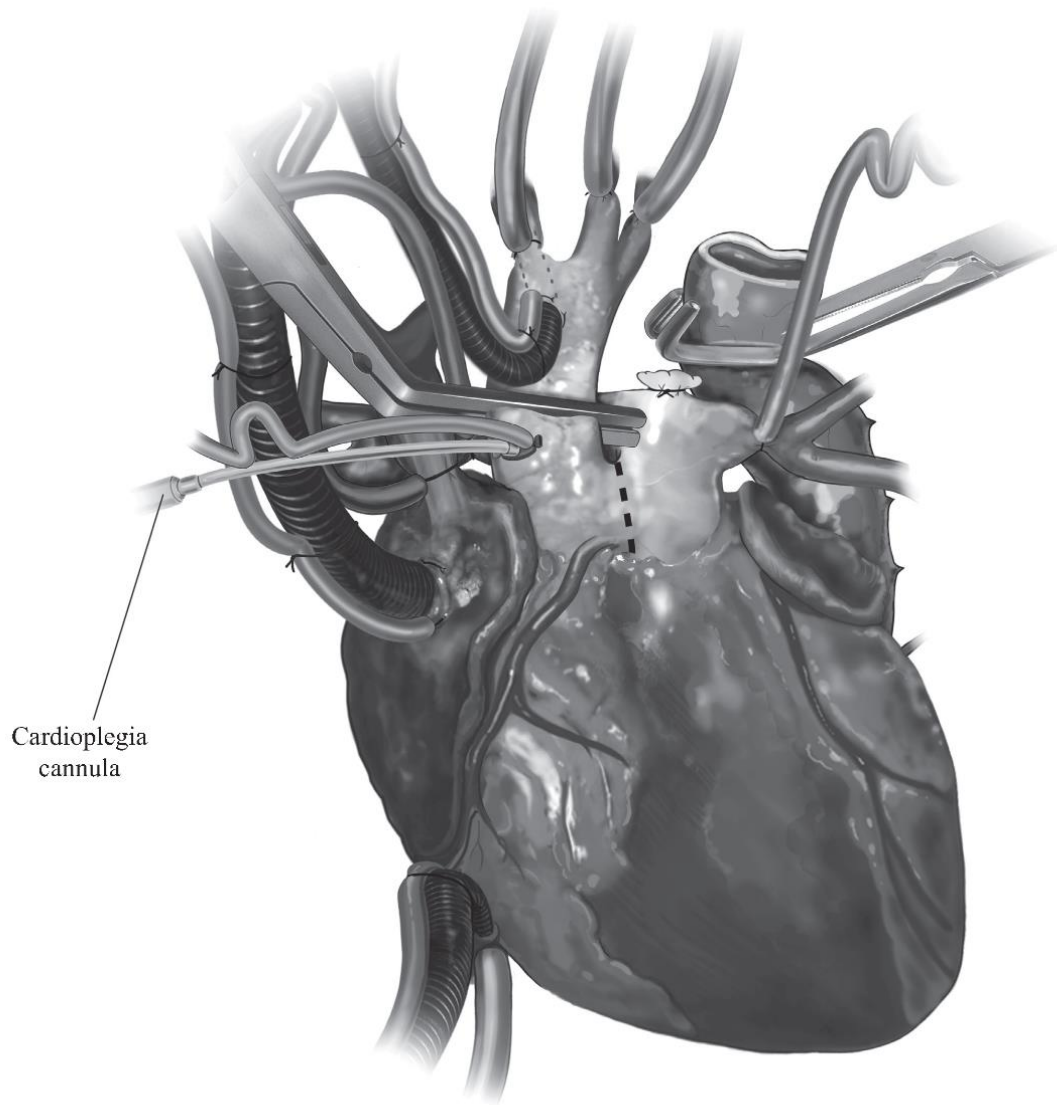


Figure 5 Tourniquets around the branch pulmonary arteries are occluded and the patient is cooled to 25°C. During cooling the descending aorta is extensively dissected and mobilized. Antegrade cardioplegia catheter is placed into the ascending aorta. Once 25°C has been reached, the patent ductus arteriosus is ligated, Castaneda clamp is placed onto the descending aorta and all ductal tissues are resected. Usually, 3 pairs of intercostal vessels are divided and cauterized to allow adequate mobilization. The aortic cannula is then advanced into the innominate artery, tourniquets around the arch vessels are occluded, aortic cross clamp is applied, and antegrade cardioplegia is administered.

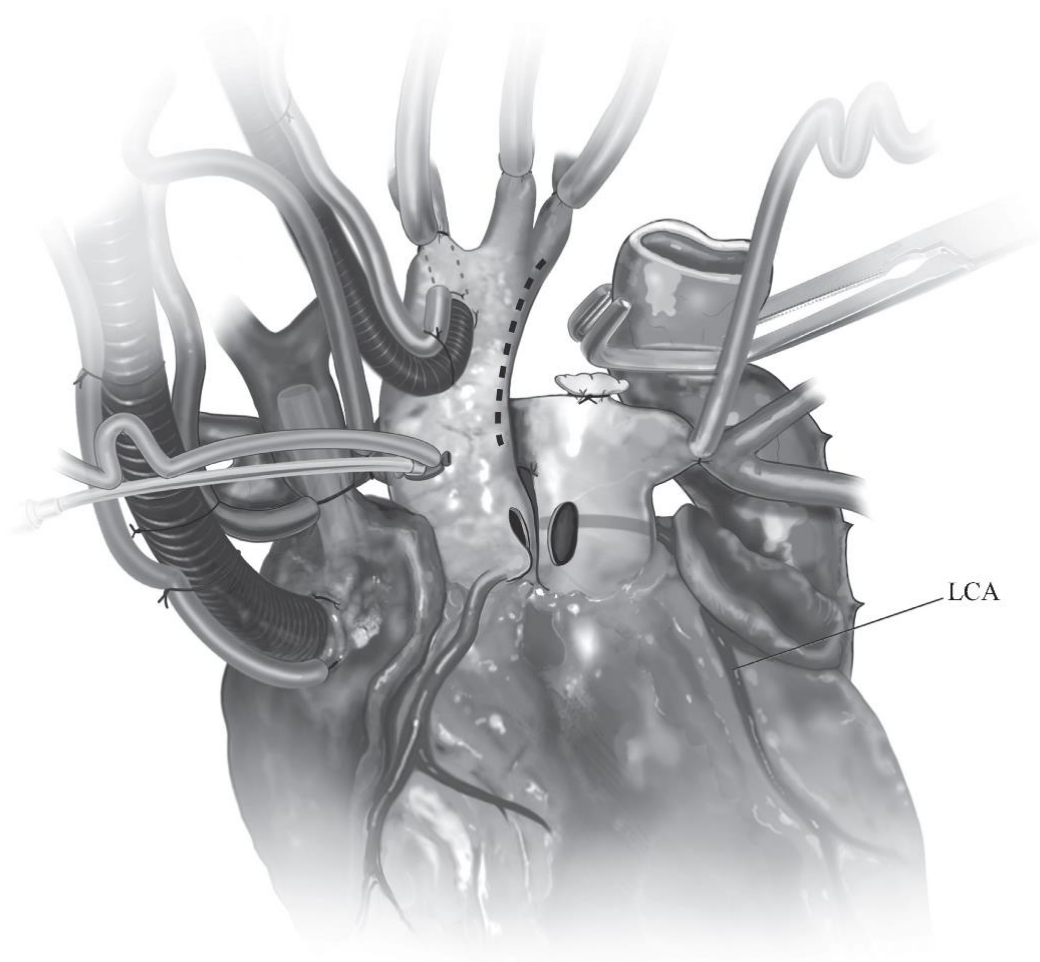


Figure 6 Aortopulmonary window is opened and the origin of both coronary arteries are visualized. It is crucial at this stage to confirm the origin of the coronary arteries, especially if the origins of the coronary arteries were not clearly demonstrated on preoperative imaging. The left coronary artery may come from the right pulmonary artery. Either one or both coronary arteries may come from the pulmonary side of the aortopulmonary window. A separate incision is then made in the aortic arch. LCA = left coronary artery.

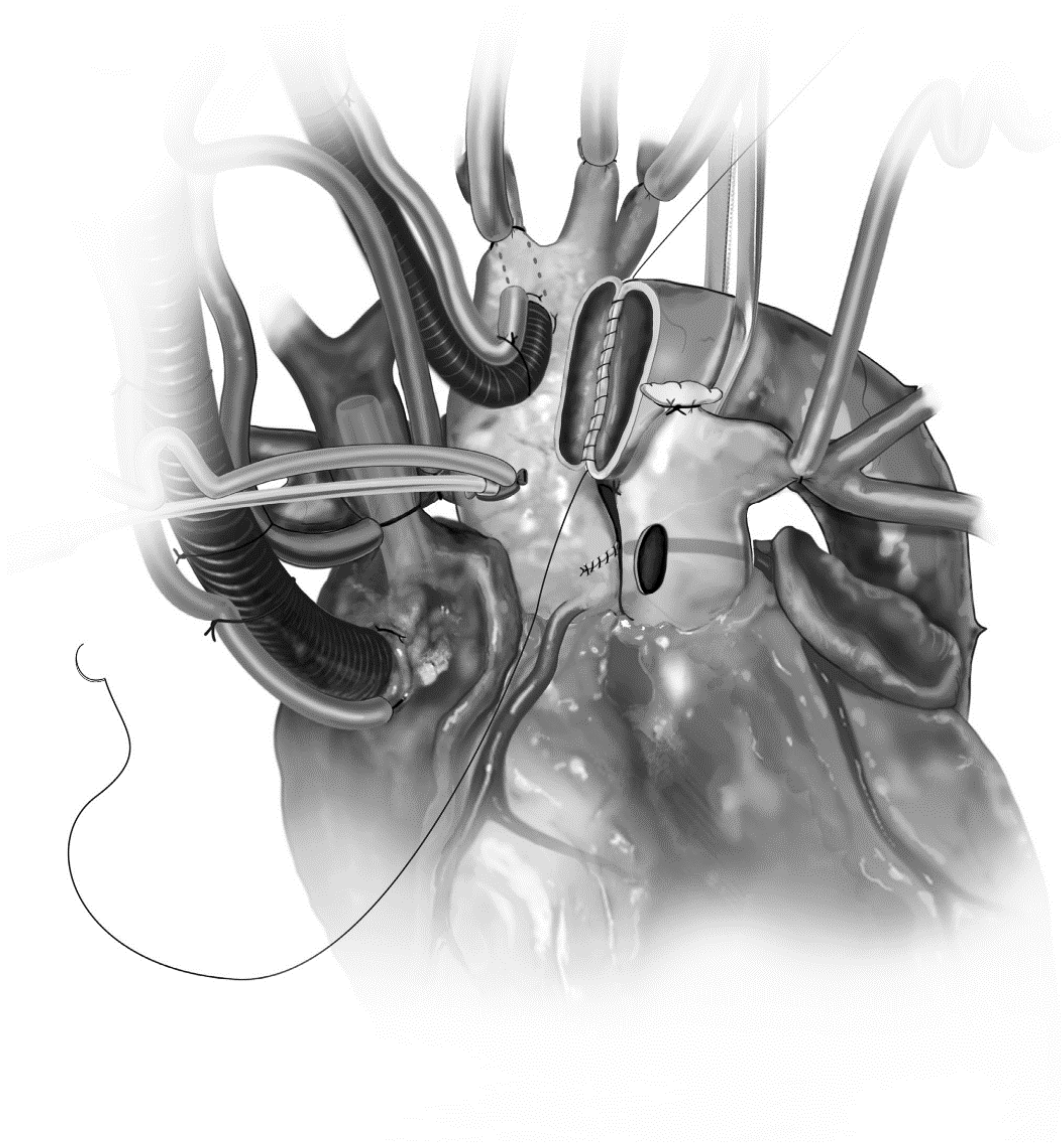


Figure 7 Direct end-to-side anastomosis of the descending aorta into the ascending aorta is performed, often extending into the proximal aortic arch. Usually, we close the aortic site of the aortopulmonary window without a patch and perpendicular to ascending aorta to avoid aortic narrowing.

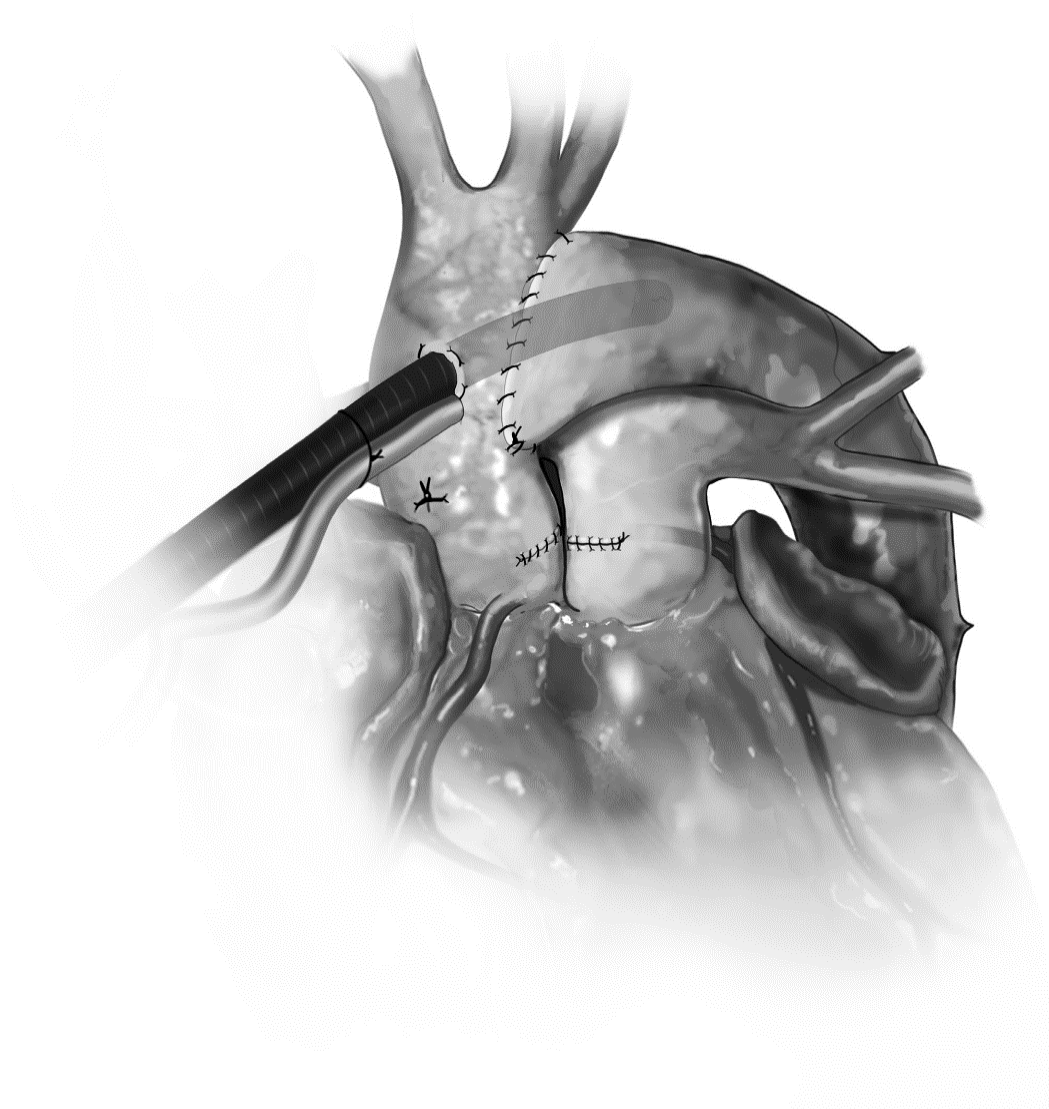


Figure 8 The aortic arch is de-aired, tourniquets are removed from the arch vessels, the aortic cannula introduced into the aortic arch and total body cardiopulmonary bypass is restored. Intracardiac defects, if any, are then repaired. De-airing is performed and aortic cross clamp is removed. The patient is rewarmed. During rewarming, the pulmonary artery is repaired, atrial and ventricular pacing wires, chest tubes and peritoneal dialysis catheter are placed.

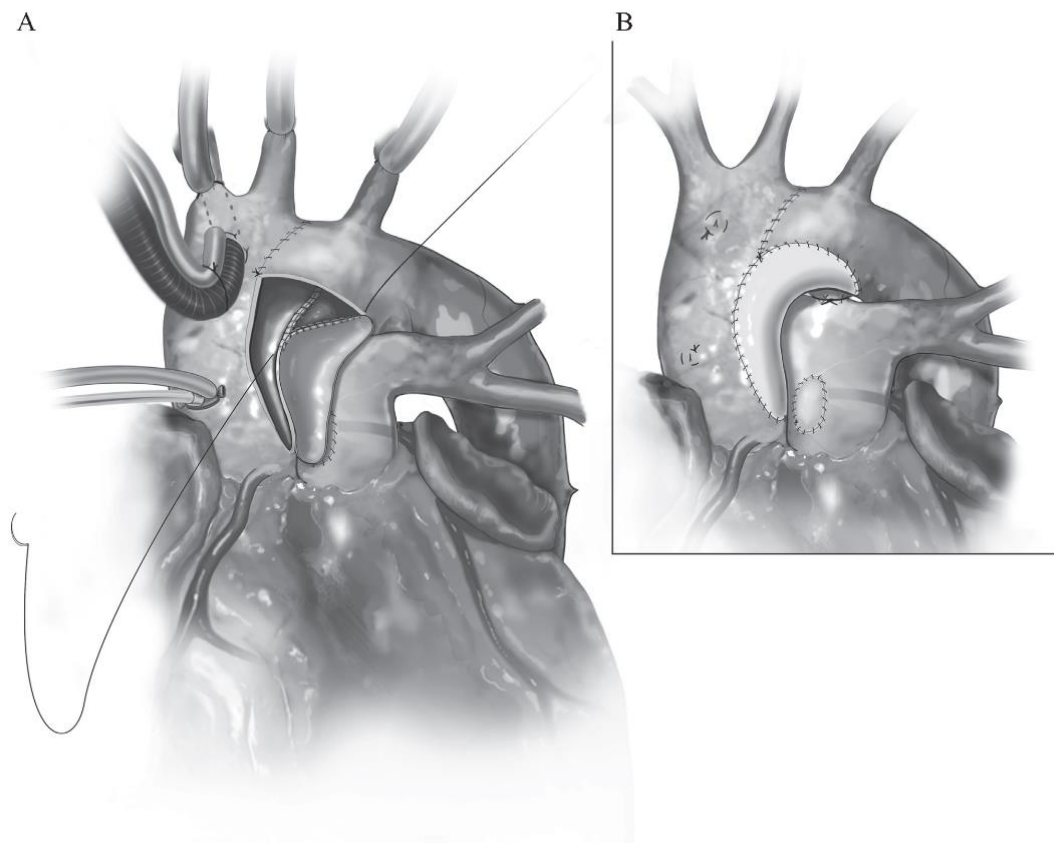


Figure 9 In the case of aortopulmonary window associated with interrupted aortic arch type B, if the descending aorta could not be properly mobilized for the advancement procedure as illustrated earlier, the arch incision could be extended into the aortopulmonary window and the aortic arch could be repair with the pericardial patch (A). Should this occur, we would prefer to use a glutaraldehyde-treated homograft pericardium. However, we have not used any patch material to restore the aortic arch in patients with aortopulmonary window in our hospital. Approximately half of our patients had pulmonary artery patched with autologous pericardium (B).

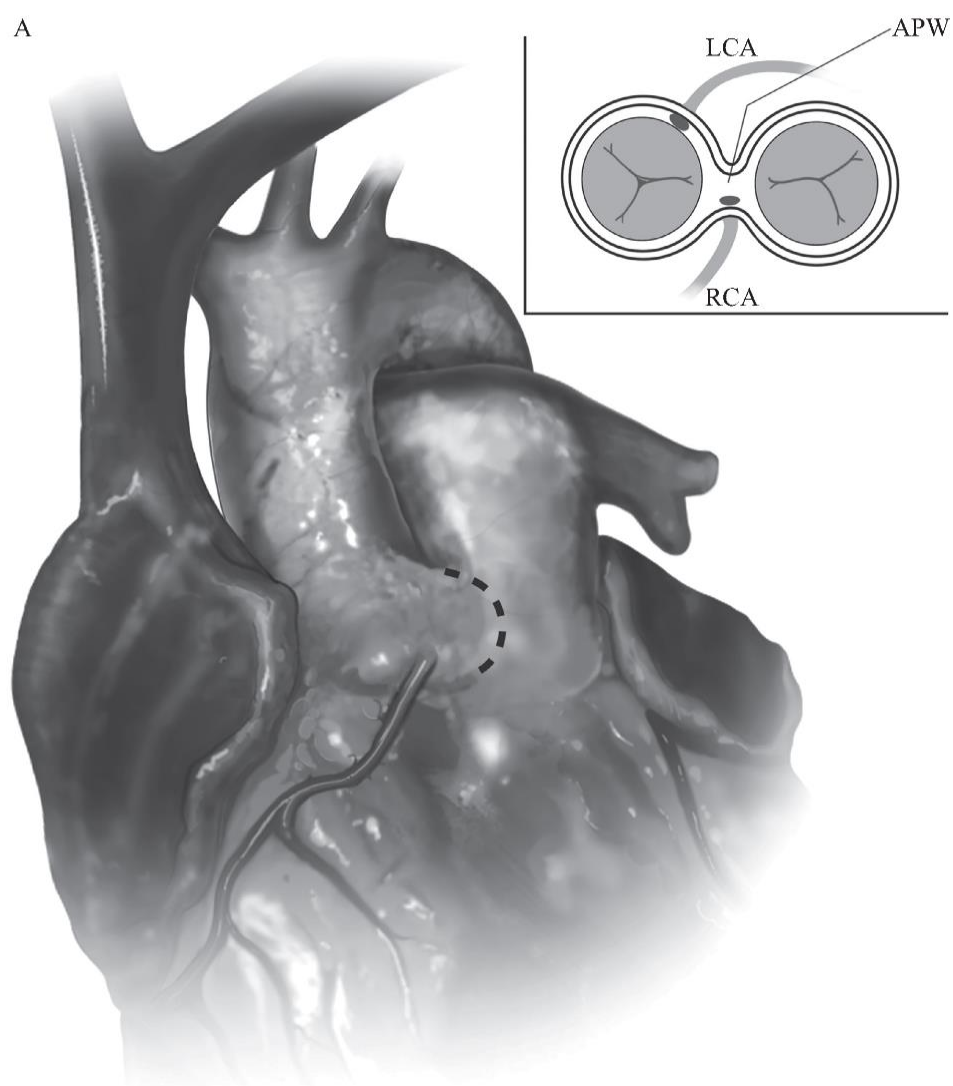


Fig. 10 If the right coronary artery (A) comes from the aortopulmonary window or pulmonary artery, it is mobilized so that the flap of autologous vascular wall could be used to ensure tension-free anastomosis to aorta, if feasible.

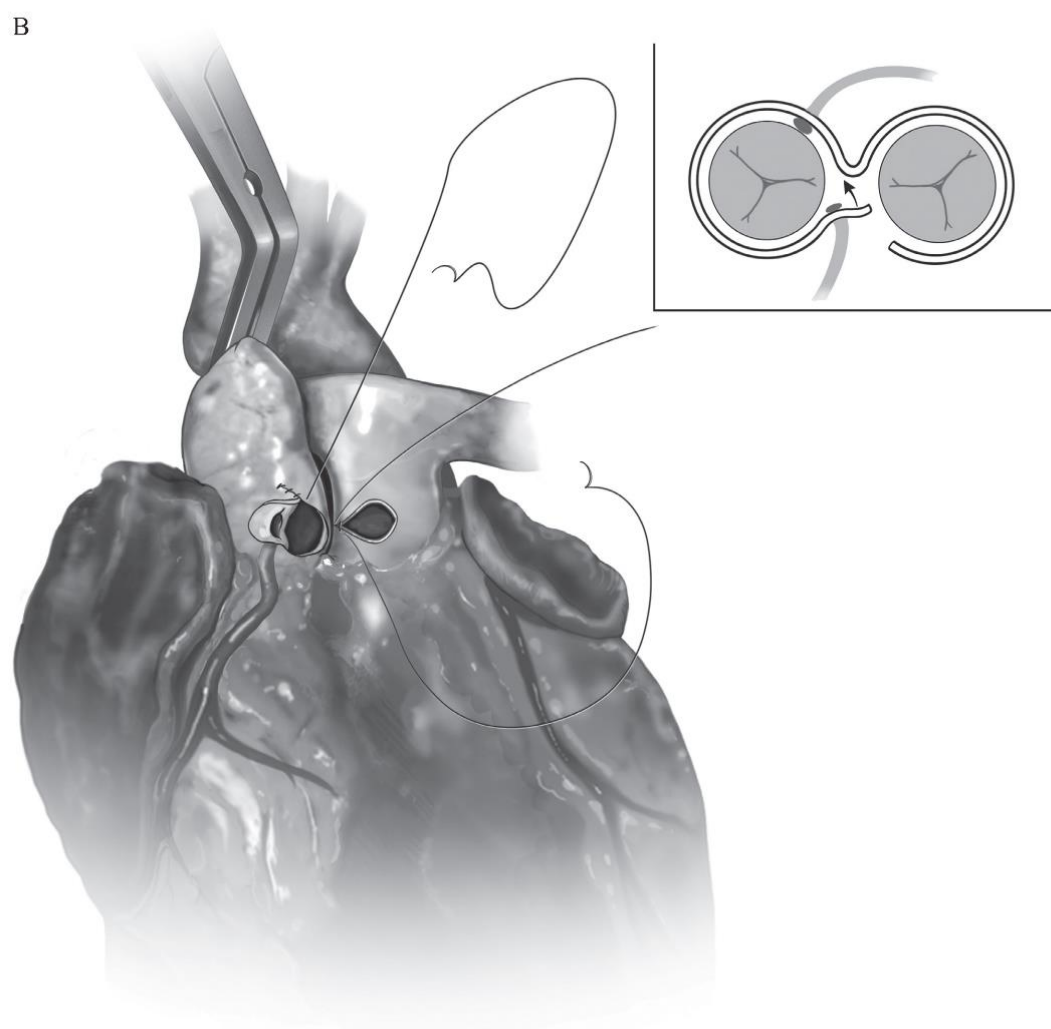


Fig. 10 (continued) (B). Alternatively a patch of pericardium can be placed.

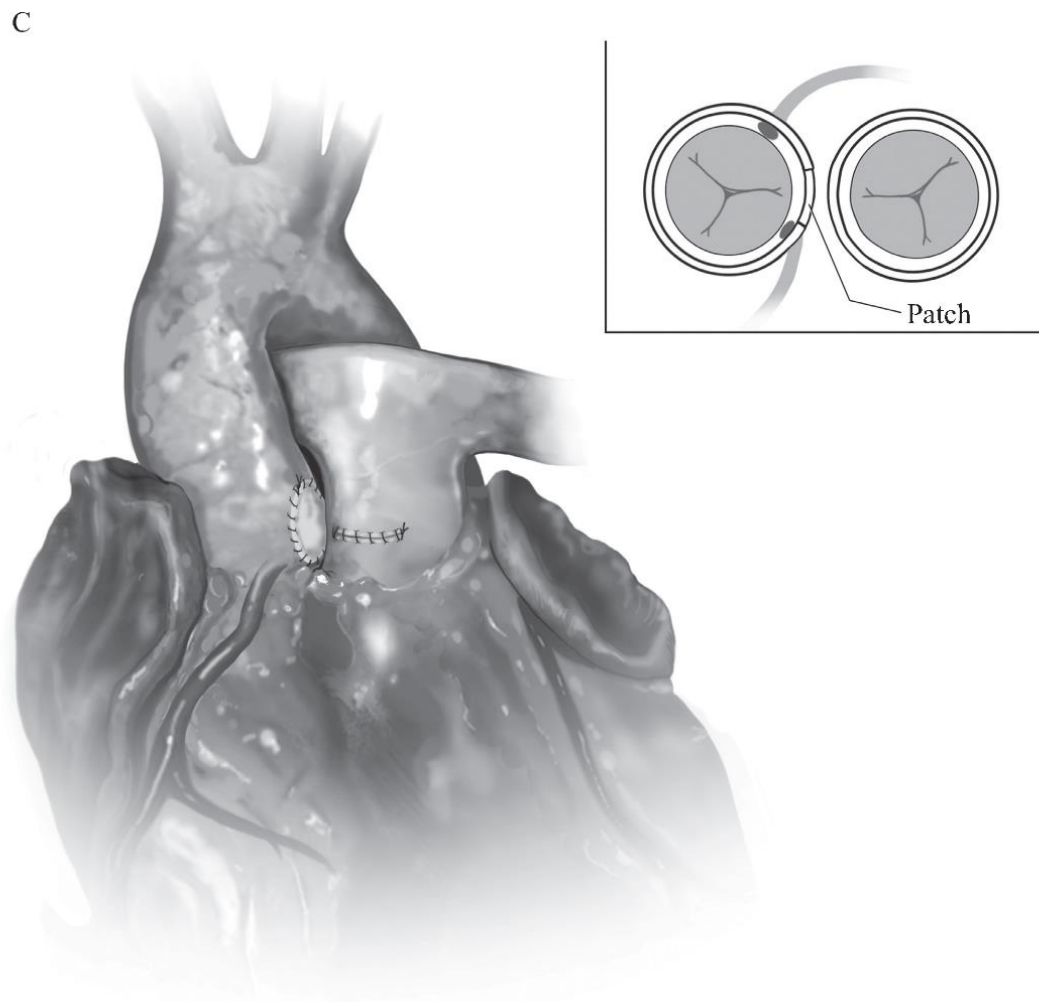


Fig. 10 (continued) (C). The aorta is closed after ensuring that both coronary arteries are committed to the aorta. Direct closure of the aorta is almost always achieved. However, patches of various materials could be used to ensure that the geometry of the aortic root is not compromised. Should the patch of the aortic arch or aortopulmonary window be required, we prefer glutaraldehyde-treated homograft pericardium for aorta and untreated autologous pericardium for the pulmonary artery. We aim to achieve repair of the aortopulmonary window and aortic arch without using patches in all children. The pulmonary artery is closed and aortic cross clamp is removed. The pulmonary artery could be closed before or after aortic cross clamp removal.

Discussion

We have previously reported on our experience with APW repair in 43 patients between 1980 and 2013 at the Royal Children's Hospital, Melbourne.^{7,12} APW was defined as simple in 15 patients and complex in 28 patients. In our experience, overall operative mortality was 14% (6 of 43). Operative mortality among patients with simple APW was 6.7% (1 of 15). The single death in the simple APW occurred early in the study period, and we have not had another operative death in 14 consecutive patients with simple APW since 1983. Contemporary repair of simple APW has an operative mortality approaching 0%.^{5,7,13} In contrast, for patients undergoing repair of complex APW operative mortality is approximately 10%-20%.^{5,7,9,10} We reported an operative mortality of 18% (5 of 28) in patients with complex APW. There have been no late deaths.

In our experience, only 1 of 43 APW patients had an anomalous right coronary artery arising from the main PA. This patient underwent division of the APW with patch closure of both the aorta and PA with glutaraldehyde-treated autologous pericardium. This patient is currently well at 10 years after APW repair. It is pertinent that both coronary ostia are visualized intraoperatively and are committed to the aorta.

Of particular interest are APW patients with concomitant IAA. We have previously reported⁷ on 9 patients (21%, 9 of 43) with APW and concomitant IAA, of whom 8 patients (88%) had type A and 1 patient (12%) had type B. Previous studies have reported that an APW with concomitant IAA is an independent risk factor for operative mortality.^{5,10} Furthermore, there is an increased risk of late deaths among patients with APW and concomitant IAA.¹⁰ In our experience, we have had a single death in a 1.7 kg premature neonate with type A of IAA due to severe tracheobronchomalacia resulting from prior repair of the tracheoesophageal fistula. Repair of the associated IAA was not a risk factor for mortality in our patients. Our surviving 8 patients who underwent repair of their APW and IAA remain asymptomatic at a median follow-up time of 20.3 years.^{7,12}

Reoperation rate for simple APW is low.⁷ Reoperations are more common in patients with complex APW owing to their concomitant anomalies.⁷ We reported freedom from reoperation of 95.3% at 10 years.⁷ Other studies suggested that reoperation for complex APW is often for recurrent aortic arch obstruction after repair of a concomitant IAA.^{8,10} Congenital Heart Surgeons' Society study reported that patients with APW and IAA had a reoperation rate of 57% at 5 years.¹⁰ None of our patients required reoperation following concomitant IAA repair. We believe this is because of our technique of extensive mobilization of the aortic arch and

descending aorta followed by end-to-side anastomosis, which allows for a tension-free anastomosis.^{7,12,14,15} However, 1 patient with APW and IAA type B underwent transcatheter balloon dilation due to mild aortic arch stenosis 13 years after initial surgery.⁷ Type B IAA is a known risk factor for reintervention.¹⁶

As experience with repair of these rare associated anomalies is limited, a thorough understanding of anatomy and surgical technique are paramount to successful outcomes.

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Double-Lumen Aortic Arch: Persistence of the Fifth Aortic Arch

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A persistent fifth aortic arch is exceptionally rare. We report a patient with a double-lumen aortic arch in association with a perimembranous ventricular septal defect and Cornelia de Lange syndrome. We also discuss the morphologic consequences of persistent fifth aortic arch, which may not be limited to the double-lumen aorta but in fact may be more common.

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Double-lumen aortic arch is an exceptionally rare anomaly with scant reports in the literature [1–4]. Herein, we report a rare case of a persistent fifth aortic arch in the form of a double-lumen aortic arch and review the morphologic consequences of fifth aortic arch persistence.

A girl who had shown poor growth on her antenatal scans was born at 31 weeks of gestational age by emergency cesarean section, with a birth weight of 900 grams. She received a postnatal diagnosis of Cornelia de Lange syndrome. A murmur was noted at 1 week of life. An echocardiogram demonstrated a moderate size perimembranous ventricular septal defect (VSD) and a double-lumen left aortic arch. She had poor feeding, frequent aspirations, and gastroesophageal reflux disease.

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She underwent fundoplication and percutaneous endoscopic gastrostomy for feeding. Computed tomographic (CT) angiography at 3 months of age confirmed a left aortic arch with a double-lumen aorta (Figs 1A and B). Four vessels arose from the superior arch: the right innominate artery, the left carotid artery, a left vertebral artery, and the left subclavian artery. She experienced progressive fibromuscular obstruction of the left ventricular outflow tract (LVOT). At 13 months of age she underwent VSD closure and resection of the LVOT fibromuscular obstruction. She is doing well at 6 months after cardiac surgical repair.

Comment

Human embryonic development reflects our phylogenetic past, with the development of six aortic arches, thought to be analogous to the development of gills in fish. These arches undergo a predictable sequence of growth or regression, resulting in the normal thoracic vascular anatomy. In approximately half of all embryos, the fifth aortic arches develop into rudimentary vessels that soon degenerate, leaving no vascular derivatives. In other embryos, the fifth aortic arches do not develop at all. Failure of resorption of the fifth aortic arch is rare and can result in formation of a double-lumen aortic arch [1–5].

The literature on the persistent fifth aortic arch is limited to case reports. Early hypotheses on development of the persistent fifth aortic arch came from Brown in 1913 [1] and Huntington in 1919 [2]; both described the fifth aortic arch as a vascular channel beneath the fourth aortic arch. In 1969, Van Praagh and Van Praagh [3] first reported a persistent fifth aortic arch in a male individual who had a double-lumen aortic arch with both arches on the same side of the trachea. Persistence of the fifth aortic arch had no hemodynamic significance and was diagnosed incidentally. Gerlis and colleagues [4] described variations of the persistent fifth aortic arch that were misinterpreted as patent ductus arteriosus or double aortic arch or that were present in cases of pulmonary or aortic atresia, describing the anomaly as a great

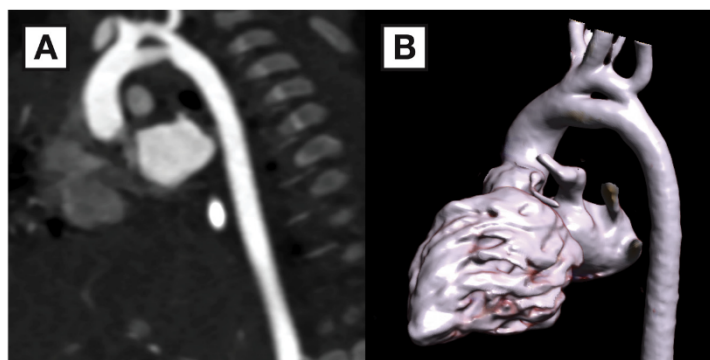


Fig 1. Computed tomographic views of double-lumen aortic arch. (A) Sagittal view. (B) Three-dimensional reconstruction.

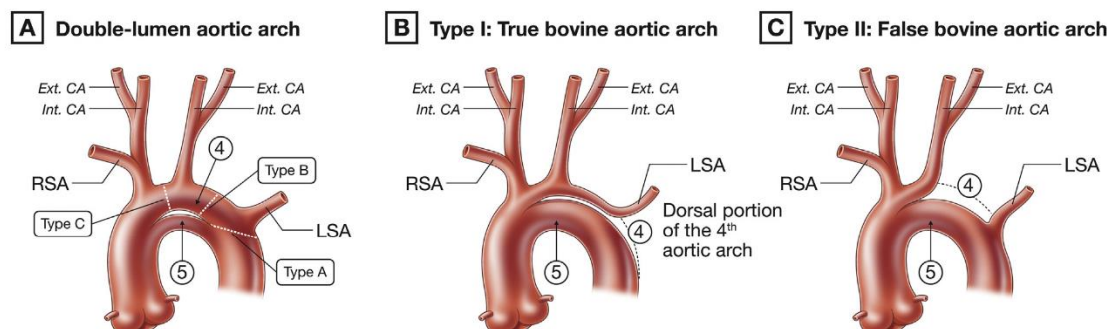


Fig 2. Interruption of fourth aortic arch with persistent fifth aortic arch. (A) Double-lumen aortic arch. Interruption of fourth aortic arch may occur distal to left subclavian (LSA) (type A) or between left common carotid artery (CA) and LSA (type B) or between brachiocephalic artery and left common CA (type C). (B) True bovine arch. Interruption of fourth aortic arch occurs distal to LSA. All branches of the aortic arch arise from a common trunk. (C) False bovine arch. Interruption of fourth aortic arch occurs between left common CA and LSA. (RSA = right subclavian artery.)

pretender. Gupta and colleagues [5] reviewed worldwide case reports of persistent fifth aortic arches and suggested that to qualify as a persistent fifth aortic arch, the arch must arise from the ascending aorta proximal to the brachiocephalic artery, take a serpentine course, and terminate in the dorsal aorta or through the sixth aortic arch into the pulmonary artery.

Persistence of both the fourth and fifth aortic arches results in a double-lumen aortic arch (Fig 2A). However, being a great pretender, a persistent fifth aortic arch associated with interruption of the fourth aortic arch may not be so easy to recognize and may in fact be more common. Thus, interruption of the fourth aortic arch distal to the left subclavian artery (LSA) (type A) would resemble the aortic arch branching pattern observed in ruminant animals: a true bovine arch (Fig 2B), in which all the major branches of the aortic arch arise from a single branch of the aorta [6]. This is a variant in human aortic arches and may not be recognized as a persistence of the fifth aortic arch. Interruption of the fourth aortic arch between the left carotid artery and the LSA (type B) results in a false bovine arch (Fig 2C). In this case, the right subclavian artery and both carotid arteries arise from a common branch of the aortic arch, whereas the LSA arises from the aortic arch separately. This is the second most common pattern of human aortic arch and has a common origin for the innominate and left common

carotid arteries. Thus, this pattern has erroneously been referred to as a bovine arch [6]. Finally, should interruption of the fourth aortic arch occur between the innominate artery and the left common carotid artery (type C), the persistent fifth aortic arch will be virtually indistinguishable from the normal aortic arch. Could an anomalous origin of innominate artery that results in occasional anterior compression of the trachea be attributed to persistent fifth aortic arch and concomitant type C interruption of the fourth aortic arch? Would we ever know? One cannot cease to be amazed by a great pretender!

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Actual application of virtual angioscopy: Is it yet to come?

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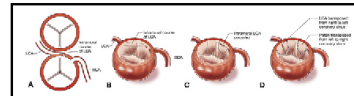
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Origin of the coronary artery from the opposite sinus with an interarterial course.

Central Message

VA using MRI is helpful in visualization of the proximal coronary arteries in children.

See Article page 205.

An interesting article by Brothers and colleagues¹ is published in the current issue of the *Journal*. The article describes the use of cardiac magnetic resonance imaging (MRI) for virtual angioscopy (VA) to evaluate coronary anatomy, myocardial injury, and left ventricular function in 9 children who underwent repair of the anomalous aortic origin of a coronary artery. The study demonstrates that high-quality imaging, showing the surgical view of coronary ostial anatomy and proximal coronary arteries, can be achieved by MRI in children with anomalous coronary arteries both before and after unroofing. As with advances in any technology, this MRI technique brings to clinicians not only new information but also an old question: "What to do about it?" A few comments seem appropriate to bring this important article into proper perspective.

Currently, surgical repair is recommended in all patients with an anomalous left coronary artery from (Figure 1, A and B) the right coronary sinus^{2,3} and in symptomatic patients with an anomalous right coronary artery from the left coronary sinus.^{2,3} In most cases, the stenotic orifice is unroofed (Figure 1, C).^{4,5} However, simple unroofing does not alter the interarterial course of the coronary artery. The latter still comes tangentially from the aorta and could be compressed between the 2 great arteries if not fully unroofed. A concept of pulmonary artery translocation has been described to prevent compression of the anomalous coronary artery.⁶ However, pulmonary artery translocation is unlikely to achieve any meaningful separation of the great arteries below the area of the sinotubular junction (ie, in the area where coronary compression is likely to occur). Thus, we prefer to translocate (Figure 1, D) the unroofed coronary artery into its natural anatomic position.⁷ A slight rotation may be required to prevent kinking of the unroofed coronary artery. An intramural course of the coronary artery behind the aortic valve commissure could complicate transfer and require detachment and reattachment of the commissure.⁷ A low threshold in translocating the unroofed coronary artery comes from our experience in dealing with intramural coronary arteries during the arterial switch operation.⁸ Surgeons who perform

the arterial switch operation would be comfortable translocating unroofed coronary arteries. Whether the unroofed coronary artery is translocated or not, a slit-like appearance of the unroofed ostium is an expected finding. It is not the shape of the unroofed coronary artery but rather its narrowing that would be of concern. A slit-like appearance may not look aesthetically pleasing, but such an appearance per se would not warrant reoperation.

Most importantly, in the hands of Brothers and colleagues,¹ MRI-VA beautifully demonstrated not only the proximal anomalous coronary arising tangentially to the aorta with an elliptical, slit-like ostium in all patients, which was confirmed intraoperatively, but also the position of the ostium relative to the aortic valve commissure to determine if the ostium was juxtacommissural. This is important for surgical planning, because the aortic valve commissure may have to be taken down and reattached after unroofing and reimplantation of the anomalous coronary artery.^{4,5} This has certainly been our experience with an anomalous aortic origin of a coronary artery.⁷ In addition to these anatomic details, the MRI technique described can be used to provide important information regarding the functional state of the myocardium, including ventricular wall motion, myocardial perfusion, and the presence of wall thinning or scar.¹

Of particular value, in our opinion, is postoperative assessment of the neo-ostium. Brothers and colleagues¹ demonstrated that 2 of their 7 patients had narrowed neo-orifices postoperatively. No reoperation was performed, because both of these patients had an anomalous right coronary artery, were asymptomatic, and had no evidence of ischemia on stress testing. The significance of the narrow neo-ostium in this situation is unknown. Current guidelines recommend that patients who have undergone repair of anomalous aortic origin of a coronary artery may return to sport activities 3 months after repair provided they have

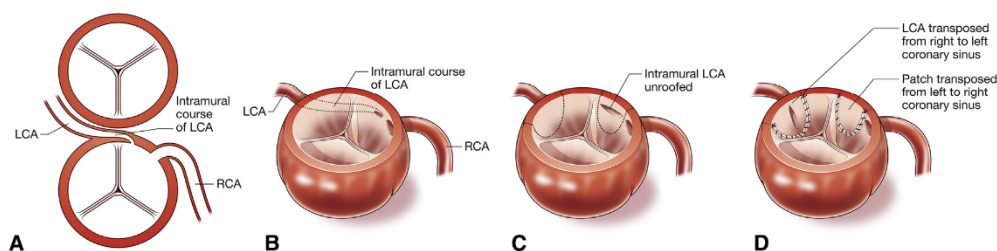


FIGURE 1. Anomalous aortic origin of the left coronary artery from the right coronary artery sinus (A and B) with a narrow origin and intramural course of the proximal interarterial portion of the coronary artery. The intramural segment of the left coronary artery is unroofed (C), and the left coronary artery is translocated to its normal anatomic position (D). A slight rotation of the translocated coronary artery may be required to prevent kinking. LCA, Left coronary artery; RCA, right coronary artery.

no evidence of ischemia on stress testing. However, a sudden death has been reported after unroofing, despite normal stress testing.⁹ The combination of anatomic information on the ostium size, shape, and location, as well as functional information on wall motion and myocardial perfusion, which can be provided by MRI-VA, would be particularly valuable in these patients.

Furthermore, it is possible that some patients have ongoing residual narrowing of the anomalous coronary arteries after unroofing or reimplantation, but this narrowing is undetected with current postoperative evaluation, and this concern is not limited to patients with anomalous aortic origin of a coronary artery. Accurate knowledge of the coronary anatomy also would be useful in patients with transposition of the great arteries, particularly when additional complexity has been encountered in children with intramural coronary arteries.⁸ Clearly, MRI-VA would have an application in this setting, both preoperatively for surgical planning and postoperatively for assessing the anatomy of the reconstructed coronary arteries. Patients with anomalous origin of the left coronary artery from the pulmonary artery require coronary translocation¹⁰ and also likely would benefit from postoperative evaluation of the reimplanted coronary artery. Noninvasive MRI-VA assessment would be beneficial to assess the long-term patency, particularly because some patients with good collaterals may remain asymptomatic and have a normal stress test result, despite significant ostial narrowing of the reimplanted coronary artery.

The application of this technique will require skills, sufficient caseload to maintain expertise, and time because it is dependent on accurate gating for image fidelity.¹ The article by Brothers and colleagues¹ is a remarkable and important

step forward. It is safe to say that MRI-VA is here to stay. The actual application of this virtual modality will need further refinement to be used routinely.

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EDITORIAL

Small Incisions for Small Children: Is Right Lateral Thoracotomy a Right Approach in Open Heart Surgery in Infants?



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Keywords

Minimally-invasive • Surgery • Congenital

An interesting article by Li and colleagues (1) is published in the current issue of Heart, Lung and Circulation that compares cosmetic right lateral thoracotomy (89 patients) to the conventional midline sternotomy approach for ventricular septal defect (VSD) closure (116 patients) in infants weighing less than 5 kg. In this retrospective study, both groups of infants were operated in Beijing Anzhen Hospital during the same time period and the choice of incision depended on the preference of the surgeon. The authors concluded that infants with right thoracotomy had shorter operative time, shorter length of incision, less drainage and transfusion. A few comments seem to be appropriate to put this excellent article into proper perspective.

Currently, repair of simple intracardiac anomalies is a very low risk surgery and children after such surgery lead normal life. Thus, anything less than a perfect outcome after such surgery is not acceptable. Therefore, the enthusiasm in cosmetic approach has traditionally been somewhat tempered. Nonetheless, a cosmetically superior incision that does not compromise patient's safety is clearly important. Thus, cosmetic incision in the axillary area is very appealing in selected patients. The evidence accumulated during the last 15 years suggests that right lateral thoracotomy in children does not increase mortality and morbidity [1–9] (Table 1). Li and colleagues (1) for the first time demonstrated safety and efficacy of right lateral thoracotomy in small infants undergoing VSD closure. While

repair of the atrial septal defect (ASD) in selected patients is routinely done through a small skin incision and partial sternotomy (Figure 1), the approach to VSD via such an incision would be difficult. Furthermore, it is not so much the length of the incision, but rather its location that is important. An incision in the axillary area is hidden by the adducted arm. As the incision does not cross the anterior axillary line, it is unlikely to interfere with normal growth of the breast gland tissue. Although a longer follow-up is needed to determine the impact of a right lateral thoracotomy incision on the development of the chest and breast tissue, the current article by Li and colleagues (1) is, certainly, a brave and admirable step forward. Will their experience change the surgical practise in selected patients with simple intracardiac anomalies worldwide? Most likely, it will. Liu and colleagues used the same approach in 683 children (2) with excellent results.

There is great pressure to perform such a cosmetic incision. However, the surgeon must view any perceived pressure through the prism of objectivity. Safety is paramount. The immediate concern that comes to mind is how the surgeon would deal with unlikely, yet, potentially, life-threatening situations. For example, what if the bleeding occurs from the ductal tissue during concomitant patent ductus arteriosus closure? The sternotomy incision can always be enlarged and any unexpected complications can be dealt with in a controlled fashion.

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Table 1 Outcomes of congenital heart defect repair via right thoracotomy in children.

Study	Year	Patients (n)	Patient age (median, range)	Patient weight (median, range)	Repaired cardiac anomalies	Mortality	Complications (n)
Liu et al (2)	2000	683	3.3 years (4 m - 7 y)	13.6 kg (5 kg - 50 kg)	ASD; VSD; TOF; MVR; Cor triatriatum; DORV	0.3%(2/683)	Atelectasis (9); right hemidiaphragm paresis (3); haemorrhage (2); neurological deficit (1); Residual VSD (1); tamponade (1); wound complication (1)
Pretre et al (3)	2005	80	4 years (1.5 y - 20 y)	15 kg (8.5 kg - 62 kg)	ASD; VSD; PAPVC; pAVSD	0	Residual defect (5); second run of CFB (3); CVA (1)
Schreiber et al (4)	2005	36	6.9 years (4y - 14 y)	23.8 kg (15 kg - 69 kg)	ASD	0	Pneumothorax (2); pleural effusion (1); residual defect (1)
Dave et al (5)	2009	123	4.7 years (5 m - 19.4 y)	16.6 kg (3.8 kg - 62 kg)	ASD; VSD; AVSD; PAPVC	0	Residual defect (6); second run of CFB (5); CVA (1); haemorrhage (1) SVC stenting (1)
Wang et al (6)	2010	274	10.5 years (6 m - 43 y)	37.8 kg (8 kg - 72 kg)	VSD	0	Residual defect (3); haemorrhage (1); wound complication (1)
Yan et al (7)	2013	104	5.7 years (1.5 y - 33.7 y)	18 kg (9 kg - 63 kg)	ASD; VSD; PAPVC	0	Pleural effusion(9); pneumonia (2); atelectasis (1)
da Silva et al (8)	2014	25	2 years (1.5y - 6 y)	13 kg (9.6 kg - 23.5 kg)	ASD; VSD	0	NR
Li et al (1)	2015	89	4.2 ± 1.76* months	4.76 ± 0.12* kg (all <5 kg)	VSD	0	Atelectasis (1); residual defect (1); wound complication (1)

ASD, atrial septal defect; AVSD, atrioventricular septal defect; CFB, cardiopulmonary bypass; CVA, cerebrovascular accident; DORV, double-outlet right ventricle; *m*, months; MVR, mitral valve repair; NR, not reported; PAPVC, partial anomalous pulmonary venous connection; pAVSD, partial atrioventricular septal defect; SVC, superior vena cava; TOF, Tetralogy of Fallot; VSD, ventricular septal defect; *y*, years. *Indicates mean value

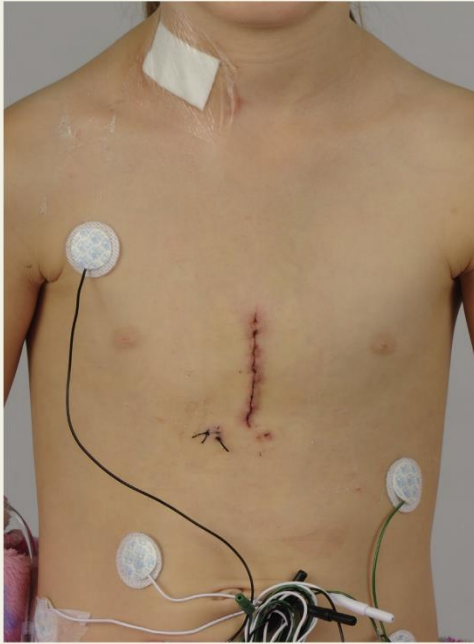


Figure 1 Small cosmetic skin incision in a child after atrial septal defect closure performed at the Royal Children's Hospital in Melbourne.

It becomes clear that simple heart anomalies in children can be repaired via right lateral thoracotomy. Are we all prepared to use this approach?

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Aspirin resistance in the era of personalized medicine: Should we not take it personally?

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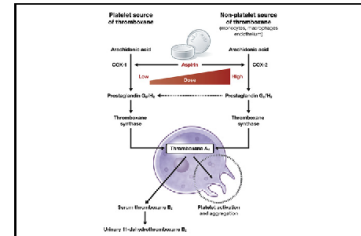
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Schematic of aspirin impact on platelets.

Central Message

Aspirin resistance is an important problem in patients with cardiovascular disease. Personalized antiplatelet therapy is emerging.

See Article page e97.

An interesting and thought-provoking article by DeNino and colleagues¹ appears in the current issue of the *Journal*. This article describes 2 patients with HeartMate II (Thoratec Corporation, Pleasanton, Calif) left ventricular assist device (LVAD) in whom pump thrombosis developed despite what appeared to be an appropriate initial anticoagulation regimen. Both initially received aspirin at low dose (81 mg daily), heparin, and warfarin. The initial responsiveness to aspirin, defined as less than 550 aspirin reaction units (ARU), was confirmed in both patients. Both became unresponsive to aspirin. Both appeared noncompliant with their anticoagulation regimens. Did both have aspirin resistance, or resistance to taking aspirin? How can one determine the causes of diverse prothrombotic conditions that are pulled together and called “aspirin resistance”? What is this elusive aspirin resistance anyway? The article by DeNino and colleagues¹ poses more questions than it gives answers. Yet one has to begin somewhere, and this article is an excellent beginning. It does not provide the solution, but rather it brings attention to a complex problem yet to be solved.

As we enter the era of personalized medicine, a few comments on aspirin resistance and its relevance to cardiac surgeons appear timely. Aspirin resistance is a real phenomenon and defined as the inability of aspirin to reduce platelet production of thromboxane A₂ (TXA₂; Figure 1) and thereby platelet activation and aggregation.² Aspirin is a nonselective and irreversible inhibitor of both forms of cyclooxygenase (COX), but is weakly more selective for COX-1. Aspirin inhibition of COX-1 is rapid and saturable at low doses. This may leave some COX-2, which is greatly upregulated by proinflammatory conditions, uninhibited. Thus TXA₂ can be produced by activated macrophages, monocytes, and endothelial cells through COX-2. Interestingly, higher doses of aspirin cause greater inhibition of COX-2 and dramatically lower concentration of urinary 11-dehydrothromboxane B₂.^{3,4} The Heart Outcomes

Prevention Evaluation study⁵ demonstrated that patients in the highest quartile of urinary-11-dehydrothromboxane B₂ levels had significantly higher risk of myocardial infarction, stroke, or cardiovascular death compared with patients in the lower quartile.

Laboratory diagnosis of aspirin resistance can be established by measuring platelet TXA₂ production or TXA₂-dependent platelet function. The light or optical transmittance aggregometry has been the criterion standard, yet it is time consuming and clinically impractical. The VerifyNow Rapid Platelet Function Test (Accumetrics, Accriva Diagnostics, San Diego, Calif) has demonstrated excellent correlation with optical aggregometry and the rate of cardiovascular events.⁶ It allows rapid bedside analysis of blood and monitoring of not only aspirin but also other antiplatelet agents, including thienopyridines and IIB/IIIa inhibitors. The test is performed in a sample of whole blood by adding an agonist, arachidonic acid, to measure platelet aggregation to fibrinogen-coated beads. Platelet aggregation increases light transmittance, which is recorded as ARU. Values of 550 ARU or higher indicate persistent aggregation and thus unresponsiveness. The test requires 2 mL of blood and has also been used in children, including neonates, after cardiac surgery.⁷

It would certainly be helpful to determine aspirin resistance before the clinical thrombotic event occurred. Once aspirin resistance has been determined, what should we do about it? Simple increase of aspirin dose can be sufficient in some patients but detrimental in others. Ideally,

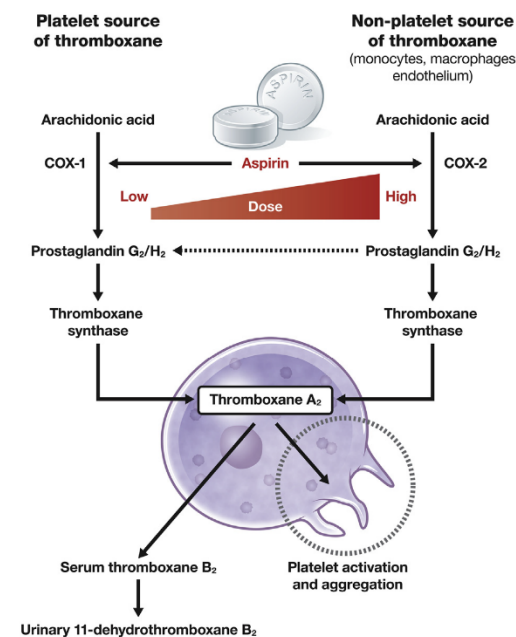


FIGURE 1. Schematic impact of low-dose aspirin on platelet activation and aggregation. Aspirin in low doses may leave some COX-2, production of which may significantly increase in inflammatory conditions, uninhibited, and result in increased platelet activation and aggregation. COX, Cyclooxygenase.

the cause of aspirin resistance should be identified to guide an individualized antiplatelet therapy. The causes of aspirin resistance, however, are numerous.^{1,6} As many as 40% of patients with cardiovascular disease are noncompliant with aspirin therapy.^{1,8} Other major causes of aspirin resistance include drug interaction, hyperglycemia, increased serum catecholamine level, tachyphylaxis with prolonged administration, and, in as many as 30% of patients, genetic polymorphism.^{2,9} Aspirin resistance in anticoagulated patients becomes more complex because of variable genotype polymorphism for both antiplatelet and anticoagulation agents.¹⁰ After all, a simple flu can activate platelets¹¹ and change the response to aspirin. Is it possible to individualize antiplatelet and anticoagulation therapy in our surgical patients?

The cost of sequencing the human genome has fallen so dramatically during the last decade¹² that within a few years clinically affordable sequencing can be done in every patient. An individualized “aspirin response genomic signature” is being identified.^{13,14} The time of personalized antiplatelet and anticoagulation therapy is coming fast.¹⁵ We had better be ready for it.

Early identification and stratification of nonresponders as well as personalized therapy would bring dramatic benefits not only to patients requiring anticoagulation for LVADs or mechanical heart valves but also to millions of people taking aspirin.

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A.15 Naimo PS, Konstantinov IE. J Thorac Cardiovasc Surg. 2015;150(5):e77-8

Cor triatriatum sinister: Is it less sinister in older patients?

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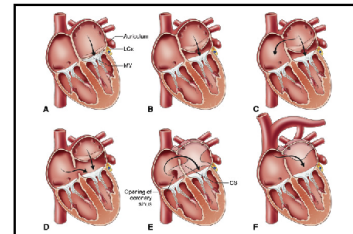
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In a brief article in the current issue of the *Journal*, Said and colleagues¹ describe a teenager with persistent hemoptysis. The patient underwent extensive evaluation, including bronchoscopy and computed tomography, to rule out infectious or hematologic causes of the hemoptysis. Referral to a tertiary hospital was made for further management of hypersensitivity pneumonitis and pulmonary fibrosis. This patient had a surprisingly sinister history until echocardiogram demonstrated a cor triatriatum sinister (CTS). The surgical management was then straightforward and simple. The article emphasizes the fact that hemoptysis can be of cardiac origin, particularly in those with pulmonary venous drainage obstruction. A simple auscultation of the heart should not be scorned when examining any patient with persistent hemoptysis.

CTS is indeed a very rare anomaly, and it is even rarer in older patients. CTS can occur in isolation (classic) or in association with other congenital cardiac anomalies (atypical). The atypical form occurs in 50% to 85% of all patients with CTS,²⁻⁴ although it is rare in adolescents and adults. Older patients more often have an isolated type of CTS.

A previously published article from our institution³ described 28 patients with CTS seen from 1981 to 2003. Seven patients (25%) were neonates and 8 patients (29%) were infants. Most patients (86%; 24/28) were seen by 5 years of age, and all but 1 patient had been seen by 10 years of age. To date, of 42 patients with CTS operated on from 1981 to 2015 at the Royal Children's Hospital in Melbourne, only 4 patients were older than 10 years. Although this pattern may vary slightly according to the era of diagnosis and the referral pattern,^{2,4} the finding of CTS in older patients is uncommon. Typically, older patients with CTS do not have obstruction and thus may remain free of symptoms until later in life. Nonetheless, elderly patients with CTS have been described.^{5,6} If patients do not have restriction of blood flow through the membrane, their disease may be evidenced later in life as the fibrosis or calcification of the membrane progresses, causing obstruction of pulmonary venous blood flow.⁵⁻⁸



Spectrum of pulmonary venous obstruction in congenital heart disease.

Central Message

Cor triatriatum sinister is rare and usually diagnosed early in life. Most older patients have isolated cor triatriatum sinister.

See Article page e73.

As a result, older patients may first be seen with new-onset atrial fibrillation, syncope, shortness of breath, and orthopnea.⁵⁻⁸

Apart from mitral stenosis, a spectrum of congenital anomalies may result in pulmonary venous blood flow obstruction and have similar clinical presentations. A supramitral membrane (Figure 1, A) is distinguished from the membrane in CTS by its location below the left atrial appendage. This is an important differentiation, because as a result of its proximity to the mitral valve and left circumflex coronary artery, the resection of a supramitral membrane is more difficult than the resection of a simple CTS membrane.^{9,10} A supramitral membrane is often adherent to the mitral valve leaflets. The obstruction of CTS may occur at the membrane orifice (Figure 1, B) as in Lam type A¹¹ or as in type A1, also at the atrial septal defect (Figure 1, C). In patients with CTS type A2, the obstructing membrane is located above the atrial septal defect, and these patients may be seen with severe hypoxia as a result of the combination of pulmonary venous obstruction and intermittent right-to-left shunting (Figure 1, D). CTS draining into the coronary sinus, Lam type B (Figure 1, E) is a misnomer and, in fact, is not different from the intra-cardiac type of the total anomalous pulmonary venous drainage, unless there is a separate communication of the pulmonary venous confluence with the left atrium.⁸ Obstruction in patients with total anomalous pulmonary venous drainage (Figure 1, E and F) occurs at the atrial septal defect or the emissary vein.

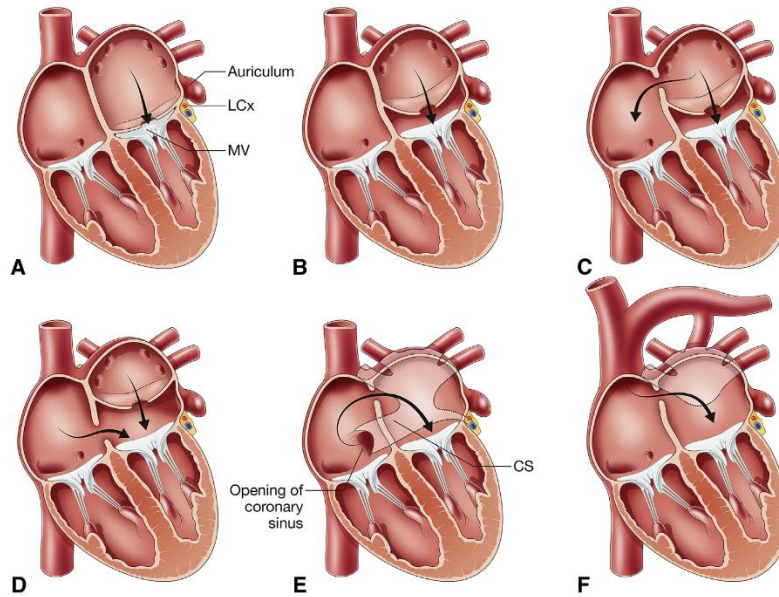


FIGURE 1. Spectrum of congenital supramitral obstruction of the pulmonary venous blood flow. A, A supramitral membrane (arrow) is located below the left atrial appendage (Auriculum), attached to the base of the mitral valve (MV) and in close proximity to the left circumflex coronary artery (LCx). B, C, and D, The pulmonary venous confluence in cor triatriatum sinister is separated from the mitral valve by a membrane located above the left atrial appendage (arrow) and may have an associated atrial septal defect (curved arrow in C and D runs through the defect). E and F, Pulmonary confluence in total anomalous pulmonary venous drainage (arrow) does not have a direct connection to the left atrium but instead occurs through the emissary vein into the coronary sinus (CS in E), superior vena cava (F), or inferior vena cava and can be obstructed at the level of the atrial septal defect.

Surgery in patients with CTS is performed with good outcomes. Mortality and reoperation rate are nearly 0% in patients with classic CTS and are determined by the repair of associated anomalies in atypical CTS. Because of natural selection, congenital cardiac anomalies that present in adolescents and adults have a more benign course. The vast majority of older patients have an isolated CTS membrane that could easily be removed by simple surgery. If the anomaly is not recognized, however, the clinical presentation may indeed appear much more sinister than its underlying cause.

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CASE REPORT – CONGENITAL

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Outcomes of repair of left partial anomalous pulmonary venous connection in children

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Abstract

Herein, we report a case series of patients who underwent repair of left partial anomalous pulmonary venous connection (L-PAPVC) via anastomosing the anomalous pulmonary vein (PV) to the left atrial appendage. Fifteen children underwent repair of L-PAPVC between 1980 and 2014. The median age at surgery was 3.6 years (range: 5 days to 17.2 years). Concomitant anomalies were present in 87% (13/15). There were no early deaths. There was 1 late death occurring 63 days following surgical repair due to pneumococcal septicaemia in a patient with prior atrial septal defect closure and Ehlers–Danlos syndrome. The overall survival rate was 93.7% at 15 years. A single patient (1/15, 7%) required reoperation 1 year after L-PAPVC repair for PV stenosis due to several thrombi located throughout the PV. The rate of freedom from PV reoperation was 90% at 10 years. The follow-up was 100% complete with a median time of 11 years (range: 52 days to 20 years). To our knowledge, this is the youngest cohort of patients who have undergone surgical repair of L-PAPVC. Repair of L-PAPVC in children can be achieved via anastomosis of the anomalous vessel to the left atrial (LA) with excellent outcomes. The rate of anastomotic stenosis at the site of implantation on the LA is low.

Keywords: Partially anomalous pulmonary venous connection • Surgery • Congenital heart disease

Left partially anomalous pulmonary venous connection (L-PAPVC) is a rare condition, in which part or all of the left pulmonary veins (PVs) drain indirectly into the right atrium (Fig. 1A). Patients with isolated L-PAPVC are often asymptomatic, although some may

have a left-to-right shunt and develop pulmonary hypertension or right ventricular (RV) failure [1, 2].

Although surgical repair of L-PAPVC has been performed with excellent results [3, 4], there are limited data on the outcomes of

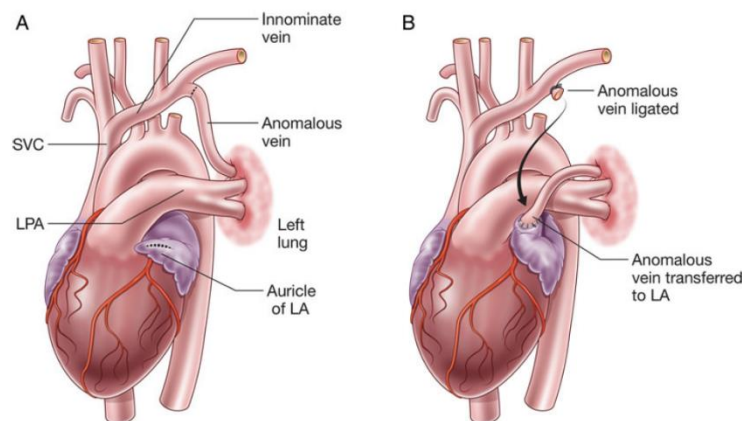


Figure 1: L-PAPVC before (A) and after (B) repair.

Table 1: Patient characteristics and outcomes

Patient no.	Years	Sex	Age at repair	Weight (kg)	Concomitant anomalies	Prior surgery	Concomitant repair with L-PAPVC repair	Reoperations	Status
1	1980	M	299 days	7.6	None	None	None	None	Alive
2	1992	F	60 days	3.6	CoA, PDA, VSD	None	CoA repair; PDA ligation; VSD closure	None	Alive
3	1994	M	99 days	5.2	Hypoplastic RV; PDA; tricuspid atresia; VSD; hypoplastic left lung	None	PA banding	1. PV stenosis relief 2. MBTS 3. BCPC and RPA patch augmentation 4. Take-down of BCPC and rerouting of LPA to SVC	Alive
4	1996	F	1.2 years	8.8	PA sling; TOF	MBTS 9 months earlier	PA sling repair; VSD closure	RVOT resection and 19 mm aortic homograft in RVOT to function with the native valve	Alive
5	1998	M	4.8 years	15.5	R-PAPVC	None	R-PAPVC repair	None	Alive
6	1999	M	4.4 years	16.0	None	None	None	None	Alive
7	2000	M	17.1 years	40.3	ASD; Ehlers-Danlos syndrome	ASD repair 6 years earlier	None	None	Late death
8	2000	M	3.6 years	13.3	ASD	None	ASD closure	None	Alive
9	2001	M	12.2 years	38.0	ASD	None	ASD closure	None	Alive
10	2001	F	4.1 years	14.8	CoA; PDA	None	CoA repair; PDA ligation	None	Alive
11	2001	M	25 days	3.5	ASD; VSD	None	ASD closure	None	Alive
12	2002	F	1.4 years	10.5	ASD; cor triatriatum; pulmonary valve stenosis; R-PAPVC	None	ASD closure; cor triatriatum repair; R-PAPVC repair	None	Alive
13	2007	M	5 days	2.6	ASD; CoA; PDA; VSD	None	ASD closure; CoA repair; PDA ligation; VSD closure; PA banding	PA band tightening and plication of left hemi-diaphragm	Alive
14	2011	F	4.3 years	16.8	Bicuspid aortic valve; CoA; PDA; ASD	CoA repair; PDA ligation 4 years earlier	ASD closure	None	Alive
15	2011	F	112 days	5.1	TOF; R-PAPVC	None	TOF repair; R-PAPVC repair	1. Warden procedure 2. RVOT resection	Alive

ASD: atrial septal defect; BCPC: bidirectional cavopulmonary connection; CoA: coarctation of aorta; LA: left atrium; LPA: left pulmonary artery; MBTS: modified Blalock-Tausig shunt; PA: pulmonary artery; PAPVC: partially anomalous pulmonary venous connection; PDA: patent ductus arteriosus; PV: pulmonary vein; RA: right atrium; RPA: right pulmonary artery; RV: right ventricle; RVOT: right ventricular outflow tract; SVC: superior vena cava; TOF: tetralogy of Fallot; VSD: ventricular septal defect.

repair in children, particularly the rate of anastomotic stenosis following implantation of the anomalous vein onto the left atrial (LA) appendage. We, therefore, sought to review the outcomes of these rare patients at the Royal Children's Hospital.

CASE SERIES

Between 1980 and 2014, 15 patients underwent repair of L-PAPVC via anastomosis of the anomalous vein to the LA (Fig. 1B). Surgery was performed via median sternotomy ($n = 13$) with cardiopulmonary bypass (CPB) or posterolateral thoracotomy ($n = 2$) without CPB. The LA was opened by an oblique incision from the LA appendage to the posterior LA in 11 patients, and the LA appendage was amputated in 4 patients. Anastomosis was achieved with continuous Prolene suture (6/0, $n = 6$; 7/0, $n = 7$; 8/0, $n = 2$) in all patients.

Patient characteristics and surgical procedures are summarized in Table 1. The median age at surgery was 1.4 years (interquartile range: 110 days to 4.4 years) and the median weight at surgery was 12 kg (interquartile range: 4.9–15.1 kg). Concurrent repair of concomitant cardiovascular anomalies was undertaken in 80% (12/15) of patients. Postoperatively, 1 patient with concomitant tetralogy of Fallot, left pulmonary artery sling and tracheal stenosis required extracorporeal membrane oxygenation for 6 days due to respiratory failure and poor cardiac function. This patient is doing well at 18 years after surgery.

The follow-up was 100% complete with a median time of 11 years (range: 52 days to 20 years). There were no early deaths. There was 1 late death 63 days postoperatively due to pneumococcal septicaemia in a patient with prior ASD repair and Ehlers–Danlos syndrome. It was noted that this patient had not had a pneumococcal vaccination. The overall survival rate was $93 \pm 7\%$ (95% confidence interval: 59, 99) at 15 years.

Four patients underwent a total of nine reoperations. All of these patients had concomitant cardiovascular anomalies. Echocardiography identified anastomotic PV stenosis in 1 patient 81 days postoperatively. Cardiac catheterization confirmed anastomotic stenosis. However, during surgery, the anastomotic site was widely patent and the stenosis was located at the entry of the left PVs into the confluence of PVs, and was due to thrombi. The thrombi were removed and the PVs were enlarged with a patch of autologous pericardium. At the last follow-up, echocardiogram demonstrated no anastomotic stenosis in any patient. Additionally, RV dilation had regressed in all but 1 patient, though RV function was normal in all patients. Mild tricuspid regurgitation was present in 2 patients.

DISCUSSION

To our knowledge, we describe the youngest cohort of patients who have undergone repair of L-PAPVC. Mortality and anastomotic

stenosis following repair of L-PAPVC is low. A single patient required reoperation for suspected anastomotic stenosis on the LA appendage. However, during surgery, the anastomosis was patent and the stenosis was due to thrombi in the confluence of PVs. Alsoufi *et al.* [4] described 22 patients who underwent L-PAPVC repair between 1982 and 2006 with a median age of 5.3 years, with no deaths or anastomotic stenosis, after a mean follow-up of 9.1 years. Similarly, ElBardissi *et al.* [3] described 27 patients who underwent L-PAPVC repair between 1954 and 2006 with a median age of 33 years, with no deaths or anastomotic stenosis, after a mean follow-up of 10.6 years.

Indications for surgery in asymptomatic patients with L-PAPVC has been similar to that of ASD repair and the surgery was recommended in patients with a pulmonary-to-systemic flow ratio ($Q_p:Q_s$) >1.5 [5]. ElBardissi *et al.* [3] suggested that surgical repair take place early in patients with RV dilation or mild to moderate tricuspid regurgitation, or in early stages of pulmonary vascular disease, to prevent pulmonary hypertension. We would agree that the isolated L-PAPVC should be repaired when $Q_p:Q_s >1.5$ or with clinical signs of RV dilatation as described by ElBardissi *et al.* [3]. However, in patients with concomitant cardiovascular anomalies that require surgical repair, simultaneous repair of L-PAPVC can be done safely and with excellent outcomes.

Repair of L-PAPVC in younger children can be achieved via anastomosis of the anomalous vein to the LA appendage with excellent outcomes. The rate of anastomotic stenosis is low. Large, multi-institutional studies are required to determine definitive guidelines for surgical indications.

Conflict of interest: none declared.

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Appendix B: Book chapters authored during candidature

B.1 Naimo PS, Asakai H, Konstantinov IE. Key Questions in Congenital Cardiac Surgery. First Edition. Expected Publication Jun 2020

Aortopulmonary Window

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What is an aortopulmonary window?

Aortopulmonary window is a communication between the ascending aorta and the main pulmonary artery in the presence of two distinct semilunar valves. The presence of two separate semilunar valves distinguishes aortopulmonary window from persistent truncus arteriosus.

How is the conotruncus formed embryologically?

From the 3rd week of gestation, the tubular heart elongates and develops alternate dilations and constrictions forming the sinus venosus, an atrium, a ventricle and the bulbus cordis. The bulbus cordis subsequently forms a common outflow tract, the truncus arteriosus. Together, the bulbus cordis and the truncus arteriosus form the conotruncus. The truncus arteriosus extends distally to the margins of the pericardial cavity, where it becomes continuous with the aortic sac. As truncal and bulbar ridges develop (**Figure B.1-1A**), separation of the truncus arteriosus and the ventricles occurs and involves rotation (**Figure B.1-1B**) of the truncus arteriosus relative to the ventricles (1). This rotation results in formation of great arteries with blood flow direction in each vessel almost perpendicular to each other (**Figure B.1-1C**).

Formation of the conotruncal region is complex. During the 5th week of gestation, active proliferation of a number of mesenchymal cells causes a variety of swellings to develop (2). Initially, a mesenchymal wedge of tissue develops between the 4th and 6th aortic arches in the roof of the aortic sac. Additional swellings develop in the walls of the bulbus cordis resulting in the formation of bulbar ridges, as well as ridges in the truncus arteriosus (collectively called conotruncal ridges). The conotruncal ridges separating the outflow tract run in a spiral course along the walls of the bulbus cordis and truncus arteriosus rather than running in a straight line. This is required for the right ventricle to connect to the future pulmonary circulation and the left ventricle to connect to the systemic circulation (2, 3). The wedge of tissue between the 4th and 6th aortic arch projects inferiorly towards the conotruncal ridges and fuses with them (2). Following this, fusion of the spiraled conotruncal ridges occur, commencing distally and

progressing proximally. Once fused, this forms the aortopulmonary septum which divides both the bulbus cordis and truncus arteriosus into two separate arterial channels – the pulmonary trunk and the ascending aorta (1, 2). Complete segregation of the right and left ventricles and their respective outflow tracts is only complete when the muscular interventricular septum fuses with the conotruncal septum and the ventricular side of the atrioventricular septum (3).

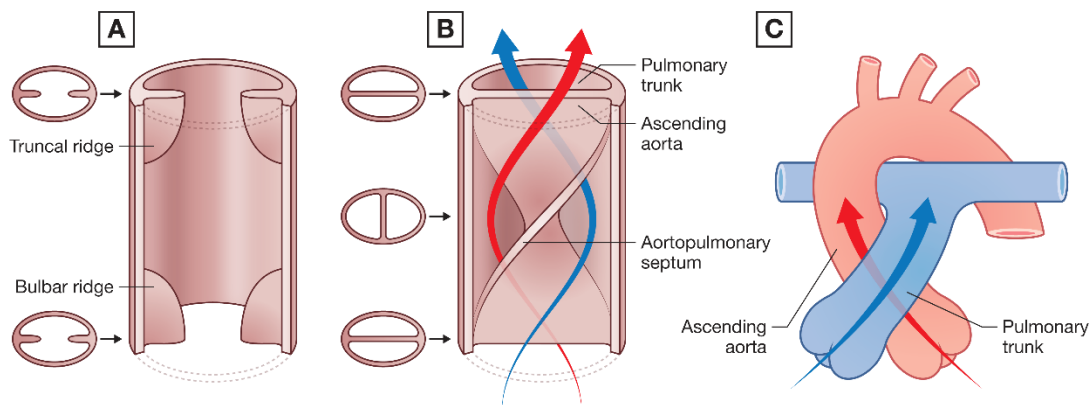


Figure B.1-1. Embryological development of the conotruncal region. A: Development and approximation of the bulbar and truncal ridges. B: Rotational arrangement of the fused bulbar and truncal ridges. C: Final anatomical relationship between the ascending aorta and main pulmonary artery

As a result of the spiral course of the ridges, the left and right ventricular outflow tracts and, eventually, the aorta and pulmonary trunk twist around each other in a helical arrangement. The reason for this spiraling is not yet known. Several reasons have been proposed including rotational and torsional forces on the outflow tract generated as a consequence of cardiac looping and the forces caused by streaming of blood from the ventricles (2–4).

The eventual fate of the embryological truncus arteriosus is that it will be divided to form the proximal portions of the ascending aorta and the pulmonary trunk; while the bulbus cordis will be incorporated as the infundibulum in the right ventricle (1).

When partitioning of the truncus arteriosus is nearly complete, the semilunar valves begin to develop from three swellings around the orifices of the pulmonary artery and the ascending aorta respectively. These swellings are reshaped to form three thin walled cusps which are completed by the 9th week of gestation (2).

How are aortopulmonary windows classified?

Initial classification of aortopulmonary window came from Mori et al (5) in 1978, who described three distinct types of aortopulmonary window – proximal, distal and total (**Figure B.1-2A, 2B and 2C**). Proximal defects were determined to be the most common and were located a few millimeters above the sinus of Valsalva. Distal defects were described as a communication between the posterolateral wall of the ascending aorta and the junctional portion of the right pulmonary artery and pulmonary trunk. Total defects involved the entire length of the pulmonary trunk from just above the semilunar valves to the bifurcation of the pulmonary trunk and, occasionally, included part of the right pulmonary artery (5).

This system of classification was slightly amended by Ho et al (6) in 1994, who included a fourth type of aortopulmonary window – an intermediate defect (**Figure B.1-2D**). Additionally, they further defined each type of aortopulmonary window as follows:

- Type I (proximal defect) – a communicating window located just above the sinus of Valsalva (aortic sinus), a few millimeters above the semilunar valve, with a superior rim but little inferior rim separating the aortopulmonary window from the semilunar valve.
- Type II (distal defect) – a communicating window located in the uppermost portion of the ascending aorta, with a well-formed inferior rim but little superior rim.
- Type III (total defect) – a communicating window involving the majority of the ascending aorta, with little superior or inferior rims

- Type IV (intermediate defect) – a communicating window similar to a total defect but with well-formed superior and inferior rims

It is this classification system, combining works from Mori et al and Ho et al which is currently used by The Society of Thoracic Surgeons (7).

An alternative classification system was proposed by Richardson et al (8) in 1979, who again described three distinct types of aortopulmonary windows. Type I of the Richardson classification was described as a 'typical' aortopulmonary window between the posteromedial wall of the ascending aorta – just above the sinus of Valsalva – and the main pulmonary artery (**Figure B.1-3A**). Type II defects were located between the posterior wall of the ascending aorta and the origin of the right pulmonary artery (**Figure B.1-3B**). Thus, Types I and II were similar in all 3 classifications. However, Type III defects in Richardson classification were defined as having an anomalous origin of the right pulmonary artery from the posterolateral wall of the ascending aorta (**Figure B.1-3C**). This became a source of confusion as this anomaly was often referred to as 'hemitruncus arteriosus'. The term 'hemitruncus' is a misnomer as it implies that the anomalous vessel arises from a common arterial trunk, whereas it arises from the ascending aorta (9). We believe that the term 'hemitruncus' should not be used. Instead, this anomaly should be referred to as an anomalous origin of the right pulmonary artery from the ascending aorta with (**Figure B.1-4A**) or without (**Figure B.1-4B**) concomitant aortopulmonary window.

Richardson and colleagues described their type III defects as severe unequal partitioning of the aortopulmonary trunk by severe malalignment of the conotruncal ridges, resulting in more dorsal development of the aorta (8). However, it has been argued that Type III defect of the Richardson classification is not aortopulmonary window as it does not result from a defect in aortopulmonary septation (7). Thus, for all practical reasons, to avoid confusion the aortopulmonary should be referred to a defect between the ascending aorta and the main pulmonary artery.

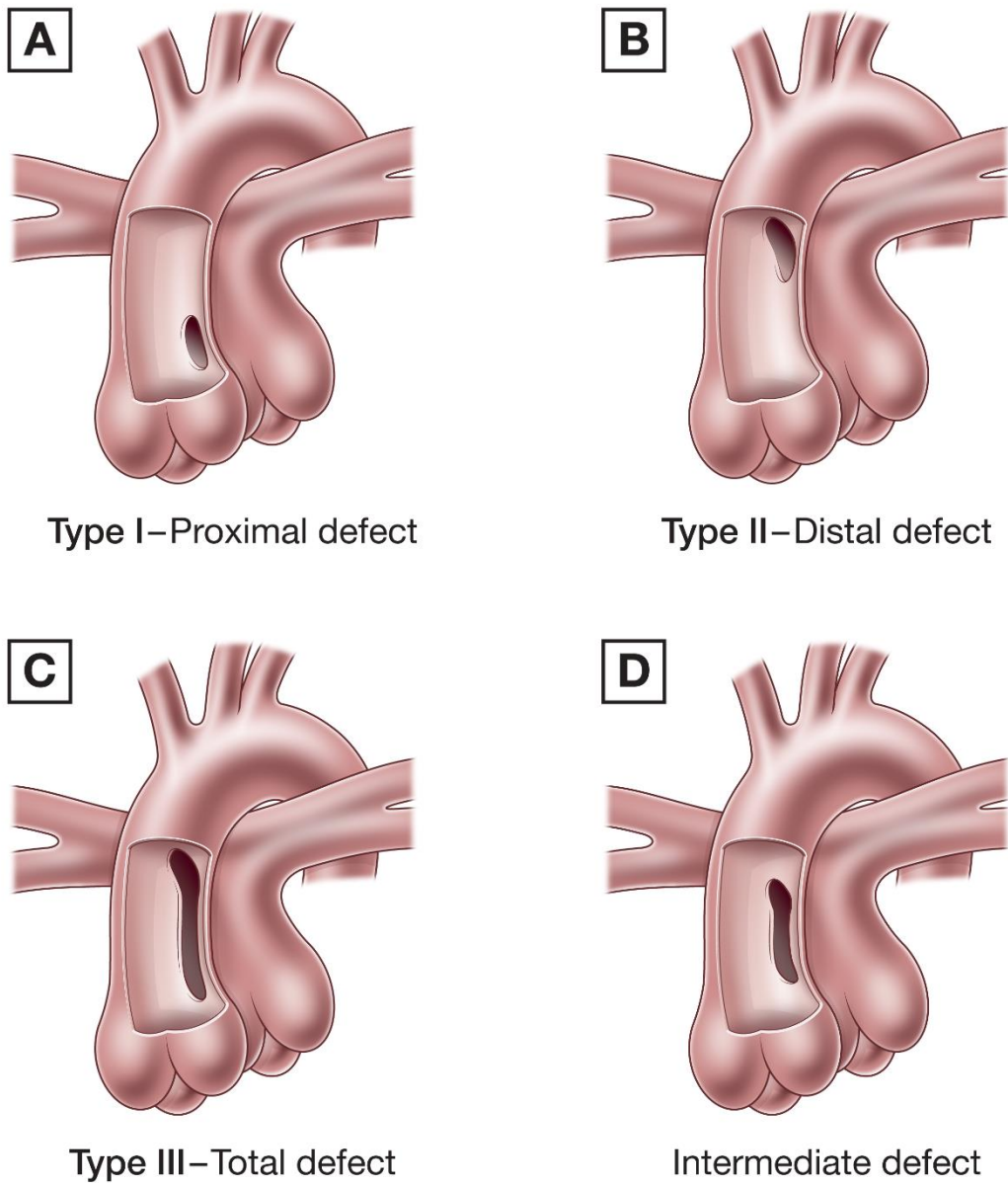


Figure B.1-2. Classification of aortopulmonary window used by The Society of Thoracic Surgeons adapted after Mori et al (5). A: Type I - proximal defect; B: Type - II being distal defect; C: Type III - total defect and modified by Ho et al (6) by adding D: Type IV - intermediate defect.

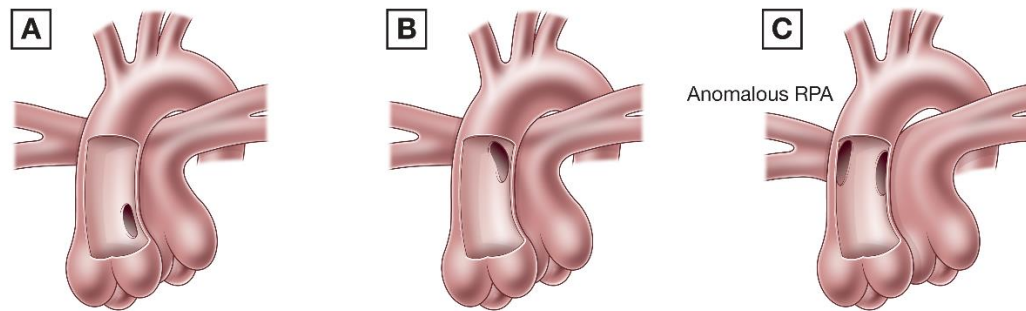


Figure B.1-3. Classification of aortopulmonary window as proposed by Richardson and colleagues. A: Type I is a 'typical' aortopulmonary window between the posteromedial wall of the ascending aorta and the main pulmonary artery. B: Type II located between the posterior wall of the ascending aorta and the origin of the right pulmonary artery. C: Type III defects are defined as an anomalous origin of the right pulmonary artery from the posterolateral wall of the ascending aorta. *RPA*, right pulmonary artery.

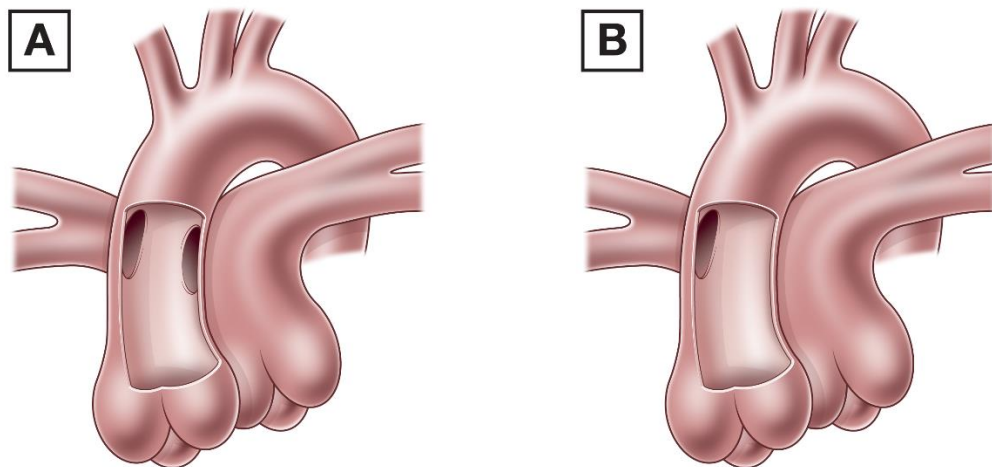


Figure B.1-4. Anomalous origin of right pulmonary artery from ascending aorta. A: Anomalous origin of the right pulmonary artery from the ascending aorta with concomitant aortopulmonary window. B: Anomalous origin of the right pulmonary artery from the ascending aorta without concomitant aortopulmonary window

What cardiovascular abnormalities are associated with an aortopulmonary window?

Approximately 25 – 60% of patients with the aortopulmonary window have at least one concomitant cardiovascular anomaly (10 – 25). The frequency of concomitant cardiovascular anomalies described in the previous studies (10 – 25) are summarised in **Table B.1-1**. Of interest, frequent association with patent ductus arteriosus is a likely consequence of the similar frequent association with an interrupted aortic arch. However, 6 - 25% of patients may have aortopulmonary window with concurrent patent ductus arteriosus without an interrupted aortic arch (11, 12, 17, 18, 22). Interestingly, Bhan and colleagues reported aortopulmonary window and patent ductus arteriosus with an incidence of 36% (20). We observed that aortopulmonary window was associated with patent ductus arteriosus in 7% of patients that did not have a concomitant interrupted aortic arch and were operated at the Royal Children's Hospital in Melbourne.

One of the most common anomalies for patients with aortopulmonary window is an interrupted aortic arch, with an average prevalence of 20.8% and range of 0 and 50% (10 – 25). Of patients with aortopulmonary window and concomitant interrupted aortic arch, it has been shown that 85% (17/20) of interrupted aortic arches were of type A whilst 15% (3/20) were of type B (26) (**Figure B.1-5**). Interestingly, however, patients with interrupted aortic arch have a concomitant aortopulmonary window in only 3.5 – 4.2% of cases (26 – 28).

About 20% of patients with aortopulmonary window have a concomitant ventricular septal defect (10-25). It appears that ventricular septal defects occur most commonly in a perimembranous location (12, 22). In our experience 20.8% (9/43) of children with aortopulmonary window had concomitant ventricular septal defects and 77.8% (7/9) of those were perimembranous and 22.2% (2/9) were muscular.

Occasionally aortopulmonary window may have concomitant anomalous coronary artery. Although this is a rare anomaly, delineation of the coronary anatomy is vital for successful correction of aortopulmonary window. A few case

reports (8, 15, 19, 29–45) indicate that the anomalous coronary vessel is often the right coronary artery arising from the main pulmonary artery or from the aortopulmonary window itself (**Table B.1-2**). Although this is a very rare anomaly, the right coronary artery is most commonly involved (**Figure B.1-6**). Only one of our 43 patients had an anomalous right coronary artery arising from the main pulmonary artery (**Figure B.1-6B**).

Less frequent concomitant cardiovascular anomalies include tricuspid atresia, subaortic stenosis, pulmonary artery stenosis, aberrant right or left subclavian artery and absent left pulmonary artery (15, 16, 19, 21).

Table B.1-1. Mean incidence of concomitant cardiovascular anomalies associated with aortopulmonary window in the literature and The Royal Children's Hospital.

Cardiovascular Anomaly	Mean reported in the literature (n=296) (mean, range, %)	Mean from The Royal Children's Hospital (n=43) (mean, %)
PDA	21.3 (0 – 50)	27.9
IAA (nearly always type A) / CoA	20.8 (0 – 50)	20.9
VSD	19.4 (0 – 70)	20.8
ASD / PFO	19.3 (0 – 53)	34.9
TOF	5.0 (0 – 20)	4.7
RAA	5.0 (0 – 21.5)	4.7
Persistent LSVC	3.7 (0 – 18)	9.3
Anomalous origin of coronary artery	2.0 (0 – 15.5)	2.3
Origin of the RPA from ascending aorta	2.0 (0 – 18)	2.3
TGA	1.9 (0 – 9)	0
Aortic valvular stenosis	1.7 (0 – 20)	0
Pulmonary atresia	1.6 (0 – 9)	0
Pulmonary valvular stenosis	1.3 (0 – 10)	4.7

ASD, atrial septal defect; *CoA*, coarctation of the aorta; *IAA*, interrupted aortic arch; *LSVC*, left superior vena cava; *PDA*, patent ductus arteriosus; *PFO*, patent foramen ovale; *RAA*, right aortic arch; *RPA*, right pulmonary artery; *TGA*, transposition of the great arteries; *TOF*, tetralogy of Fallot; *VSD*, ventricular septal defect

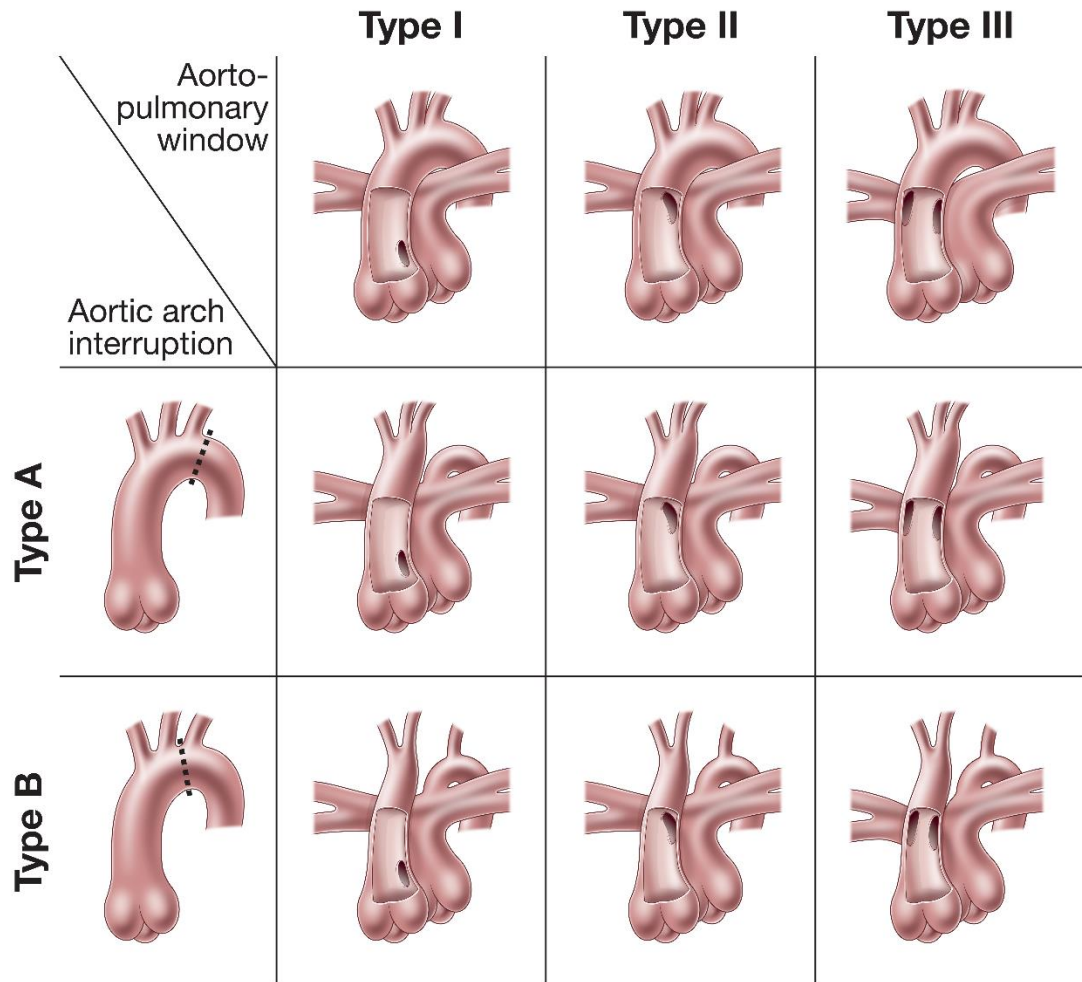


Figure B.1-5. Aortopulmonary window with concomitant interrupted aortic arch. Appearance of aortopulmonary window (using Richardson's classification) with concomitant types A or B interrupted aortic arch.

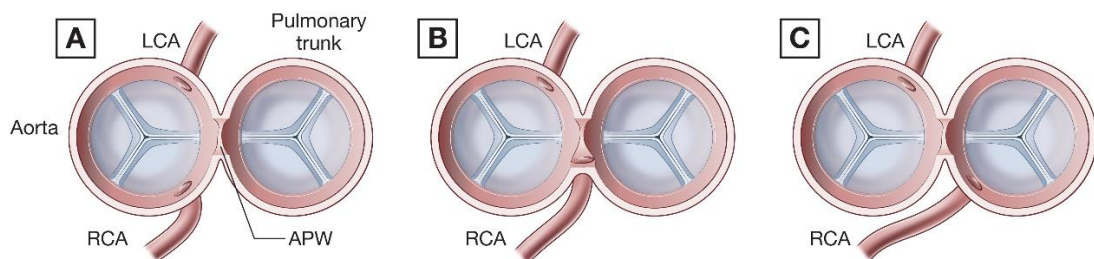


Figure B.1-6. Anomalous origin of the right coronary artery from the main pulmonary artery with (A) and without (B) aortopulmonary window. APW, aortopulmonary window; LCA, left coronary artery; RCA, right coronary artery.

Table B.1-2. Anomalous origin of coronary arteries in aortopulmonary window. Summary of case reports of anomalous right and left coronary arteries with their sites of origin. Of these patients, there were 4 deaths from 25 patients (16%).

Study	Year	Number of cases	Coronary artery	Site of origin	Survived
Richardson et al (8)	1979	2	Left	AP window	Yes
			Single coronary artery	MPA	Yes
Luisi et al (29)	1980	1	Right	MPA	Yes
Bourlon et al (30)	1981	1	Left	AP window	Yes
Doty et al (31)	1981	1	Left	MPA	No
Shore et al (32)	1983	1	Single coronary artery	AP window	Yes
Kutsche et al (15)	1987	1	Right	MPA	No
Lloyd et al (33)	1987	1	Both coronaries	MPA	No
Corno et al (34)	1988	1	Right	AP window	Yes
Brouwer et al (35)	1990	1	Right	MPA	Yes
Chopra et al (36)	1994	1	Left circumflex	MPA	Yes
D'Souza et al (37)	1996	2	Right	MPA	Yes
			Right	AP window	Yes
Gruenfelder et al (38)	1999	1	Right	MPA	Yes
Izumoto et al (39)	1999	1	Right	AP window	Yes
Hew et al (25)	2001	1	Right	MPA	No
McMahon et al (40)	2002	1	Left	RPA	Yes
Bagtharia et al (19)	2004	1	Right	MPA	Unknown
Greenway et al (41)	2006	2	Right	MPA	Yes
			Right	MPA	Yes
Gabbieri et al (42)	2008	1	Right	MPA	Yes
Bockeria et al (43)	2010	1	Right	MPA	Yes
Napoleone et al (44)	2011	2	Right	MPA	Yes
			Right	MPA	Yes
McMahon et al (45)	2013	1	Left	MPA	Yes

AP window, aortopulmonary; *MPA*, main pulmonary artery; *RPA*, right pulmonary artery

What extra-cardiac anomalies are associated with aortopulmonary window?

Extracardiac anomalies may also be present. There have been associations of aortopulmonary window to VATER complex (or VACTERL) which involves the following features: vertebral anomalies, imperforate anus, tracheoesophageal fistula with oesophageal atresia, cardiac anomalies, renal dysplasia, and limb defects. The incidence of this condition in association with aortopulmonary window varies but has been reported between 2 – 10% (15, 19, 22) and 2.3% (1/43) in our patients.

Unlike other conotruncal malformations, aortopulmonary window does not seem to be associated with DiGeorge syndrome and other chromosomal defects involving chromosome 22q11 (12).

What is the epidemiology of an aortopulmonary window?

Aortopulmonary window is a rare congenital cardiac anomaly, accounting for 0.1 – 0.2% of all cardiac malformations; with a male-to-female prevalence of approximately 2:1 (6 – 8, 10 – 25).

What is the pathophysiology of an aortopulmonary window?

Due to the difference in pressure between the pulmonary artery and the ascending aorta, an aortopulmonary window usually results in an unrestricted left-to-right shunt. During the foetal period, however, there is high pulmonary vascular resistance with equal pressures within the aorta and pulmonary artery. Therefore, during this time there is minimal flow across the aortopulmonary window.

Following birth, pulmonary vascular resistance decreases as the newborn starts to breath. This drop in pulmonary arterial resistance increases the left-to-right shunt. The sustained increase in blood flow within the pulmonary circulation may lead to pulmonary hypertension and to significant pulmonary vascular

changes. If not reverted early, the latter may develop into pulmonary vascular obstructive disease. In its turn pulmonary hypertension will lead to increase work for the right ventricle, leading to right ventricular hypertrophy and eventual dysfunction. Similarly, due to the left-to-right shunt, to maintain adequate cardiac output the work of the left ventricle also increases. Over time this leads to left ventricular hypertrophy and eventual dysfunction.

What is the natural history of an aortopulmonary window?

The outcome of an unrepaired aortopulmonary window is poor with approximately 40% mortality within the first year of life that often results from the sequelae of congestive cardiac failure (17). Small defects may not manifest clinically. However, aortopulmonary windows do not close or contract over time, therefore progression of disease is likely (19). Progression of the symptoms and the timing of patient's deterioration depend on the size of the defect (10, 17, 19, 46) and subsequent development of cardiac failure or Eisenmenger's syndrome (48).

What are the symptoms of an aortopulmonary window?

The symptoms of aortopulmonary window depend on the extent of the left-to-right shunt and the degree of cardiac failure. Patients with small aortopulmonary windows and a small left-to-right shunt may have minimal or no symptoms. However, the defect is often large, and patients will typically present within the first weeks of life with symptoms consistent with congestive cardiac failure. These include dyspnoea, diaphoresis, poor feeding and failure to thrive (10, 17, 22). Frequent respiratory infections are common (10, 22).

What are the signs of an aortopulmonary window?

The physical signs again are determined by the size of the defect and the magnitude of the left-to-right shunt. Physical examination usually reveals a

tachypnoeic infant using accessory muscle to facilitate respiratory effort and chest wall retraction. Additionally, cardiac examination may reveal an enlarged heart with a systolic murmur best heard along the left sternal border and a loud S2 may be heard as a result of pulmonary hypertension (10). Cyanosis is usually absent unless there is severe pulmonary vascular disease.

What are the differential diagnoses?

The differential diagnosis of aortopulmonary window includes (46):

- Patent ductus arteriosus
- Ventricular septal defect
- Persistent truncus arteriosus
- Ruptured aneurysm of the sinus of Valsalva

What are the electrocardiographic features of aortopulmonary windows?

There are no specific findings on electrocardiogram (ECG) to suggest aortopulmonary window. ECG findings may vary depending on the extent of disease progression, but generally may demonstrate tachycardia, univentricular or biventricular hypertrophy and/or signs of atrial enlargement.

What are the features of an aortopulmonary window on chest X-ray?

There are no specific findings on chest x-ray which suggest aortopulmonary window. However, patients with aortopulmonary window may demonstrate cardiomegaly, prominent main pulmonary artery as well as increased pulmonary vascular markings due to increased pulmonary blood flow (10).

What are the echocardiographic features of an aortopulmonary window?

Foetal echocardiography has become the principal diagnostic tool for aortopulmonary window (48). However, it is not uncommon for this anomaly to be overlooked in the presence of other malformations or missed entirely. One reason for this is an over-reliance on Doppler imaging which can be ineffective in foetal life as there are relatively equal pressures within the aorta and pulmonary trunk allowing for minimal flow between the two vessels (10, 13, 48, 49). A combination of multiple echocardiographic views including precordial, subcostal and suprasternal can help to confirm the diagnosis and minimise inter-technician errors. Diagnosis of aortopulmonary window relies upon recognition of a deficiency between the adjacent walls of the aorta and pulmonary trunk through cross-sectional imaging of the area (Figure 7).

Other common findings on echocardiography include (48, 49):

- Enlargement of the left and/or right heart chambers
- Increased pulmonary venous return
- Increased flow across the mitral and aortic valves
- Enlarged pulmonary arteries
- Reversal of diastolic flow in the descending aorta
- Prominent pulsatility of the thoracic aorta

The distance between the semi-lunar valves and coronary arteries from the proximal end of the defect should be ascertained, as well as the distance between the branch pulmonary artery and the distal end of the aortopulmonary window.

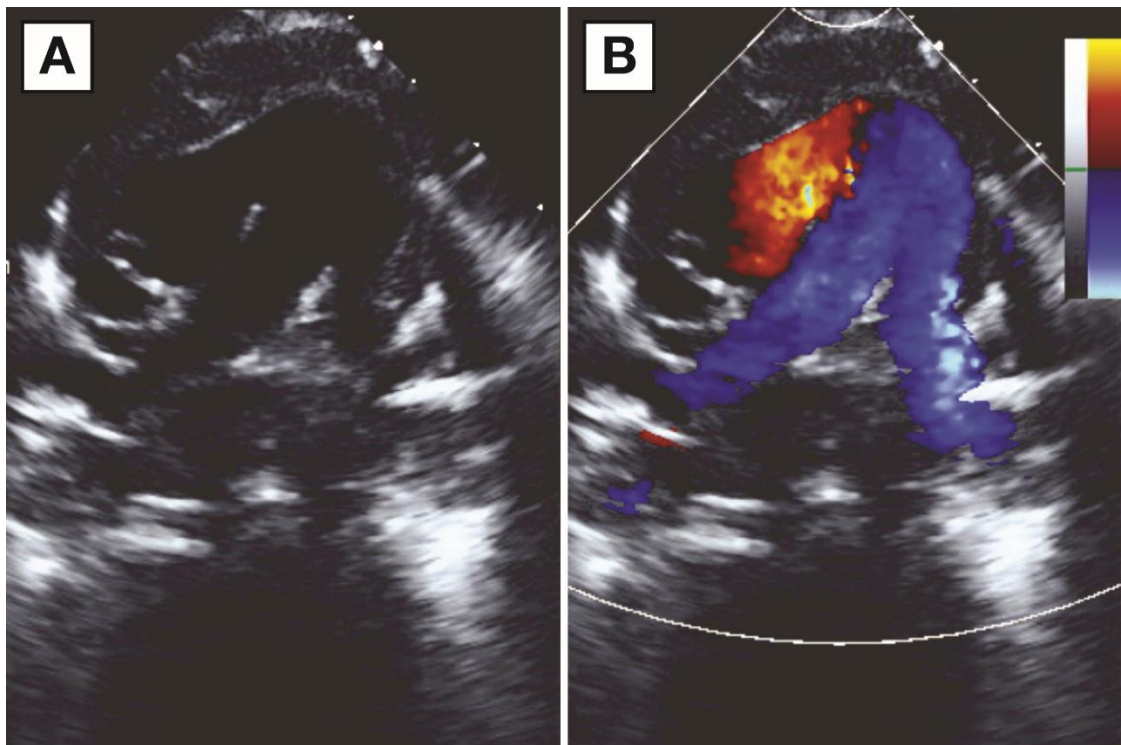


Figure B.1-7. Echocardiogram of 5-month-old child with aortopulmonary window demonstrating communication between ascending aorta and main pulmonary artery with left-to-right shunt.

Are other imaging modalities of value in assessing aortopulmonary window?

Alternative methods for diagnosis include computed tomography (CT) which has a better ability to delineate the great arteries and coronary anatomy than echocardiography (50). This does provide clear delineation of the anatomy in the chest. However, CT scan is not required in diagnosis of aortopulmonary window and usually performed to assess other concomitant anomalies.

Is cardiac catheterisation required in patients with an aortopulmonary window?

Cardiac catheterisation is not often performed in cases of aortopulmonary window. However, in patients older than 6 months, some reports recommended cardiac catheterisation to evaluate the degree of pulmonary hypertension (10,

51). If significant pulmonary hypertension is present, a trial of pulmonary vasodilators can be used to demonstrate reversibility (51). In the past, cardiac catheterisation was performed to confirm diagnoses and further delineate adjacent anatomy. Today, cardiac catheterisation is rarely required.

What are the therapeutic options for a patient with an aortopulmonary window?

Closure of aortopulmonary window is indicated for all patients. For most patients, repair should be undertaken early in infancy when the diagnosis is made to prevent development of heart failure or irreversible pulmonary hypertension.

Patients often present with congestive cardiac failure which may require stabilisation with diuretics, inotropes and other anti-failure medications (10). All efforts are aimed at improving systemic circulation and limiting pulmonary blood flow. Intubation may be used as mechanical ventilation allows for a degree of hypercapnoea, which will increase the pulmonary vascular resistance thereby decreasing the left-to-right shunt and improving systemic circulation (10). Additionally, for patients with a concomitant interrupted aortic arch, prostaglandin infusion may be required to maintain patency of the ductus arteriosus.

These measures should ensure adequate systemic circulation and oxygenation prior to prompt closure of the defect. The defect is nearly always closed by surgical intervention. Rarely, the defect may be closed via a transcatheter approach.

What are the contraindications to closure?

The only contraindication to surgical closure of an aortopulmonary window is demonstrated irreversible pulmonary hypertension.

What are the risk factors for operative mortality?

Surgical repair of simple aortopulmonary window has a very good outcome with mortality rates approaching zero (10). Operative mortality is often due to repair of concomitant anomalies or general poor preoperative state, rather than repair of the aortopulmonary window per se. Interrupted aortic arch has been reported to be an independent risk factor for mortality in patients undergoing repair of aortopulmonary window (18, 19, 25, 26) with mortality rates from 0% to 15% (26). Though, a recent review of 5 patients with aortopulmonary window and interrupted aortic arch from our centre had mortality of 0% (52).

What are the surgical approaches to aortopulmonary window?

Aortopulmonary windows are approached through a median sternotomy and cardiopulmonary bypass with a subsequent incision through the pulmonary trunk, ascending aorta or the aortopulmonary window itself. It seems logical to open aorta first and properly assess the location of the aortopulmonary window and coronary orifices. If only one coronary orifice is found, then inspection of the pulmonary artery is performed either via the aortopulmonary window or a separate incision.

What structures are at risk during repair?

The most important structures at risk during repair of aortopulmonary window are the coronary arteries – particularly for proximal aortopulmonary defects (**Figure B.1-8**). Anomalous coronary artery arising from the pulmonary artery in association with aortopulmonary window often does not pose a problem pre-operatively due to the pulmonary pressures being high enough to allow adequate perfusion (43). Post-operatively, if the coronary artery remains on the pulmonary side of repair, sudden decreases in perfusion pressure may lead to myocardial ischaemia (44). Additionally, normal coronary arteries may also be at risk from direct suturing of proximal defects if tension from suturing disrupts the course of the coronary arteries.

Further structures at risk during repair of aortopulmonary windows include the pulmonary and aortic valve leaflets as well as the right and left pulmonary arteries. Other structures at risk are dependent on the concomitant malformations undergoing single-staged repair. For example, patients undergoing concurrent aortic arch repair are at risk of damage to the thoracic duct, phrenic nerve or the recurrent laryngeal nerve.

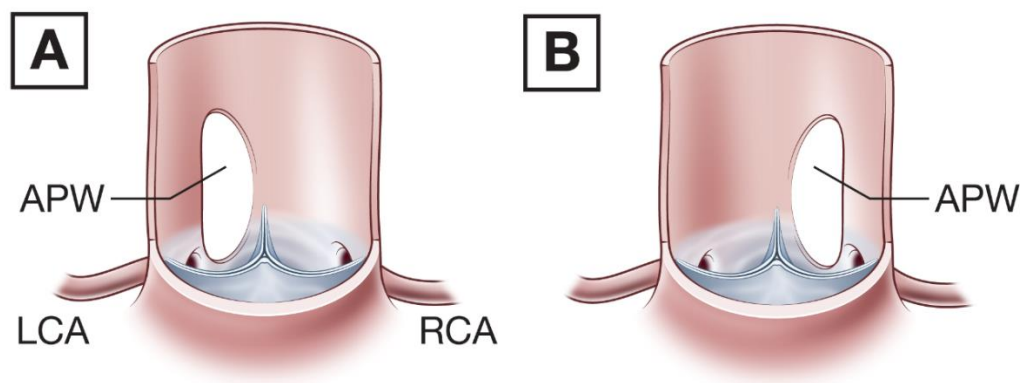


Figure 10. Proximity of coronary orifice to aortopulmonary window. Aortopulmonary window in close proximity to either left (A) or right (B) coronary artery orifice must be identified prior to closure of the window to ensure that the coronary blood flow is not compromised following the repair. *APW*, aortopulmonary window; *LCA*, left coronary artery; *RCA*, right coronary artery.

What are the principles of surgery of an aortopulmonary window?

In general, division of the aortopulmonary window and subsequent closure of the aorta and pulmonary artery is performed. Defects in the aorta and pulmonary artery are closed either by directly suturing the defect, or by patch repair when appropriate. Recent studies have shown little to no mortality with transaortic patch closure of the aortopulmonary window (11). In patients with concurrent cardiovascular anomalies, single-stage repair of all defects should be performed as this has been shown to reduce overall mortality (10, 11, 14, 26).

Closure of the defect is performed via median sternotomy with cardiopulmonary bypass. In preparation, an aortic cannula should be inserted as distally as possible from the defect in the ascending aorta so that cross-clamping of the aorta does not interfere with repair. The pulmonary arteries are occluded with tourniquets and occluded when cardiopulmonary bypass commences. Cardioplegic solution is infused while the pulmonary arteries are snared, and the procedure performed under mild hypothermia. The defect can be repaired via an incision through the window itself, through the aorta, or through the pulmonary artery. Most importantly, whatever approach is undertaken, it must provide good visualisation and assessment of the origin of both coronary arteries and the right pulmonary artery. We believe that ligation of aortopulmonary window is obsolete and should not be performed.

The defects in the aorta and pulmonary artery are closed with a patch or directly to ensure that the closure do not compromise coronary arteries or semilunar valves.

If the coronary artery originates from the pulmonary artery or aortopulmonary window, repair should include the coronary artery on the aortic side of repair. If this is via patch repair, placement should be such that the coronary artery is included on the aortic side of the patch, provided that the patch would not obstruct pulmonary blood flow. Alternatively, the coronary artery can be re-implanted directly to aorta (**Figure B.1-9**).

What are the principles of device closure?

In rare selected patients, the aortopulmonary window can be closed using a trans-catheter approach (53 – 58). The procedure is limited by a number of factors that include the large size of the defect, the small size of the femoral vessels for access, associated cardiovascular anomalies and the fact that the coronary anatomy may be difficult to appreciate prior to closure based solely on echocardiography (53 – 58).

In a few carefully selected patients, the aortopulmonary windows has been successfully using double umbrella occluder system, button device closure or

Amplatzer device closure (53 – 58). Echocardiography was used in all of these patients to size the defects prior to intervention. The defects mostly ranged in size between 3 – 6mm in diameter (53 – 58), while one particularly large window of 8.7mm (58). Though these defects were successfully closed with no residual leaks, there was limited follow-up beyond 12 months.

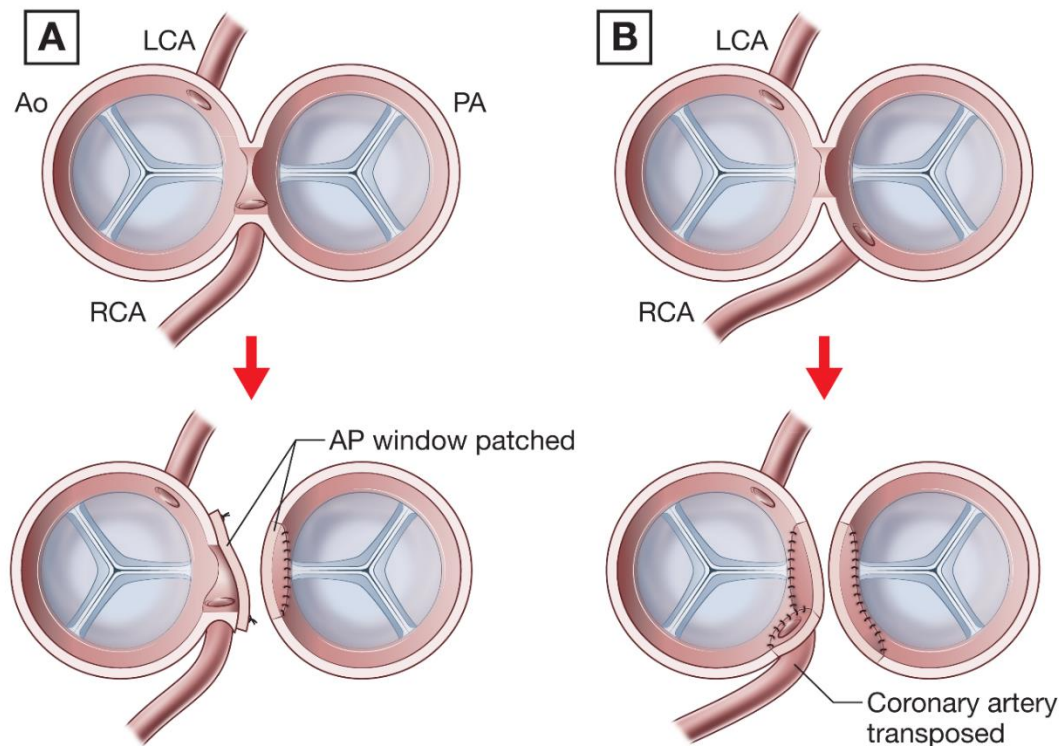


Figure B.1-9. Surgical correction of the anomalous origin of the coronary artery from aortopulmonary window (A) or pulmonary artery (B). The patched on the aorta is fashioned to ensure unobstructed blood flow into the coronary artery. *Ao*, aorta; *AP window*, aortopulmonary window; *LCA*, left coronary artery; *PA*, pulmonary artery; *RCA*, right coronary artery.

What are the complications of surgery following repair of an aortopulmonary window?

Specific complications following surgical repair of aortopulmonary window are mostly centred on a residual defect following repair or disruption of normal coronary blood flow. Residual lesions may cause a similar picture to first

presentation in which symptoms of pulmonary hypertension and congestive cardiac failure are prominent. Management for such situations after identification of the residual lesion often prompts early reintervention for these patients.

If there is distortion to the coronary arteries, either due to tension imposed by local suturing or due to its misplacement on the pulmonary side of the patch, the patient may undergo myocardial ischaemia. This can be life threatening. Thus, the importance of the intra-operative visualization of the coronary anatomy cannot be over-emphasised.

Additionally, direct suturing of the defect in the aorta or pulmonary artery may lead to aortic or pulmonary artery stenosis, respectively. Long term follow up of patients is required to monitor for development of branch pulmonary artery stenosis (10).

What are the long-term outcomes of surgery?

Currently, a number of studies report no early or late deaths, if intervention were to take place in infancy and with isolated aortopulmonary window repair (10 – 14, 16, 17, 19, 20, 22).

Mortality of approximately 10 – 15% was reported (10 – 25) for patients with concomitant cardiovascular anomalies, particularly, interrupted aortic arch, which increased mortality to 15% (26).

Over time, mortality after repair of aortopulmonary window and concomitant cardiovascular anomalies has decreased. Prior to 2000 the average mortality was approximately 14% with a range of 0 – 54% (11, 13, 15, 17 – 19, 21, 23 – 25), while after 2000 average mortality decreased to approximately 8% with range of 0 – 20% (10 – 12, 16, 22). Earlier studies demonstrated higher mortality rates – some as high as 54% (15) – mainly due to interventions taking place later in infancy and, thus, often in patients with irreversible pulmonary hypertension or congestive cardiac failure (15, 18).

Late mortality is generally excellent with most studies reporting no late deaths after median follow-up of 2 to 11 years (11 – 14, 16 – 23). Isolated reports

of late mortality have occurred in the setting of persistent pulmonary hypertension (11, 19). Patients with concomitant interrupted aortic arch have increased long term mortality with survival of 91%, 86% and 84% at 1, 5, and 10 years respectively (26). Interestingly, review of patients with aortopulmonary window and concomitant interrupted aortic arch at our centre yielded no late deaths (52).

A number of studies reported no reinterventions for simple aortopulmonary window after a median follow-up of up to 7 years with range of 3 months to 25 years (11, 13, 14, 16 – 20, 22).

Patients with concomitant cardiovascular anomalies have higher rates of reintervention between 15 – 20%, when compared to simple aortopulmonary window (12, 14, 17, 18, 25, 26). Often these are for aortic arch reinterventions following concurrent repair of an interrupted aortic arch. About 57% of patients with concurrent interrupted aortic arch may require reintervention at 5 years (26). Of these, 51% required aortic arch reintervention, 6% had pulmonary artery reintervention, and only 43% were alive without any reintervention (26). Experience at our centre with these patients has required only 1 reintervention from 5 patients after follow-up of 3 to 24 years (52).

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Appendix C: Additional manuscripts co-authored during candidature

C.1 Konstantinov IE, et al. J Thorac Cardiovasc Surg. 2020; In Press

Konstantinov, Naimo, Buratto

Commentary

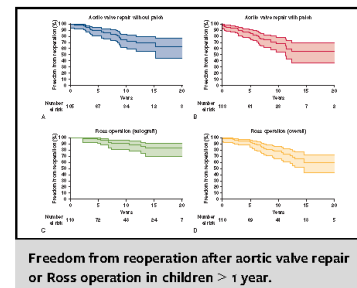
See Article page XXX.

Commentary: Ozaki valve reconstruction in children: Is it still a valve replacement?

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 Phillip S. Naimo, MD,^{a,b,c} and
 Edward Buratto, MBBS, PhD^{a,b,c}

An interesting article in the current issue of the *Journal* by Baird and colleagues¹ describes their short-term results with aortic valve reconstruction with neocuspidization (Ozaki technique) in children and young adults. They reported freedom from moderate or greater aortic valve regurgitation of 88% at 2 years, freedom from moderate or greater aortic stenosis of 88% at 2 years, and freedom from reoperation of 91% at 1.5 years, although the number of patients at each time point is unknown. There were no operative deaths and 2 late deaths after discharge. It seems important to emphasize a few points to put this fascinating article into a proper perspective. Because it is always difficult to speculate on whether others would or would not be willing to apply the Ozaki technique to children and young adults, we choose to view the results of Ozaki technique in these patients through the prism of objectivity reflecting on our current practice in Melbourne.

First, it should be noted that all but 1 of their 57 patients were aged more than 1 year. It also should be emphasized that children aged more than 1 year are naturally selected to have an aortic valve morphology best suited for repair. In Melbourne, we aim to repair the aortic valve as our first priority. In children aged more than 1 year, freedom from aortic valve reoperation is 90% at 5 years and 74% at 10 years when the valve is of sufficient quality to be repaired without any patch material (Figure 1, A). In children aged more than 1 year, freedom from aortic valve



CENTRAL MESSAGE

It is unknown whether the Ozaki technique for aortic valve reconstruction in children and young adults will provide outcomes similar to those of aortic valve repair or the Ross operation.

reoperation is 85% at 5 years and 68% at 10 years, when the valve had to be repaired with patch material (Figure 1, B). Additionally, operative mortality for aortic valve repair combined (with and without a patch) was 0.4% (1/238). When the valve is deemed not repairable, in children aged more than 1 year, we perform the Ross operation with a freedom from autograft reoperation of 98% at 5 years and 91% at 10 years (Figure 1, C), and freedom from all reoperations of 92% at 5 years and 78% at 10 years (Figure 1, D), notably, with 0% operative mortality. Thus, would we be inclined to use the Ozaki reconstruction in all our patients aged more than 1 year? Not yet. At this point in time, it is difficult to imagine that the Ozaki reconstruction would provide better results in a *growing* child.

Second, 16% (9/57) were young adults and 30% (17/57) were adolescents aged 13 to 17 years. With 26% (15/57) of patients weighing more than 60 kg, the outcomes in approximately one-quarter of their patients would be expected to be similar to the results achieved in adults and reported by Ozaki and colleagues.^{2,3} Ozaki and colleagues² recently reported their midterm results in 850 patients who underwent Ozaki aortic valve reconstruction with a mean follow-up time of 53 months. With 15 patients reaching 9 years of follow-up, Ozaki and colleagues² reported an overall survival of 85%, a cumulative incidence of reoperation of 4.2%, and a cumulative incidence of moderate or greater aortic regurgitation of 7.3%. Likewise,

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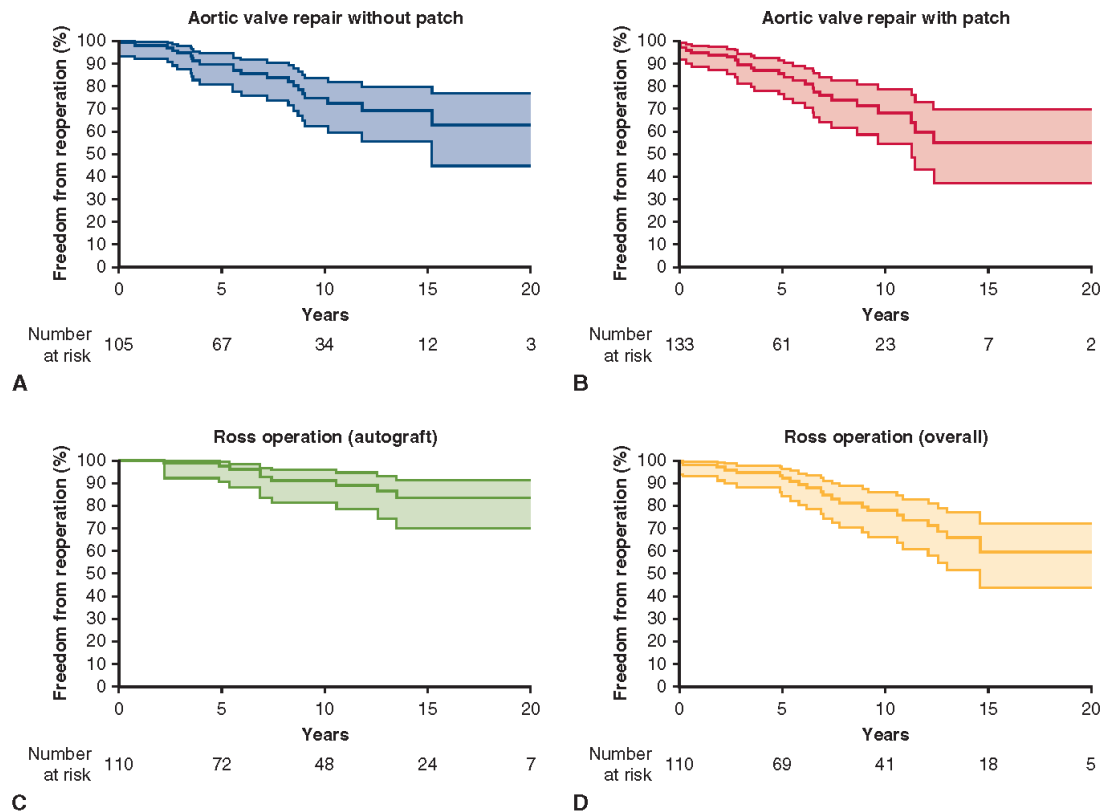


FIGURE 1. Freedom from reoperation after aortic valve repair or Ross operation performed in children aged more than 1 year at The Royal Children's Hospital in Melbourne. A, Freedom from aortic valve reoperation after aortic valve repair without the use of a patch. B, Freedom from aortic valve reoperation after aortic valve repair with a patch. C, Freedom from autograft reoperation after Ross operation. D, Overall freedom from reoperation after Ross operation (autograft and homograft). Shaded area represents 95% confidence interval.

Wiggins and colleagues⁴ used the Ozaki reconstruction in 58 young adults and children with aortic valve disease with a median age of 14.8 years and median follow-up of 14 months. They reported 1 late death.⁴ One-quarter of their patients had greater than moderate aortic regurgitation, and 12% of patients required aortic valve reoperation at 3 years.⁴ Thus, would we be inclined to use Ozaki reconstruction in *fully grown* adolescents and young adults? No, definitely not at this stage. It would be prudent to await longer-term outcomes, particularly because it must be remembered that the long-term outcomes of the Ross operation in adults are superb.^{5,6} In Melbourne, survival after the Ross operation in 392 adults was 98% at 10 years and 95% at 20 years,⁵ and the freedom from autograft reoperation was 96% at 18 years.⁶

Third, 7% (4/57) of their patients had truncus arteriosus and 3.5% (2/57) had quadricuspid valve. Clearly, the Ross operation is not feasible in patients with truncus arteriosus.

The durability of the truncal valve repair has been poor.⁵ We have previously shown that most patients with moderate or greater truncal valve insufficiency and a quadricuspid valve are likely to require truncal valve surgery.⁷⁻⁹ However, often the diameter of the truncal valve annulus is large, which provides an excellent substrate for tricuspidization of the truncal valve and reduction of the annulus.^{7,8} We have recently reported freedom from truncal valve reoperation of 64% at 10 years after tricuspidization of the quadricuspid truncal valve.¹⁰ In fact, freedom from truncal valve reoperation after tricuspidization was superior to truncal valve replacement in children aged less than 6 years, in whom an adult-sized mechanical prosthesis may not be feasible.^{8,10} Thus, would we be inclined to use Ozaki reconstruction in children who require truncal valve repair? Perhaps we would, provided that the long-term results of Ozaki reconstruction in children with truncus arteriosus will be better than those after truncal valve replacement.

Finally, bovine pericardium was used in 65% (37/57), and autologous pericardium treated with glutaraldehyde was used in 35% (20/57). Thus, the Ozaki reconstruction is still a valve replacement, although with autologous tissue in some patients, with no growth capacity. Therefore, one would not expect that Ozaki valve replacement would give better results compared with other biological tissue valve replacements in a growing child.

We must remain pragmatic when approaching the aortic or truncal valve repair. It is fascinating and somewhat bewildering to think that autologous tissue with the ability to regenerate may become available in the future.¹¹ If Ozaki valve replacement could be modified using autologous tissue with preserved growth capacity and preserved regenerative ability to ensure resistance to calcification, it may prove to be an extremely valuable technique in selected patients. Until then, it will remain a valve replacement with the expected outcomes similar to those of biological prostheses or homografts.

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C.2 Donald JS, et al. Ann Thorac Surg. 2020;109:1251-9

ORIGINAL ARTICLES: CONGENITAL HEART SURGERY



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Ross Operation in Children: 23-Year Experience From a Single Institution



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Background. Data on the long-term outcomes in children after the Ross operation are limited. This study aimed to assess the long-term outcomes in children who underwent the Ross operation at a single institution.

Methods. The study reviewed all children ($n = 140$) who underwent the Ross operation at the Royal Children's Hospital in Melbourne, Australia between 1995 and 2018.

Results. Mean follow-up time was 8.9 years. Median age at operation was 7.4 years. The root replacement ($n = 120$, Ross-Konno; $n = 38$), root inclusion ($n = 17$), and subcoronary implantation ($n = 3$) techniques were used. Operative mortality was 5.0% (7 of 140; 3 neonates and 4 infants). There were 6 late deaths. Overall survival at 10 years was 96.2% in children older than 1 year of age and 78.9% in children younger than 1 year of age at operation ($P = .003$). Freedom from autograft reoperation was 86.0% at 10 years. Age younger than 1-year at operation was a risk factor for autograft reoperation ($P = .02$). Patients younger than 1 year of age at operation experienced

a higher incidence of moderate or greater aortic insufficiency compared with patients who were older than 1 year of age ($P = .006$). In patients who had a poly-(p-dioxanone)-filament band placed around the sinotubular junction, freedom from moderate or greater aortic insufficiency at 10 years was 100%, compared with 83.1% in patients with no band ($P = .09$).

Conclusions. In children older than 1 year of age, the Ross operation has excellent outcomes with no operative mortality and a low incidence of aortic insufficiency. In children younger than 1 year of age, the Ross operation is associated with higher operative mortality and a higher incidence of aortic insufficiency. Where possible, the Ross operation should be delayed beyond infancy. Poly-(p-dioxanone)-filament banding may reduce the incidence of aortic insufficiency after the Ross operation.

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Congenital aortic stenosis is an often lifelong condition accounting for approximately 6% of congenital heart disease.¹ It frequently necessitates repeated intervention and, in severe cases, aortic valve (AV) replacement. Replacement of the AV with a pulmonary autograft (the Ross operation) was first described in 1967.² The Ross operation has proved to be a robust AV replacement option in children; however, high operative mortality in young children, progressive dilatation of the neo-aortic root leading to aortic insufficiency (AI), and reoperation on the left ventricular outflow tract (LVOT) and right ventricular outflow tract (RVOT) remain key concerns.³⁻⁵ At our center, prevention of neo-aortic root dilatation was attempted through reinforcement of the autograft by using a poly-

(p-dioxanone)-filament (PDS) band. Here we describe the long-term results of the Ross operation in children.

Patients and Methods

Patients

This study was approved by the Human Research Ethics Committee at the Royal Children's Hospital in Melbourne, Australia. All patients who underwent the Ross operation at the Royal Children's Hospital between 1995 and 2018 were included in this study. Medical records were retrospectively reviewed until last cardiology follow-up.

Definitions

Early mortality was defined as death occurring within 30 days of the Ross operation or before hospital discharge. All other deaths were considered late.

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Abbreviations and Acronyms

AI	= aortic insufficiency
AV	= aortic valve
BAV	= balloon aortic valvotomy
CI	= confidence interval
HR	= hazard ratio
IQR	= interquartile range
LVOT	= left ventricular outflow tract
MV	= mitral valve
PDS	= poly-(p-dioxanone)-filament
RVOT	= right ventricular outflow tract
RV-PA	= right ventricle-to-pulmonary artery
ST	= sinotubular

Operative Techniques

All patients underwent surgery through a median sternotomy with standard cardiopulmonary bypass. The median cardiopulmonary bypass time was 216 minutes (interquartile range [IQR], 180 to 269 minutes), and the median aortic cross-clamp time was 157 minutes (IQR, 131 to 189 minutes). Circulatory arrest was used for 1 patient for 12 minutes. The root replacement (n = 120, Ross-Konno; n = 38), root inclusion (n = 17), and sub-coronary implantation (n = 3) techniques were used. The Ross-Konno operation was performed if widening of the LVOT was required. Right ventricle-to-pulmonary artery (RV-PA) continuity was established using a homograft (pulmonary, n = 75; aortic, n = 20), a Contegra conduit (n = 41) (Medtronic, Minneapolis, MN), or a Freestyle conduit (n = 4) (Medtronic). The median conduit size was 20 mm (IQR, 17 to 22 mm). A total of 26 patients had an absorbable PDS band applied to the sinotubular (ST)-junction with the aim of preventing aortic root dilatation and progressive AI. In these cases, the ST junction was banded to the same diameter as the aortic annulus. PDS band application was at the operating surgeon's discretion and was not randomized.

Data Analysis

Data were analyzed using Stata software version 13 (StataCorp, College Station, TX). Descriptive statistics for continuous data are expressed as means $\pm$ SDs (range), whereas skewed continuous data are expressed as medians (IQR). Categorical data are summarized as frequencies and percentages. Kaplan-Meier actuarial survival curves were used to analyze and plot time-related end points. Univariable and multivariable logistic regression and Cox proportional hazard modeling were used to determine risk factors for mortality and reoperation. The log-rank test was used to compare survivor functions. Statistical significance was set at $P < .05$.

Results**Patient Characteristics**

Patient characteristics, AV morphology, and concomitant cardiovascular anomalies are described in Table 1. A total of 92 patients (66%; 92 of 140) underwent 108 interventions

Table 1. Aortic Valve Morphology and Concomitant Anomalies of Children Undergoing the Ross Operation

Variable	Value
Sex	
Male	66.4 (93/140)
Female	33.6 (47/140)
Median age	7.4 y (IQR, 1.6–13.4 y)
Median weight	23.6 kg (IQR, 11.6–48.5 kg)
Age group	
Neonate	3.6 (5/140)
Infant	17.9 (25/140)
Child	78.5 (110/140)
Aortic valve morphology	
Tricuspid	48.6 (68/140)
Bicuspid	47.1 (66/140)
Unicuspid	4.3 (6/140)
Concomitant anomalies	
Coarctation of the aorta	12.1 (17/140)
Ventricular septal defect	7.9 (11/140)
Interrupted aortic arch	2.9 (4/140)
Endocardial fibroelastosis	2.1 (3/140)
Transposition of the great arteries	1.4 (2/140)
Rheumatic heart disease	1.4 (2/140)
Atrial septal defect	0.7 (1/140)

Values are % (n/N) unless otherwise indicated.

IQR, interquartile range.

on their AV before the Ross operation, including balloon aortic valvotomy (BAV) (28.6%; 40 of 140) and AV repair (48.6%; 68 of 140). A total of 16 patients underwent both BAV and AV repair (11.4%; 16 of 140). The median time between BAV and the Ross operation was 3.9 years (IQR, 0.6 to 7.7 years). There was no significant difference in age at Ross operation between children who underwent previous BAV and those who did not ($P = .53$). The median time between AV repair and the Ross operation was 4.4 years (IQR, 0.9 to 9.7 years). There was no significant difference in age at Ross operation between children who underwent previous AV repair and those who did not ($P = .11$). Previous intervention on the AV did not affect mortality or reoperation after the Ross operation. Previous interventions for concomitant anomalies were aortic arch repair in 24 patients (17.1%; 24 of 140), ventricular septal defect closure in 10 patients (7.1%; 10 of 140), and the arterial switch operation in 2 patients (1.4%; 2 of 140).

Indications for the Ross operation were aortic stenosis (27.9%; 39 of 140), AI (19%; 27 of 140), combined aortic stenosis and AI (44%; 63 of 140), and endocarditis (7.9%; 11 of 140).

Concomitant procedures were performed in 30 patients, including 1 or more of the following: mitral valve (MV) repair (n = 10), subaortic membrane resection (n = 6), aortic arch repair (n = 6), patent ductus arteriosus ligation (n = 2), MV replacement (n = 2), patent foramen ovale closure (n = 2), ventricular septal defect closure (n = 1), left atrial aneurysm repair (n = 1), septal myectomy (n = 1), atrial septal defect closure (n = 1) resection

of endocardial fibroelastosis ($n = 1$), and resection of paravalvular abscess ($n = 1$).

Mean follow-up was 8.9 ± 6.7 years (range, 1 week to 22 years). Among patients surviving hospital discharge, 119 (90%; 119 of 133) had at least 1 year of follow-up. Of the surviving patients, 124 were followed up within the last 5 years (98%; 124 of 127).

Mortality

The causes of death are summarized in Table 2. Early mortality was 5.0% (7 of 140), with 3 deaths occurring in neonates (60%; 3 of 5) and 4 deaths occurring in infants (16%; 4 of 25). There were 6 late deaths, which all occurred in children older than 1 year of age at surgery. Overall survival was $93.7 \pm 0.1\%$ (95% confidence interval [CI], 87.7 to 96.8) at 5 years, $92.5 \pm 0.1\%$ (95% CI, 86.0 to 96.1) at 10 years, and $86.6 \pm 0.1\%$ (95% CI, 76.3 to 92.7) at 15 years (Figure 1A). Of the 30 patients younger than 1 year of age at surgery, early mortality was 23.3% (7 of 30). Overall survival in children younger than 1 year of age at surgery was $78.9 \pm 0.1\%$ (95% CI, 58.9 to 89.9) at 10 years compared with $96.2 \pm 0.1\%$ (95% CI, 88.8 to 98.8) in children older than 1 year of age ($P = .003$) (Figure 1B). Risk factors for early mortality identified on univariable analysis included the Ross-Konno operation ($P = .02$; odds ratio [OR], 7.6; 95% CI, 1.4 to 40.9), and concomitant MV repair ($P = .005$; OR, 10.3; 95% CI, 2.0 to 53.4). Risk factors for late mortality identified on univariable analysis included concomitant MV repair ($P = .01$; HR, 9.5; 95% CI, 1.7 to 52.1). The small number of deaths prevented a multivariable analysis.

Reoperation

A total of 39 patients required reoperation. Freedom from any reoperation was $82.6 \pm 0.1\%$ (95% CI, 73.9 to 88.6) at 5 years, $66.6 \pm 0.1\%$ (95% CI, 55.5 to 75.6) at 10 years, and $48.6 \pm 0.1\%$ (95% CI, 34.9 to 60.9) at 15 years.

Autograft reoperation was required in 14 patients (10.5%; 14 of 133). A total of 11 patients underwent autograft reoperation because of neo-aortic root dilatation and moderate or greater AI. Other indications for autograft reoperation included the following: 1 patient with neo-aortic dilatation, mild AI, and global systolic dysfunction; 1 patient with stenosis of the ascending aorta; and 1 patient with subaortic stenosis. Mean time to autograft reoperation was 7.5 ± 3.3 years (range, 2.2 to 13.5 years). Freedom from autograft reoperation was $95.9 \pm 0.1\%$ (95% CI, 89.4 to 98.4) at 5 years, $86.0 \pm 0.1\%$ (95% CI, 75.9 to 92.1) at 10 years, and $79.5 \pm 0.1\%$ (95% CI, 66.9 to 87.7) at 15 years (Figure 2A).

Risk factors for autograft reoperation identified on univariable analysis were age younger than 1 year at time of surgery ($P = .02$; HR, 3.7; 95% CI, 1.2 to 11.1) and autograft size ($P = .009$; HR, 0.8; 95% CI, 0.7 to 1.0). The small number of autograft reoperations prevented a multivariable analysis. Freedom from autograft reoperation was significantly lower ($P = .03$) in those ($n = 23$) children, who underwent Ross operations as neonates or infants, compared with older children ($n = 110$). Namely, freedom from autograft reoperation was $84.4 \pm 0.1\%$ (95% CI, 50.4 to 95.9) at 5 years and $61.6 \pm 0.2\%$ (95% CI, 25.5 to

84.2) at 10 and 15 years for neonates and infants and $97.6 \pm 0.02\%$ (95% CI, 90.7 to 99.4) at 5 years, $89.7 \pm 0.04\%$ (95% CI, 79.4 to 95.0) at 10 years, and $82.5 \pm 0.05\%$ (95% CI, 69.1 to 90.5) at 15 years for older children.

Replacement of the RV-PA conduit was required in 32 patients (24.1%; 32 of 133). Freedom from RVOT reoperation was $87.7 \pm 0.1\%$ (95% CI, 79.7 to 92.7) at 5 years, $74 \pm 0.1\%$ (95% CI, 63.1 to 82.2) at 10 years, and $54.5 \pm 0.1\%$ (95% CI, 40.4 to 66.6) at 15 years (Figure 2B). The risk factor for RVOT reoperation on univariable analysis was age younger than 1 year at time of surgery ($P < .001$; HR, 4.9; 95% CI, 2.4 to 10.1). Risk factors for RVOT reoperation identified on multivariable analysis were homograft size ($P < .001$; HR, 0.7; 95% CI, 0.7 to 0.8) and postoperative endocarditis ($P < .001$; HR, 11.0; 95% CI, 3.0 to 39.9).

Aortic Insufficiency

In 16 patients (12.0%; 16 of 133) moderate or greater AI developed after the Ross operation. Freedom from moderate or greater AI was $91.5 \pm 0.1\%$ (95% CI, 84.2 to 95.5) at 5 years, $85.8 \pm 0.1\%$ (95% CI, 76.5 to 91.7) at 10 years, and $83.4 \pm 0.1\%$ (95% CI, 72.6 to 90.2) at 15 years. There were 6 (26.1%; 6 of 23) patients in whom moderate or greater AI developed and who were younger than 1 year of age at surgery, and 10 (9.1%; 10 of 110) patients who were older than 1 year of age ($P = .02$). Freedom from moderate or greater AI in patients younger than 1 year of age at surgery was $53.2 \pm 0.2\%$ (95% CI, 22.2 to 76.8) at 10 years, compared with $91.7 \pm 0.1\%$ (95% CI, 83.3 to 96.1) in patients older than 1 year of age at surgery ($P = .006$) (Figure 3). On univariable analysis, age younger than 1 year at the time of the Ross operation was a risk factor for moderate or greater AI ($P = .01$; HR, 3.8; 95% CI, 1.4 to 10.6). The small incidence of AI prevented a multivariable analysis. A total of 11 patients with AI after the Ross operation underwent autograft reoperation. Of these patients, 7 had no AI or trivial AI, and 2 patients had mild AI at last follow-up. One patient died of cardiogenic shock secondary to a thrombosed mechanical AV. One patient died after attempted autograft replacement, RV-PA conduit replacement, and tricuspid valve annuloplasty in the context of severe heart failure. At last follow-up, there was no AI or trivial AI in 88 patients (69.3%; 88 of 127), mild AI in 35 patients (27.6%; 35 of 127), and moderate or severe AI in 4 patients (3.1%; 4 of 127).

A total of 26 patients had a PDS band applied to the ST junction with the aim of preventing aortic root dilatation and progressive AI. Freedom from moderate or greater AI in patients with PDS banding was 100% at 5 and 10 years, compared with $89.8 \pm 0.1\%$ (95% CI, 81.3 to 94.6) at 5 years and $83.3 \pm 0.1\%$ (95% CI, 72.3 to 90.0) at 10 years in patients with no PDS band ($P = .09$) (Figure 4).

Comment

The Ross operation has proved to be an excellent long-term intervention for AV disease in adults,⁶ and it is now extensively used in the pediatric population. Here we report a 23-year experience at a single institution using the Ross operation in children.

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Table 2. Description of Deaths After the Ross Operation

Age	Year of Operation	Weight, kg	Cardiac Comorbidities	Previous Interventions	Concomitant Operation	Death (y)	Cause of Death
19 d	2001	2.5	VSD Aortic arch hypoplasia	Nil	Aortic arch repair VSD closure PDA division ASD closure	Early	Failure to wean off bypass; ECMO declined
16 d	2003	3.6	Mitral regurgitation Endocardial fibroelastosis	Surgical aortic valvotomy	MV repair	Early	Sepsis and multiorgan failure
1 y	2003	11	Endocarditis Aortic root abscess Preoperative cardiac arrest	Nil	Nil	Early	Cardiac arrest, origin unclear
1 mo	2008	2.7	Trisomy 21 Endocarditis Aortic root abscess	Nil	Reconstruction of fibrous skeleton of heart	Early	Sepsis and multiorgan failure
4 mo	2010	4.4	Shone complex	MV repair AV repair Supraaortic stenosis repair Hypoplastic aortic arch repair	Nil	Early	Low cardiac output after chest closure after multiple reoperations
4 d	2010	3.3	Endocardial fibroelastosis	Surgical aortic valvotomy LVAD ECMO	Aortic arch repair Resection of fibroelastosis	Early	Failure to wean off ECMO and stroke; decision to withdraw treatment
3 mo	2014	3.3	Shone complex	Coarctation repair PDA ligation	MV replacement	Early	Sepsis
5 y	1996	14	Endocarditis	Resection of subaortic stenosis Surgical aortic valvotomy	Nil	Late (2002)	Accidental traumatic injury
11 y	1996	38	Shone complex	Coarctation repair BAV LVOT reconstruction Resection of subaortic stenosis	Aortic arch repair	Late (2007)	Stroke at reoperation on stenotic aortic arch and RV-PA conduit replacement
3 y	1997	14	Endocardial fibroelastosis	BAV	Nil	Late (2011)	Cardiac failure, with total artificial heart replacement after RV-PA conduit and aortic root replacement
17 y	2003	56	Rheumatic heart disease	MV repair	MV repair	Late (2007)	Thrombosed mechanical AV
18 y	2003	61	Nil	BAV	Nil	Late (2016)	Severe AI, left and right ventricular dysfunction, cardiac arrest from arrhythmia
12 y	2004	38	Rheumatic heart disease	MV repair	MV repair	Late (2006)	Unknown origin

AI, aortic insufficiency; ASD, atrial septal defect; AV, aortic valve; BAV, balloon aortic valvotomy; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; LVOT, left ventricular outflow tract; MV, mitral valve; PDA, patent ductus arteriosus; RV-PA, right ventricle-to-pulmonary artery; VSD, ventricular septal defect.

Mortality

In this study, we observed an early mortality of 5% (7 of 140), but all early death occurred in children younger than 1 year of age. Early mortality in patients younger than 1 year of age was 23.3% (7 of 30). High rates of early

mortality in neonates and infants are commonly reported (Table 3).^{5,12-14} Brancaccio and colleagues¹⁴ reported on 55 patients from 1993 to 2012 with an early mortality rate of 13% (7 of 55), with most deaths (86%; 6 of 7) occurring in children younger than 1 year of age. Mookhoek and

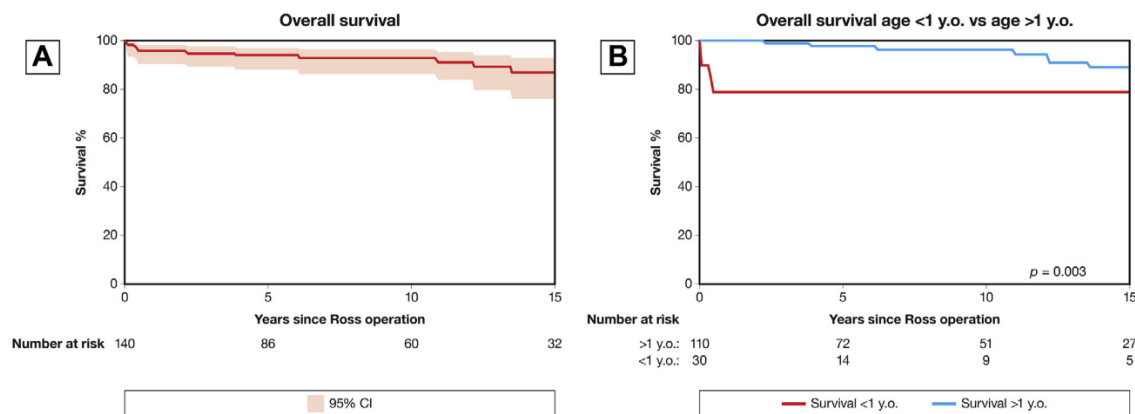


Figure 1. Survival after the Ross operation. (A) Overall survival curve after the Ross operation. (B) Survival curve comparing children younger than 1 year of age vs older than 1 year of age at surgery. (CI, confidence interval.)

colleagues¹³ reported on 76 infants from 1990 to 2013 with an early mortality rate of 17.1% (13 of 76). A systematic review and meta-analysis conducted by Etnel and colleagues⁴ in 2018 reported an early mortality range of 0.9% to 15.6% across 24 pediatric studies from 2000 to 2017, with a pooled early mortality rate of 4.2%, consistent with our result. In an earlier analysis involving only neonatal and infant studies, Etnel and colleagues²¹ reported a pooled early mortality of 16.9%, a much higher rate when compared with the entire pediatric age range. We believe that most AVs in neonates and infants are repairable. Although such neonatal AV repair may not be durable in the long term, it buys some time to allow somatic growth. Thus, our approach to patients younger than 1 year of age consists of undertaking AV repair and postponing the Ross operation. Since 1995, the number of patch and nonpatch AV repairs performed at the Royal Children's Hospital has increased over time (Figure 5), and we reserve the Ross operation for patients unsuitable for AV repair. Thus, only patients unsuitable for AV repair, or

those in whom previous AV repair failed, underwent the Ross operation in infancy. This may explain higher mortality for infants undergoing the Ross operation at our institution. Ideally, the Ross operation should be performed in late adolescence or adulthood when the aortic root can be stabilized with excellent results.²²

In this study, we had 6 late deaths and a 10-year survival of 92.5%, which are consistent with results of previous studies.^{16,17} Of the late deaths, 2 were caused by complications after reoperation, 1 was a result of cardiac arrest in the context of cardiac failure, 1 was a result of inadequate anticoagulation after mechanical valve replacement, 1 was of unknown cause, and 1 was a result of accidental trauma. Among long-term pediatric studies, rates of late mortality after the Ross operation range from 0% to 7.4% (Table 3).^{5,8,12,15-17} Etnel and colleagues⁴ reported a pooled late mortality rate of 0.64% per year across the entire pediatric age range and a rate of 0.76% per year in the infant and neonatal group. In our study, overall survival of children older than 1 year of age at the

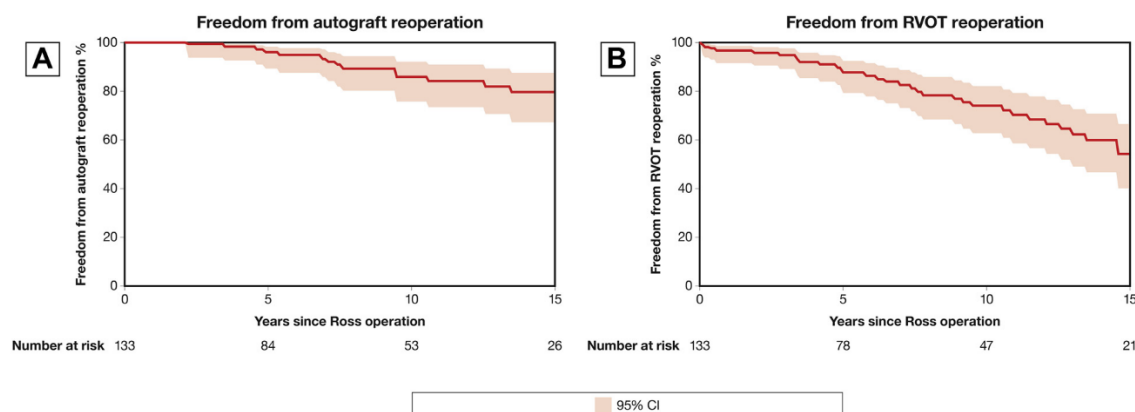
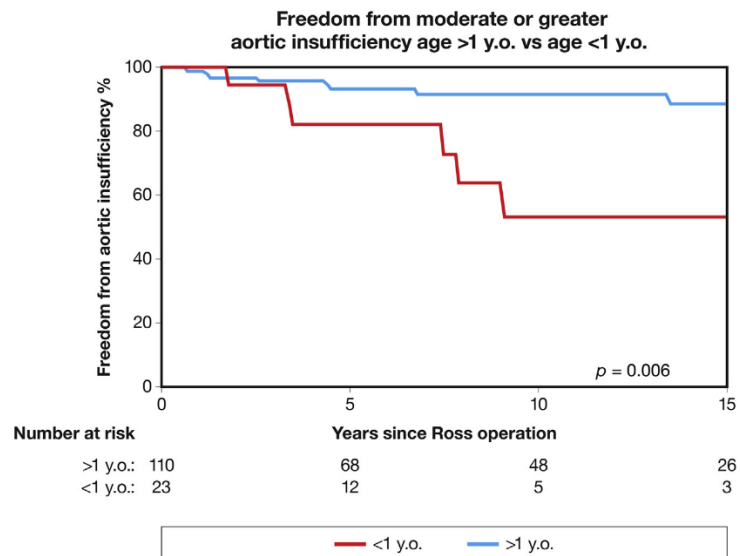


Figure 2. Autograft and right ventricular outflow tract (RVOT) reoperation after the Ross operation. (A) Freedom from autograft reoperation after the Ross operation. (B) Freedom from RVOT reoperation after the Ross operation. (CI, confidence interval.)

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Figure 3. Freedom from moderate or greater aortic insufficiency after the Ross operation in children older than 1 year of age vs children younger than 1 year of age at surgery.



time of the Ross operation was superior to survival in those younger than 1 year of age ($P = .003$).

Left Ventricular Outflow Tract Reoperation and Aortic Insufficiency

Reoperation because of neo-aortic dilatation and AI remains a concern after the Ross operation in children. A solution for protecting the autograft and simultaneously

permitting somatic growth has yet to be found. In our study, autograft reoperation was required in 14 patients (10.5%; 14 of 133). We report a 10-year freedom from autograft reoperation of 86%. Multiple long-term studies have also reported promising results for autograft durability in the first decade after the Ross operation.^{8,12,16,20,23} However, results of 2 long-term studies indicated that in autograft reoperation, rates may increase after the first

Figure 4. Freedom from moderate or greater aortic insufficiency after the Ross operation in children with a poly-(p-dioxanone)-filament (PDS) band vs children with no band.

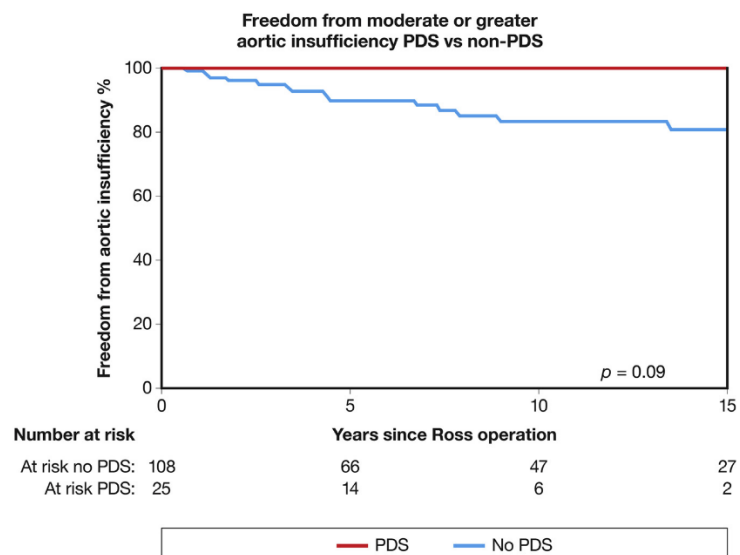


Table 3. Studies of the Ross Operation in Children

Study	Year of Publication	Study Period	Patients (n)	Early Mortality (%)	Late Mortality (%)	Early Mortality age <1 y (%)	10-y Survival (%)	10-y Freedom From Reoperation (%)	10-y Freedom From Autograft Reoperation (%)	Mean Follow-up (y)
Matsuzaki ⁸	2019	1996-2016	43	2.3 (1/43)	2.4 (1/42)	NR	NR	NR	91.9	13.5
Sames-Dolzer ^{7a}	2018	2008-2017	44	7 (3/44)	2 (1/41)	7 (3/44)	90.5	28.4	NR	5.9
Lögers ⁹	2018	2001-2009	49	0	6.1 (3/49)	0 (0/6)	91.9 (4 y)	NR	NR	4.6
Tran ¹⁰	2017	1998-2012	75	0	0	NR	NR	NR	92	5.2 ^b
Brown ¹¹	2016	1993-2015	115	0.9 (1/115)	3.5 (4/114)	NR	94	NR	NR	7.8
Kallio ¹²	2015	1994-2009	51	10 (5/51)	6 (3/46)	30.8 (4/13)	94	76	98	11.5 ^b
Mookhoek ^{13a}	2015	1990-2013	76	17 (13/76)	9 (5/63)	17.1 (13/76)	NR	NR	98	3.6 ^b
Nelson ⁵	2015	1991-2013	240	4.2 (10/240)	7.4 (17/230)	18.2 (8/44)	89	NR	75	10.7 ^b
Brancaccio ¹⁴	2014	1993-2012	55	13 (7/55)	NR	46.2 (6/13)	84.9	NR	73.7	5.5 ^b
Ruzmetov ¹⁵	2014	1993-2011	78	4 (3/78)	5.3 (4/75)	22.2 (2/9)	91 (15 y)	58 (15 y)	65 (15 y)	9.9
Luciani ¹⁶	2014	1990-2012	305	3.3 (10/305)	4.1 (12/295)	21.6 (8/37)	93	76	86	8.7 ^b
Elder ¹⁷	2013	1991-2010	34	12 (4/34)	0	12 (3/25)	88.2	NR	95.5	10.6 ^b
Tan Tanny ³	2013	1995-2012	100	6 (6/100)	4.3 (4/94)	31.6 (6/19)	90.8	65.8	85.6	7.0
Charitos ¹⁸	2012	1988-2011	263	3.4 (9/263)	NR	NR	95 (12 y)	76 (12 y)	95 (12 y)	6.9
Alsoufi ¹⁹	2010	1991-2004	227	3.1 (7/227)	1.4 (3/220)	NR	NR	NR	82 (15 y)	7.8
Hörner ²⁰	2010	1988-2006	152	2.6 (4/152)	4.7 (7/148)	NR	90.4	77.5	95.5	6.1

^aInfant- or neonate-only studies; ^bMedian.

NR, not reported.

decade.^{5,15} In a large single-center study, Nelson and colleagues⁵ reported on 240 children between 1991 and 2013 with a 15-year freedom from autograft reintervention rate of 59%. Ruzmetov and colleagues¹⁵ reported on 78 patients between 1993 and 2011 with a 15-year freedom

from autograft reoperation of 65%. We report a 15-year freedom from autograft reoperation of 79.5%. Etnel and colleagues⁴ reported a pooled 15-year freedom from LVOT reintervention of 77.3% in children after Ross operation. In multiple studies, high durability of the

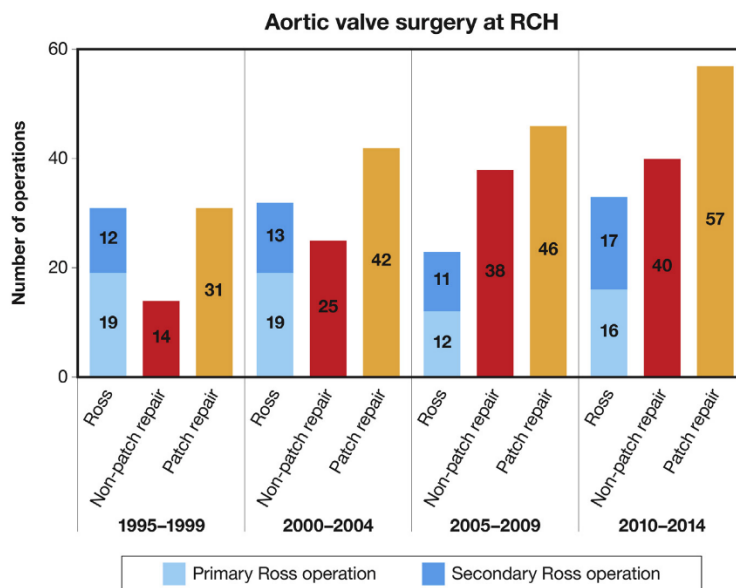


Figure 5. Frequency of aortic valve surgery performed at the Royal Children's Hospital in Melbourne, Australia (RCH) from 1995 to 2014. Primary Ross operation refers to children with no previous aortic valve surgery.

pulmonary autograft has been observed in younger children and infants, a finding suggesting that the autograft may be able to better adapt to systemic pressures when it is transplanted at a young age.^{5,24} In our cohort, however, univariable analysis revealed that age younger than 1 year at the time of operation was a risk factor for LVOT reoperation, although multivariable analysis was not possible because of the low number of autograft reoperations. Additionally, at our institution, we found that patients who underwent surgery when they were older than 1 year of age had a lower rate of development of AI and superior freedom from autograft reoperation.

Dilatation of the neo-aortic root commonly occurs at the aortic sinus and ST junction.^{3,25} We aimed to ameliorate this issue through placement of a PDS band around the ST junction. Previously, we found a reduction in the incidence of AI in those patients with a PDS band applied.³ In the current study, freedom from moderate or greater AI in patients with a PDS band applied was 100% at 10 years, compared with 83.3% in patients with no PDS band ($P = .09$). These results are promising and may translate to fewer autograft reoperations in PDS band recipients in the future.

Right Ventricular Outflow Tract Reoperation

Children undergoing the Ross operation at a young age will invariably outgrow their RV-PA conduits inserted at time of surgery and will require reoperation. In our study, 32 patients required RVOT reoperation, and freedom from RVOT reoperation at 10 years was at 74.0%. Considerable heterogeneity exists in the literature regarding RVOT reoperation rates. Luciani and colleagues¹⁶ reported on 305 patients from 1990 to 2012 with an estimated a 15-year freedom from RVOT reintervention of 82%. Nelson and colleagues⁵ reported on 240 patients between 1991 and 2013 with a 15-year freedom from homograft reintervention of 53%. Etnel and colleagues⁴ calculated a freedom from RVOT reintervention of 67.4% at 15 years. Risk factors for RVOT reoperation consistently reported in the literature include younger age, lower body weight, and small RVOT conduit size at time of operation.^{4,5,16,24} On univariable analysis, we were able to identify age younger than 1 year as a risk factor for homograft reoperation, and on multivariable analysis, smaller homograft size and postoperative infective endocarditis were found to be risk factors for RVOT reoperation. The burden of RVOT reoperation represents a drawback of the Ross operation.

Study Limitations

This study is retrospective and is limited by its design. Over the study period, surgical and perioperative techniques may have varied among patients. The selection of patients who underwent PDS banding was not prospectively randomized.

Conclusion

In children older than 1 year of age, the Ross operation has excellent outcomes with no operative mortality, a low incidence of AI, and a low autograft reoperation rate. In

children younger than 1 year of age, the Ross operation is associated with a higher operative mortality and a higher incidence AI. Where possible, the Ross operation should be delayed beyond infancy. PDS banding may reduce the incidence of AI after the Ross operation.

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CONGENITAL: TRUNCUS ARTERIOSUS: SURGICAL TECHNIQUE

Neonatal quadricuspid truncal valve repair with left coronary artery unroofing



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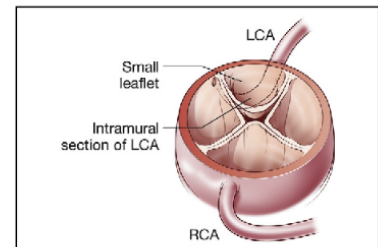
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Neonatal quadricuspid truncal valve and ostial stenosis of intramural left coronary artery.

Central Message

Truncal valve tricuspidization with left coronary artery unroofing resulted in excellent repair in a newborn infant with truncus arteriosus and severe truncal valve insufficiency.

See Editorial Commentary page 712.

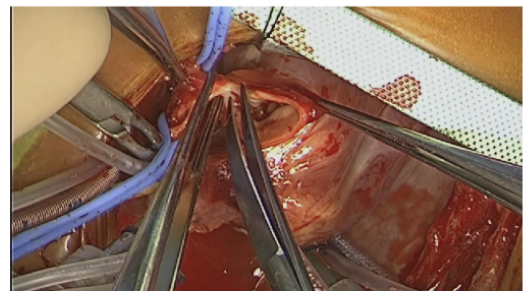
Video clip is available online.

Repair of a severely regurgitant truncal valve in a newborn infant is challenging. Herein we describe a surgical approach to repair a quadricuspid truncal valve in a neonate with concomitant ostial stenosis and intramural course of the left coronary artery (LCA). We performed a tricuspidization of the truncal valve with resection of the rudimentary cusp, reduction of the annulus and unroofing of the LCA, followed by ventricular septal defect patch closure and reconstruction of the right ventricular outflow tract.

CLINICAL SUMMARY

A newborn girl weighing 2.8 kg with type I truncus arteriosus and severe truncal valve insufficiency was referred to our institution with heart failure. The repair was undertaken at age 4 days through a standard midline sternotomy with hypothermic cardiopulmonary bypass (30°C) and intermittent antegrade cold blood cardioplegia (Video 1). The truncal artery was transected and the branch pulmonary arteries were separated from the aorta. The LCA had a high take-off with stenotic ostium located immediately above the posterior commissure of the quadricuspid truncal valve and an intramural course (Figure 1, A). All 4 cusps of the truncal valve appeared thickened. The cusp adjacent to the LCA was rudimentary and prolapsing. The intramural segment of the LCA was unroofed. The corresponding sinus was longitudinally opened and the prolapsing cusp was partially

resected together with the wall of its sinus. The cusp to the left of the resected cusp was mobilized by commissural detachment (Figure 1, B). The truncal root was reduced from the annulus to the sinotubular junction with a continuous 8-0 polypropylene suture (Figure 1, C), effectively decreasing the diameter of the neo-aortic root. The same 8-0 polypropylene suture was continued to the cusp tissues to reconstruct a new left coronary cusp by suturing the remaining portion of the rudimentary cusp to the mobilized



VIDEO 1. Intraoperative technique for the repair of common arterial trunk with severely regurgitant quadricuspid truncal valve and intramural left coronary artery in a neonate. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32550-9/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32550-9/fulltext).

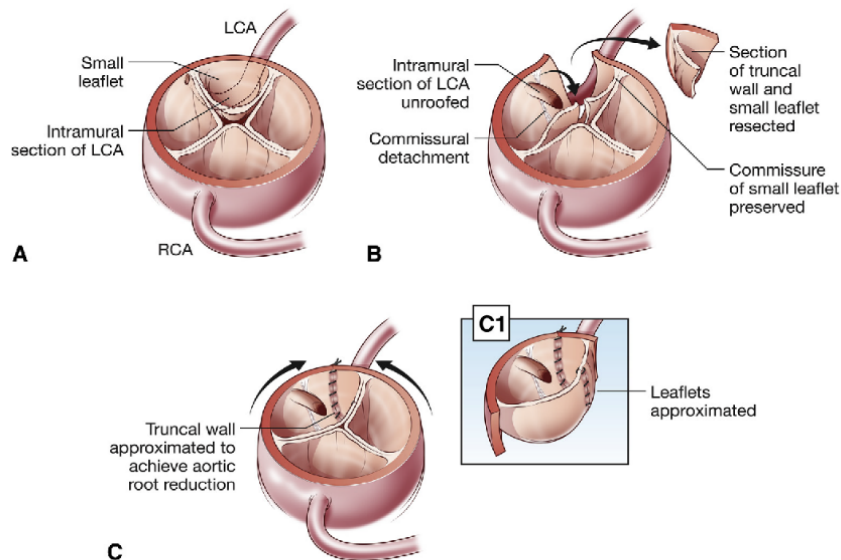


FIGURE 1. A, Quadricuspid anatomy of the truncal valve, position of the rudimentary cusp and the coronary arteries (A). B, Technique of repair with excision of the rudimentary cusp and sinus, unroofing, and detachment of the left coronary artery (LCA). C and C1, reconstruction of the root and the valve with plication of the annulus. RCA, Right coronary artery.

posterior cusp (Figure 1, C1) to achieve a normal trileaflet neo-aortic valve anatomy. A right ventriculotomy was performed. The neo-aorta was reconstructed primarily with end-to-end anastomosis. The ventricular septal defect was closed through the right ventriculotomy with glutaraldehyde-treated autologous pericardium using 6-0 pledgeted continuous polypropylene suture. A 10-mm polytetrafluoroethylene graft was placed from the right ventricle to the confluent pulmonary arteries. Following de-airing, the aortic crossclamp was removed. Normal sinus rhythm was restored. The patient was separated from cardiopulmonary bypass. Epicardial echocardiography showed a tricuspid truncal valve with trivial regurgitation. Cardiopulmonary bypass time was 206 minutes. Aortic crossclamp time was 154 minutes. The chest was closed on the following day. The patient was extubated on postoperative day 2 and discharged from the hospital on postoperative day 11. At 6 months of age, the patient was asymptomatic, had normal feeding and weight gain, and only trivial truncal valve insufficiency.

DISCUSSION

We have previously demonstrated that anomalous coronary anatomy was a risk factor for death after truncus arteriosus repair.¹ Although the intramural course of the LCA is rare, the influence of this anatomy on surgical planning is important and, if not appreciated, may contribute to significant morbidity and mortality.¹⁻³ The preoperative diagnosis of an intramural course of the LCA is difficult.² It is rarely

associated with quadricuspid aortic valve, the latter is often insufficient. We have also recently demonstrated that most patients with moderate or greater truncal valve insufficiency and a quadricuspid valve will require truncal valve surgery.⁴ Although successful repair of truncal valve can be achieved in neonates,^{4,5} concomitant intramural course of the LCA and quadricuspid valvular anatomy, requiring unroofing of the coronary artery with partial valvular resection and reduction of the annulus, is challenging. This report illustrates that successful repair of the truncal valve can be achieved in a neonate despite quadricuspid anatomy and concomitant intramural course of the LCA. Unroofing of the intramural coronary artery combined with the partial resection of the prolapsing cusp with adjacent vascular wall permitted effective reduction of the neo-aortic root and provided an excellent early result in our patient.

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ORIGINAL ARTICLE

Outcomes of Subaortic Obstruction Resection in Children



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Background	Studies of long-term outcomes of discrete subaortic stenosis are rare. Therefore, we reviewed the long-term outcomes of fibromuscular resection in children with subaortic stenosis over 26 years from a single institution.
Methods	We conducted a retrospective review of all children (n=72) who underwent resection of subaortic obstruction for discrete subaortic stenosis between 1989 and 2015.
Results	Median age at surgery was 5.0 years (2.7–7.6 years). There were no operative deaths but three late deaths (4.2%, 3/72). Overall Kaplan-Meier survival at 10 years was 93.0 ± 3.9% (95% CI: 79.6, 97.7). Peak instantaneous left ventricular outflow tract Doppler gradient decreased from 74.2 ± 36.7 mmHg (16.0–242.0 mmHg) preoperatively to 12.8 ± 7.4 mmHg (2.6–36.0 mmHg) postoperatively ($p < 0.001$). Mean left ventricular outflow tract Doppler gradient decreased from 42.4 ± 17.2 mmHg (12.0–98.0) preoperatively to 7.5 ± 2.7 mmHg (1.4–19.3 mmHg) postoperatively ($p < 0.001$). However, over the mean follow-up period of 7.8 ± 6.1 years (0.1–25.2 years), 29.0% (20/69) of patients had recurrence and 18.8% (13/69) required reoperation at median time of 4.8 years (3.1–9.1 years) after the initial repair. Freedom from reoperation at 10 years was 71.1 ± 7.1% (95% CI: 54.6, 82.3). Risk factors for reoperation were age less than five years at initial repair ($p = 0.036$) and extension of the membrane to the aortic valve ($p = 0.001$). Aortic insufficiency was present in 54.2% (39/72) of patients preoperatively. Progression of aortic insufficiency occurred in 38.9% (28/72). Involvement of the aortic valve at initial repair was associated with need for subsequent aortic valve repair or replacement ($p = 0.01$).
Conclusions	Resection of subaortic obstruction is associated with low mortality and morbidity. Recurrence and reoperation rates are high and progression of aortic insufficiency following subaortic resection is common. Therefore, these patients warrant close follow-up into adult life.
Keywords	Subaortic stenosis • Congenital heart disease • Surgery

Abbreviations: AI, aortic insufficiency; ASD, atrial septal defect; AV, atrioventricular; CI, confidence interval; CoA, coarctation of aorta; HOCM, hypertrophic obstructive cardiomyopathy; LVOT, left ventricular outflow tract obstruction; OR, odds ratio; PDA, patent ductus arteriosus; RCH, Royal Children's Hospital; RVOT, right ventricular outflow tract obstruction; SAS, subaortic stenosis; VSD, ventricular septal defect

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Introduction

Discrete subaortic stenosis (SAS) is an often progressive disease due to membranous or fibromuscular obstruction in the left ventricular outflow tract (LVOT). Subaortic stenosis accounts for 8–30% of LVOT obstruction in children [1–4]. If untreated, severe SAS has a high morbidity and mortality [5,6]. Subaortic stenosis may also cause aortic insufficiency (AI) through turbulent blood flow resulting in scarring and prolapse of the valve, or alternatively, direct extension of subaortic tissue onto the valve. Although surgical repair of SAS has excellent short-term outcomes, it is associated with an up to 8% chance of an iatrogenic ventricular septal defect (VSD) [7,8], up to 14% chance of complete atrioventricular (AV) block [8,9], and a recurrence rate of 5–27% [1–3,9,10].

Subaortic stenosis is commonly found in conjunction with other cardiac abnormalities, such as ventricular septal defects (VSDs) and aortic arch abnormalities. The majority of studies on surgical outcomes of SAS are mixed series, including patients with complex cardiac abnormalities. Studies of discrete SAS are rare. We therefore sought to review the long-term outcomes of surgical resection of discrete SAS over the last 26 years in a cohort with similar LVOT morphology and an intact ventricular septum.

Materials and Methods

Patients

The institutional Human Research Ethics Committee at the Royal Children's Hospital (RCH) approved this retrospective study. Between 1989 and 2015, 72 patients underwent

fibromuscular resection of discrete SAS at the RCH. Indications for surgery were peak instantaneous LVOT Doppler gradient >30 mmHg and/or progressive AI. Medical records were retrospectively reviewed until last cardiology follow-up. This included inpatient notes, surgical reports and outpatient letters.

Definitions

Discrete SAS was defined as isolated SAS with otherwise normal cardiac anatomy. Patients with major concomitant intracardiac anomalies were excluded from analysis. We included only minor associated anomalies that would not alter the primary diagnosis of 'discrete SAS'. Patients with concomitant valvular abnormalities, patent ductus arteriosus (PDA), cor triatriatum, or coarctation of aorta (CoA) were included in our study. Patients with narrow LVOT obstruction, who required Konno-type LVOT enlargement were excluded, as were patients who required aortic valve replacement during initial repair. Early mortality was defined as death occurring within 30 days of surgery or prior to hospital discharge. All other deaths were considered late. Recurrence of SAS was defined as peak instantaneous LVOT Doppler gradient ≥ 40 mmHg at any time after the first postoperative month [9]. Involvement of the valves included both removal of the SAS membrane from the valve and other valve repair. Progression of AI was defined as worsening of preoperative AI, new AI developing postoperatively, or aortic valve repair or replacement occurring postoperatively.

Operative Technique

The LVOT was accessed via an aortotomy, allowing for resection of the fibromuscular subaortic membrane (Figure 1A).

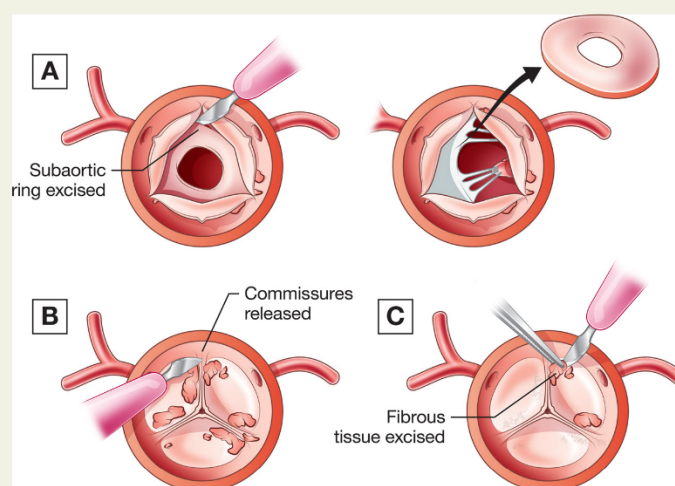


Figure 1 Resection of discrete subaortic stenosis ($n=72$) (A) and aortic valve repair ($n=16$); commissurotomy (B) and resection of nodular dysplasia (C).

Where necessary, the membrane was removed from aortic and/or mitral valves and accessory papillary muscle attachments were resected. Septal myectomy was performed if required. Subaortic stenosis has a spectrum of severity, with or without septal myocardial hypertrophy. If removing of discrete subaortic membrane was sufficient and there was no septal hypertrophy obstructing the LVOT, no septal myectomy was performed.

Data Analysis

Data was analysed using Stata version 13 (StataCorp LP, College Station, TX). Descriptive statistics for continuous data are expressed as means $\pm$ standard deviations (range), whilst skewed continuous data are expressed as medians (interquartile range). Categorical data are summarised as frequencies and percentages. Univariable and multivariable logistic regression and Cox-proportional hazard modelling were used to determine risk factors for mortality, recurrence and reoperation. Fisher exact test was used to compare groups. Kaplan-Meier actuarial survival curves were used to analyse and plot time-related endpoints. Statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

Of the 72 patients, 37 were male (51.4%, 37/72). Median age at surgery was 5.0 years (2.7-7.6 years) and median weight at surgery was 18.9 kg (13.1-27.6 kg). Three patients had their initial SAS resection performed at other centres and underwent their second procedure (two patients) or third procedure (one patient) at the RCH. These patients were excluded from calculation of recurrence and reoperation rates. Concomitant cardiovascular anomalies are described in Table 1. Eleven patients underwent cardiac surgery prior to developing SAS. These were CoA repair (n=8), aortic valve repair (n=1), cortriatriatum repair (n=1) and PDA ligation (n=1). Six patients underwent cardiac catheter interventions prior to developing SAS. These were balloon aortic valvotomy (n=2), PDA device closure (n=2), balloon dilatation of the pulmonary valve (n=1) and CoA balloon angioplasty (n=1).

All patients underwent resection of subaortic membrane (Figure 1A). Mean cardiopulmonary bypass duration was 77 ± 43 minutes (24-220 minutes). Mean aortic cross clamp duration was 53 ± 32 minutes (16-154 minutes). Repair of concomitant cardiovascular anomalies were undertaken in 44% (32/72) of patients. The SAS membrane was adherent to the aortic valve in 20 patients (27.8%, 20/72). There were a further 13 patients who underwent aortic valve repair (Figure 1B and C) but did not have the membrane adherent to the valve. The SAS membrane was adherent to the mitral valve in 18 patients (25%, 18/72). A further eight patients underwent mitral valve repair but did not have the membrane adherent to the valve. Other concomitant procedures were PDA ligation (n=6), atrial septal defect (ASD) closure (n=3), CoA repair (n=3), pulmonary valve repair (n=3), and

Table 1 Concomitant cardiovascular anomalies

Variable	Proportion (%)
CoA	18.1 (13/72)
Aortic valve	
Bicuspid aortic valve	15.3 (11/72)
Aortic stenosis	11.1 (8/72)
PDA	12.5 (9/72)
Pulmonary valve stenosis	4.2 (3/72)
Mitral valve	
Mitral regurgitation	6.9 (5/72)
Mitral valve stenosis	5.6 (4/72)
Cleft mitral valve	2.8 (2/72)
Parachute mitral valve	2.8 (2/72)
ASD	4.2 (3/72)
HOCM	1.4 (1/72)
Cortriatriatum	1.4 (1/72)
Syndromes	
Shone's	4.2 (3/72)
Down's	1.4 (1/72)

ASD, atrial septal defect; CoA, coarctation of the aorta; HOCM, hypertrophic obstructive cardiomyopathy; PDA, patent ductus arteriosus.

right ventricular outflow tract (RVOT) resection (n=2). Overall, 27 patients (37.5%, 27/72) underwent resection of SAS with no involvement of either the aortic or mitral valves (Figure 2A), 19 patients (26.4%, 19/72) had involvement of the aortic valve only at time of initial repair (Figure 2B), 12 patients (16.7%, 12/72) had involvement of the mitral valve only, and 14 patients (19.4%, 14/72) had involvement of both valves (Figure 2C).

Mean follow-up was 7.8 ± 6.1 years (median 6.5 years; range 0.1-25.2 years). Follow-up was 99% (71/72) complete. One patient was lost to follow-up. Sixty-eight patients (93%, 68/73) were followed up within the last five years.

Mortality

There was no operative mortality. Late mortality was 4.2% (3/72). The three late deaths all occurred in children that were less than one year of age at time of operation. In 2006, a nine-month-old girl weighing 7.7 kg underwent SAS resection, pulmonary valve repair and RVOT resection due to hypertrophic obstructive cardiomyopathy (HOCM). The patient died four years postoperatively after developing a severe viral pneumonia on the background of severe diastolic biventricular failure, for which the patient was awaiting heart transplantation. In 2007, a four-day-old girl weighing 1.8 kg underwent SAS resection. She later developed mitral valve stenosis, requiring one mitral valve repair and two mitral valve replacements. The patient died 5.3 years after the initial SAS resection from end-stage cardiomyopathy. In 2006, a seven-month-old boy weighing 7.0 kg underwent SAS resection with concomitant CoA, aortic and mitral valve repair. The patient died 5.6 years after SAS resection 146 due

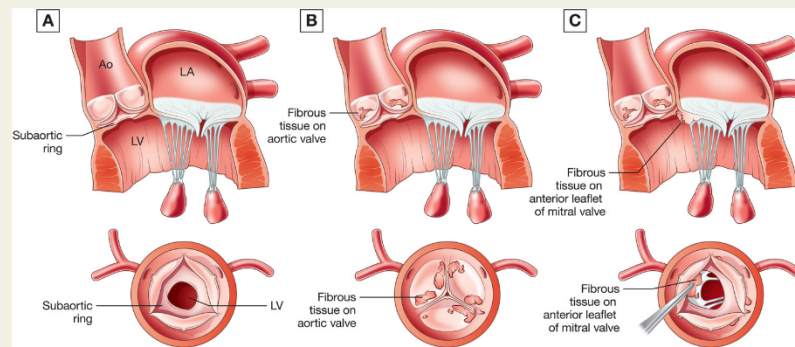


Figure 2 Schematic illustration of discrete subaortic stenosis (A), with involvement of the aortic valve (B), and mitral valve (C).

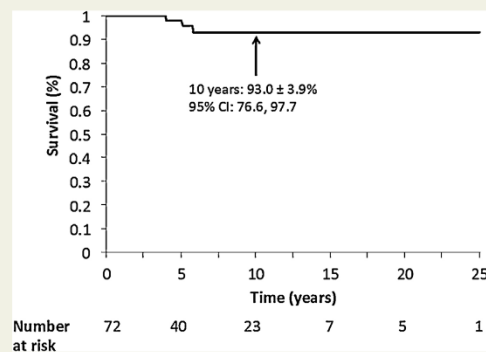


Figure 3 Kaplan-Meier survival curve after resection of subaortic stenosis.

to severe lobar pneumonia and sepsis. There were no identifiable risk factors for late mortality. Kaplan-Meier overall survival was $93.0 \pm 3.9\%$ (95% confidence interval (CI): 79.6, 97.7) at 10 and 15 years (Figure 3).

Surgical Outcomes

The mean LVOT Doppler gradient decreased from 42.4 ± 17.2 mmHg (12.0–98.0 mmHg) preoperatively to 7.5 ± 2.7 mmHg (1.4–19.3 mmHg) postoperatively ($p < 0.001$). The peak instantaneous LVOT Doppler gradient decreased from 74.2 ± 36.7 mmHg (16.0–242.0 mmHg) preoperatively to 12.8 ± 7.4 mmHg (2.6–36.0) postoperatively ($p < 0.001$) (Table 2). At latest follow-up, the peak gradient was 18.4 ± 19.0 (1.4–96.0) mmHg.

Recurrence of SAS occurred in 20 patients who underwent primary SAS operation at RCH (29.0%, 20/69). Risk factors for SAS recurrence on multivariable analysis were postoperative peak instantaneous LVOT Doppler gradient >15 mmHg (odds ratio (OR) 9.40, 95% CI: 2.48, 35.70; $p = 0.001$) and extension of the SAS membrane onto the aortic valve (OR 5.48, 95% CI: 1.45, 20.70; $p = 0.012$). Thirteen patients (18.8%, 13/69) required reoperation for SAS recurrence at a median time of 4.8 years (3.1–9.1 years) after the initial repair. Three patients (4.3%, 3/69) required a second SAS reoperation. Risk factors for SAS reoperation on multivariable analysis were age at initial surgery less than five years (OR 6.87, 95% CI: 1.14, 41.41; $p = 0.036$) and extension of the SAS membrane onto the aortic valve (OR 20.94, 95% CI: 3.7, 118.43; $p = 0.001$). Freedom

Table 2 LVOT gradient and degree of aortic insufficiency before and after surgery

Variable	Preoperative	Postoperative	Last follow-up
Peak instantaneous LVOT gradient (mmHg)	74.2 ± 36.7	12.8 ± 7.4 ($p < 0.001^*$)	18.4 ± 19.0 ($p < 0.001^{\#}$)
Aortic insufficiency			
None/trivial	33	44	31
Mild	32	28	27
Moderate	6	0	13
Severe	1	0	1

LVOT, left ventricular outflow tract. *preoperative versus early (in hospital) postoperative $^{\#}$ preoperative versus last follow-up

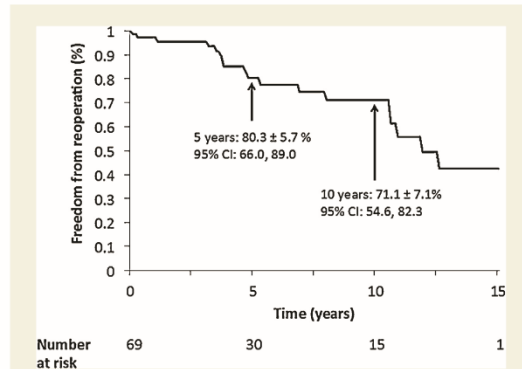


Figure 4 Kaplan-Meier freedom from reoperation curve after resection of subaortic stenosis. Note that reoperation rates were based on the 69 patients who underwent primary surgical resection of SAS at the Royal Children's Hospital, Melbourne.

from all reoperation was $71.1 \pm 7.1\%$ (95% CI: 54.6, 82.3) at 10 years and $42.5 \pm 11.0\%$ (95% CI: 21.1, 62.4) at 15 years (Figure 4). Other reoperations were aortic valve replacement ($n=7$), aortic valve repair ($n=6$), mitral valve repair ($n=3$), mitral valve replacement ($n=2$), CoA repair ($n=1$), and RVOT resection ($n=1$).

One patient (1.4%, 1/72) had an iatrogenic VSD following SAS repair that required surgical closure five days later. Additionally, two patients (2.8%, 2/72) had complete AV block following SAS reoperation; both required insertion of a permanent pacemaker.

Aortic Insufficiency

Thirty-nine patients (54.2%, 39/72) had AI preoperatively with mild AI in 32 patients, moderate AI in six patients, and severe AI in one patient. Postoperatively, 28 patients (38.9%, 28/72) had mild AI. There was no moderate or severe AI. At latest follow-up 41 patients (56.9%, 41/72) had AI: mild AI in 27 patients, moderate AI in 13 patients and severe

AI in one patient. Progression of AI occurred in 38.9% (28/72). This included five patients who had worsening of their preoperative AI (12.8%, 5/39), 16 patients who had new AI develop postoperatively (48.5%, 16/33) and seven patients who required aortic valve replacement (of whom four had preoperative AI). There were three mechanical aortic valve replacements, three Ross procedures, and one Bentall-Konno procedure. Six patients with progression of AI required aortic valve repair on reoperation. Risk factors for AI progression on multivariable analysis were age less than five years at operation (OR 3.41, 95% CI: 1.14, 10.25, $p=0.028$) and any reoperation (OR 5.94, 95% CI: 1.82, 19.35, $p=0.003$). Patients with aortic valve involvement at primary repair (membrane extension to the aortic valve or other aortic valve repair) more commonly required subsequent aortic valve repair or replacement compared to those who did not have aortic valve involvement at primary repair ($p<0.001$). Five of the aortic valve repairs (83%, 5/6) and six of the aortic valve replacements (86%, 6/7) occurred in children with initial aortic valve involvement.

Discussion

Surgical resection of SAS was first attempted in 1956 by Brock and Fleming [11]. Most studies of SAS surgical outcomes are mixed series, including concomitant repairs such as VSD closures and aortic valve replacements [2,9,12–14]. We chose to exclude these patients for two reasons. Firstly, VSDs have been shown to be associated with altered LVOT morphology, namely, a deviated ventricular septum, resulting in abnormal flow through the LVOT [15]. This could trigger development of SAS and increase the likelihood of SAS recurrence [16]. Secondly, complex concomitant repairs such as aortic valve replacement and Ross procedures will affect mortality and reoperation rates. By excluding these patients, we focussed on a patient cohort with similar LVOT morphology undergoing a relatively similar surgical procedure. There are only a few studies of discrete SAS in patients with an intact ventricular septum (Table 3).

Table 3 Studies of discrete SAS

Study	Study Period	Surgical patients (n)	Early mortality (%)	Late mortality (%)	Recurrence (%)	Reoperation (%)	Progression of AI (%)	Mean follow-up (median, range, years)
Lampros et al. [17]	1982-1996	36	0 (0/36)	0 (0/36)	36.1 (13/36)	27.7 (10/36)	NR	7.4 (NR, 0.3-21)
Serraf et al. [3]	1980-1997	160	3.1 (5/160)	2.6 (4/155)	27.0 (42/155)	12.9 (20/155)	14.4 (23/160)	NR (13.3, NR)
Rohlicek et al. [7]	1985-1998	42	0 (0/42)	2.4 (1/42)	NR	19.0 (8/42)	35.7 (15/42)	3.7 (NR, NR)
Talwar et al. [18]	1990-1998	45	0 (0/45)	0 (0/45)	8.9 (4/45)	0 (0/45)	6.7 (3/45)	5.6 (NR, 1.5-9.4)
Babaoglu et al. [4]	1990-2004	24	0 (0/24)	0 (0/24)	16.7 (4/24)	8.3 (2/24)	33.3 (8/24)	4.8 (5, 0.2-14)
Drolet et al. [1]	1985-2005	49	0 (0/49)	0 (0/49)	NR	20.4 (10/49)	59.2 (29/49)	6.2 (NR, NR)

NR, not reported. AI, aortic insufficiency.

Mortality

Surgical resection of SAS has generally excellent short-term outcomes, with low mortality. There was no operative mortality in our cohort, consistent with other studies of discrete SAS reporting an operative mortality rate close to 0% [1,4,7,17,18]. Rohlicek and colleagues studied 42 patients who underwent SAS resection between 1985 and 1998 with no operative mortality and 2.4% (1/42) late mortality [7]. Serraf and colleagues, however, in their study of 160 patients between 1980 and 1997, reported operative mortality of 3% (5/160) [3]. They found that tunnel SAS, concomitant mitral stenosis, CoA and hypoplastic aortic annulus were risk factors for overall mortality. In a mixed series that included VSD closures, aortic and mitral valve replacements, Ruzmetov and colleagues described their outcomes of SAS repair in 190 children between 1960 and 2005 [19]. They also reported a higher operative mortality rate of 4% (7/190) and higher rate of reoperations in those with tunnel-type SAS (16%, 3/50) compared to those without tunnel-type SAS 221 (3%, 4/130). In our cohort, only one patient had tunnel SAS on initial procedure. Three patients developed tunnel SAS postoperatively, all requiring reoperation. There were three late deaths in our cohort — specifically, one patient with HOCM who developed biventricular failure, one patient who developed a severe dilated cardiomyopathy and one patient who developed a severe pneumonia complicated by sepsis.

Recurrence and Reoperation

Despite successful resection of SAS, recurrence and reoperation rates remain high. In our study, recurrence occurred in 20 patients (29.0%, 20/69), over a mean follow-up period of 7.8 years, with 13 patients (18.8%, 13/69) requiring reoperation. This rate of reoperation is 2.4% per year, which is similar to other studies. Drolet and colleagues conducted a study of 92 patients diagnosed with SAS between 1985 and 1998 [1]. Forty-nine patients required surgery at a mean of 3.3 years after diagnosis and 10 patients (20%, 10/49) required reoperation during a mean follow-up period of 6.2 years. This is equivalent to a reoperation rate of 3.3% per year. Two patients (4.1%, 2/49) required a second reoperation for recurrent SAS and two (4.1%, 2/49) required aortic valve replacements on reoperation. Babaoglu and colleagues conducted a similar study, reporting a reoperation rate of 8.3% (2/24) over a follow-up period of 4.8 years, equivalent to 1.7% per year [4]. A further four patients (16.7%, 4/24) had recurrence, but did not require reoperation during the study period. Similarly, in a mixed study, Ruzmetov and associates also reported a high reoperation rate in their study of 190 patients [19]. Over the follow-up period of 9.6 years, 26.3% (50/190) of patients required reoperation for recurrent SAS, equivalent to 2.7% per year. Reoperation occurred more commonly in tunnel SAS (70%, 35/50) compared to non-tunnel SAS (11%, 15/140).

A few risk factors for SAS recurrence and reoperation have been reported in the literature [3,7,9,13]. Of particular significance is the peak instantaneous LVOT Doppler gradient,

which appears to be an indicator for poor outcomes when greater than 50 mmHg, whether at diagnosis, preoperatively or postoperatively. Rohlicek and colleagues found reoperation to be associated with a higher peak instantaneous LVOT Doppler gradient *at diagnosis*, with those requiring reoperation having a mean peak gradient of 66 mmHg compared to those who did not require reoperation, with a mean peak gradient of 34 mmHg [7]. Mixed studies have reported similar findings — Geva and colleagues, who reported a reoperation rate of 1.7% per year in their study of 111 children, found that *preoperative* peak instantaneous LVOT Doppler gradient >60 mmHg was an independent predictor of earlier time to reoperation [9]. Hirata and colleagues, in their mixed study of 106 children, also found the preoperative peak instantaneous LVOT Doppler gradient significant in predicting SAS recurrence [13]. Serraf and associates found *postoperative* peak instantaneous LVOT Doppler gradient to be a predictor of recurrence and reoperation [3]. In our cohort, we did not find any association between preoperative peak instantaneous LVOT Doppler gradient and risk of recurrence or reoperation. We did, however, find that a postoperative peak instantaneous LVOT Doppler gradient >15 mmHg predicted SAS recurrence, highlighting the importance of complete removal of all pathological subaortic tissue and the use of intraoperative echocardiography.

Other reported risk factors for recurrence and reoperation include concomitant cardiovascular defects such as CoA [3,13] and younger age at operation [9]. Serraf and colleagues, and Hirata and colleagues in their studies found CoA to be a risk factor for recurrence and reoperation, suggesting that children with CoA be regularly assessed for SAS [3,13]. In our study, we did not find any association between minor concomitant cardiovascular anomalies and SAS recurrence or reoperation. In our cohort, patients with SAS and concomitant CoA had good outcomes. Of the 13 patients in this group, there was one late death due to severe pneumonia and sepsis and only three patients had SAS recurrence at last follow-up. Two of these patients (15.4%, 2/13) have required reoperation for SAS. We did, however, find younger age to increase risk of SAS reoperation. Geva and colleagues reported that younger age at initial surgery predicted earlier reoperations, and suggested that children diagnosed earlier have more aggressive underlying pathology [9]. Our study similarly found age <5 years at SAS repair to be an independent predictor of SAS reoperation. As LVOT obstruction appears to gradually increase at a rate of 1 to 3 mmHg per year, it is logical that disease beginning at an earlier age would lead to increased risk of reoperation [19,20].

Impact of Fibrous Extension to the Valves

Extension of the SAS membrane onto the aortic or mitral valve has also been associated with poor outcomes [9]. We found that extension of the membrane onto the aortic valve (Figure 2B) was a significant risk factor for SAS recurrence and reoperation. Furthermore, patients with aortic

valve involvement at initial SAS resection, whether extension of the membrane onto the aortic valve or other aortic valve repair (Figure 1B and C), required more aortic valve surgery in the follow-up period, compared to those who did not. Geva and colleagues similarly found that the need for intra-operative peeling of the SAS membrane from the aortic or mitral valves (Figure 2C) to be associated with a shorter time to reoperation [9]. Hirata and associates stressed the importance of complete removal of all abnormal tissue from the LVOT, as residual tissue on the anterior mitral valve leaflet causes it to stay drawn towards the LVOT and septum [13]. Patients with SAS, in whom fibrous tissue extend onto aortic or mitral valves have more severe disease, and therefore warrant closer follow-up, well into adulthood.

Aortic Insufficiency

Aortic insufficiency is a known complication of SAS, thought to be due to turbulent blood flow causing damage, scarring and prolapse of the aortic valve, or alternatively, direct extension of the subaortic tissue onto the aortic valve [2,4]. Our study showed that although AI was improved immediately postoperatively, at long-term follow-up the severity of AI was variable, with improved or unchanged AI in 30 patients, worsened AI in five patients and aortic valve replacement required in seven patients. Of the patients with no preoperative AI, 48.5% (16/33) went on to develop some degree of AI. This is consistent with previous studies [2,4,7]. Babaoglu and colleagues found that 91% of patients had AI preoperatively, and 4.1 years later, *all* patients had some degree of AI [4]. Although they believed AI to be related to the severity of SAS, they concluded that progression of AI may continue even after removal of the obstruction. Similarly, Rohlicek and associates found AI to progress in *both* patients who underwent surgery during the study period (from 34% at diagnosis to 76% at latest follow-up) and patients who did not (from 14% at diagnosis to 40% at latest follow-up) [7]. They concluded that surgery had little beneficial effect on severity of postoperative AI or the development of new AI postoperatively. This is in contrast to other studies recommending early 'prophylactic' SAS resection to prevent the development of moderate-severe AI [21,22]. Our results suggest that AI may progress despite resection of SAS.

Many studies have reported higher preoperative LVOT gradient to be a risk factor for development and progression of AI [12,23]. Babaoglu and colleagues found that patients with progressive AI postoperatively had a significantly higher preoperative LVOT gradient than patients with non-progressive AI [4]. Our study did not find this. Risk factors for progression of AI were age <5 years at operation and the need for reoperation, which suggests a more aggressive underlying pathology. We also found that children who had aortic valve involvement at the time of initial repair were more likely to require further aortic valve intervention. Of the six aortic valve repairs that occurred in our cohort, five of them (83%, 5/6) occurred in the 33 patients who had some degree of aortic valve involvement at initial SAS resection. Likewise, six out of the seven aortic valve replacements

(86%, 6/7) that occurred in the follow-up period were in children with initial aortic valve involvement. These children require close monitoring of their aortic valve function.

Other Surgical Complications

Previous studies of outcomes of SAS resection have found a high number of patients developing complete AV block and iatrogenic VSDs [1,8]. In a mixed series of 37 patients conducted by Parry and colleagues, all patients underwent an aggressive circumferential resection of fibromuscular SAS [8]. Although they showed no recurrence of SAS at two years postoperatively, some patients had complete AV block (14%, 5/37) and iatrogenic VSD (8%, 3/37). Drolet and colleagues found the rate of AV block to be similarly high, at 6% (3/49), with all requiring a permanent pacemaker [1]. In contrast, there were no patients in our study who had complete AV block following their primary SAS procedure. However, two patients (2.8%, 2/72) developed complete AV block following reoperation for recurrence of SAS. These patients subsequently went on to have a permanent pacemaker inserted. Other mixed series have shown a rate of complete AV block of 3-5% [2,3,9]. In our study, iatrogenic VSD occurred in only one patient (1.4%, 1/72), who required surgical repair shortly after. This rate is also consistent with other studies [7,9].

Limitations

This study is subject to the usual limitations of a retrospective study. Statistical analyses were limited due to the relatively small number of patients and outcomes. Perioperative techniques have varied during the study period.

Conclusion

Resection of SAS provides safe and effective relief of LVOT obstruction in children, with low mortality. Nevertheless, recurrence and reoperation rates remain high, and these patients warrant close long-term follow-up.

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EDITORIAL COMMENTARY

Intramural ventricular septal defect after repair of conotruncal anomalies: Is there light at the end of the tunnel?



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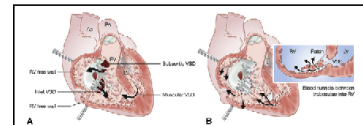
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Intramural ventricular septal defects occur when blood flows underneath the trabeculations.

Central Message

Precise echocardiographic evaluation is essential for successful closure of intramural ventricular septal defect.

See Article page 688.

Patel et al¹ present an interesting article on intraoperative transesophageal echocardiography (TEE) to identify intramural ventricular septal defect (VSD) following the repair of conotruncal anomalies. The article raises a very important issue regarding the sensitivity of a well-established imaging technique to detect a rare, yet potentially life-threatening, complication.

Intramural VSD is defined as a tunnel-like communication that may occur when the VSD patch is not sutured to the edge of the VSD proper, but rather to right ventricular (RV) trabeculations, so that blood can flow from the left ventricle around the trabeculations into the RV cavity (Figure 1). Intramural VSD often has multiple exit points through intertrabecular spaces into the RV free wall. Intramural VSD was originally described in children with conotruncal anomalies undergoing subaortic VSD closure.² It should be emphasized that similar VSDs may occur following closure of any VSD, provided that it is, at least, partially surrounded by trabeculations so that a residual VSD occurs underneath trabeculations with an exit point into the free wall of the RV. VSDs with additional exit points through the free wall of the RV are notoriously difficult to close and can be associated with increased morbidity and mortality.³ Furthermore, although residual intramural VSD may not appear hemodynamically significant immediately after surgery, the interventricular shunting may increase with regression of RV hypertrophy.^{2,4}

Given the clinical importance of intramural VSDs, it is essential that surgeons have a high index of suspicion in all cases of conotruncal defects where VSD margins are in proximity to trabeculae. The best way to resolve the problem would be to prevent it. Thus, preoperative echocardiography in those children with conotruncal anomalies would alert a surgeon of higher risk of postoperative intramural VSD. Once intramural VSD occurs, it would be extremely helpful to visualize its location intraoperatively. This can be achieved by thorough intraoperative TEE assessment. However, intraoperative TEE is not without flaws. Thus,

Patel et al¹ excluded 22.7% of patients (105 out of 462) because they did not have adequate imaging. Most importantly, the excluded children were younger and had lower weight. These children also had higher early mortality. It is these patients who would benefit most from intraoperative identification of intramural VSD. Unfortunately, performance of TEE in detecting intramural VSD—and even peripatch VSD—in older children was not perfect either. It was described by the authors as modest, with sensitivities of 56% for intramural VSD, which was not much different from that of 63% for peripatch VSD.¹

Moreover, patients with correct identification of intramural VSD made by TEE were more likely to be older than age 30 days and have higher body weight at operation. Thus, again, smaller children were disadvantaged. In nearly half of the children with missed intramural VSD, a subsequent transthoracic echocardiogram demonstrated residual intramural VSD > 2 mm. Is there a better alternative to TEE intraoperatively? Epicardial echocardiography is sensitive for the detection of residual VSDs.^{5,6}

At the Royal Children's Hospital in Melbourne, surgeons routinely perform epicardial echocardiograms on children with conotruncal anomalies after VSD closure, particularly in those with trabeculations obscuring the edge of the VSD and those with multiple VSDs.⁷ In our experience epicardial echocardiograms give superb imaging quality and are perfect for assessment of residual VSDs. This is of particular importance in small children. Clearly, a randomized controlled trial between TEE and epicardial echocardiography will not be feasible in neonates and smaller children. A surgeon with immediate knowledge of intraoperative anatomy is ideally suited to perform epicardial

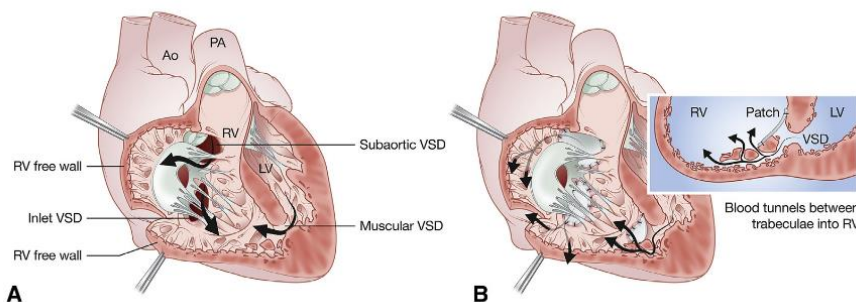


FIGURE 1. A, Intramural ventricular septal defect (VSD) may occur when the edge of the VSD is partially covered by trabeculations. It was originally described in subaortic area, but may occur in inlet or anteroapical septum, if the patch is sutured to right ventricular (RV) trabeculations rather than a true septal margin of the VSD. B, The defining feature of intramural VSD is a tunnel underneath the trabeculations that persists with often multiple exit points at the free wall of RV. Ao, Aorta; PA, pulmonary artery; LV, left ventricle.

echocardiograms. The importance of proficient acquisition of high-quality epicardial echocardiographic imaging by cardiac surgeons during neonatal surgery cannot be over-emphasized. Once the residual VSD is identified, the shunt is quantified by intraoperative assessment of Qp:Qs. Even if the residual VSD appears small on imaging, it is worth determining Qp:Qs to avoid any postoperative surprises.

Once a significant intramural VSD is identified, it should be closed, because simple pulmonary artery banding may not be a safe option in the presence of large residual VSD and would likely put a child on a rocky postoperative course.⁸ If the large residual VSD is not closed, the echocardiogram, albeit with modest sensitivity, may simply document a very sensitive surgical failure. For successful closure, one must close the entry point into the VSD because the outlets can be multiple.

TRANSATRIAL APPROACH

In the transatrial approach, a VSD patch should be at least partially removed, the edges of the VSD reassessed, and adjacent trabeculations resected if necessary so that the entry point into the VSD can be closed. Any attempt to close the often multiple exit points from this approach would be notoriously imprecise, and would likely fail. Suturing trabeculations together⁸ may open yet another exit point.

TRANSAORTIC APPROACH

To overcome the above problem, a transaortic approach has been proposed for classical intramural VSD,⁹ so that the entry point is closed through the aortic valve. This approach is not foolproof because the entry point into the intramural tunnel may not be easy to visualize.

TRANSAPICAL APPROACH

For defects in the apical region of the septum a small incision in the apex of either ventricle may be performed, allowing the VSD to be closed from the left ventricular side. Whereas this approach provides excellent visualization of

the VSD, an incision in the left ventricular apex is more likely to cause ventricular dysfunction.¹⁰ Thus, we prefer to open the right ventricle to avoid risk of left ventricle dysfunction and aneurysm formation.

Regardless of the approach, precise echocardiographic guidance would dramatically facilitate surgery. *Praemonitus praemunitus!* After all, failure to close intramural VSD occurs when surgeons do not realize how close they were to success when they gave up.

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HOW-TO-DO-IT

Prevention of Right Pulmonary Artery Stenosis in Fontan Circulation: The Melbourne Modification of T-Fontan Operation



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Currently, the extracardiac Fontan operation is a procedure of choice in patients undergoing a staged palliation for univentricular hearts. However, it is not always easy to prevent the right pulmonary artery twisting after implantation of the extracardiac conduit. Herein, we described a simple modification, which we referred to as T-Fontan procedure, to prevent right pulmonary artery stenosis after extracardiac Fontan operation.

Keywords

Fontan operation • Pulmonary artery stenosis

The outcomes for patients with univentricular palliation have improved significantly in our unit with the introduction of the extracardiac Fontan operation [1,2]. We have previously described our technique for extracardiac Fontan operation that ensures a long-term patency of the fenestration [3]. Although an early failure of the Fontan circulation has become exceedingly rare in our unit [1], some patients may require takedown of the Fontan circulation [4]. However, large ongoing chest drain losses that persist beyond 10 days after Fontan operation is an indication for cardiac catheterisation in our unit, to ensure that there is no obstruction to the Fontan circulation that is amenable to surgical intervention. Cardiac catheterisation may reveal twisting of the right pulmonary artery (RPA) that may not be apparent in sagittal view (Figure 1, A1), but becomes obvious with slight rotation (Figure 1, A2). We found that such twisting of the RPA is not always easy to appreciate intraoperatively. Thus we introduced a modification to the

extracardiac Fontan operation that we refer to as T-Fontan operation.

Technique

As the RPA stenosis appears to occur after the heart is fully filled and the special geometry of the conduit and RPA changed (Figure 1A and 2A), it is not always easy to foresee and prevent the RPA narrowing intraoperatively. Thus, place the Gore-Tex patch made of the same conduit onto the under-surface of the pulmonary arteries and opposite to the previously placed bidirectional cavo-pulmonary shunt. This patch extends from the hilum of one lung to the hilum of another to ensure optimal augmentation of the pulmonary arteries. The 18 mm Gore-Tex conduit is anastomosed to this patch in end-to-side fashion resembling a T-shaped connection (Figure 1B and Figure 2B).

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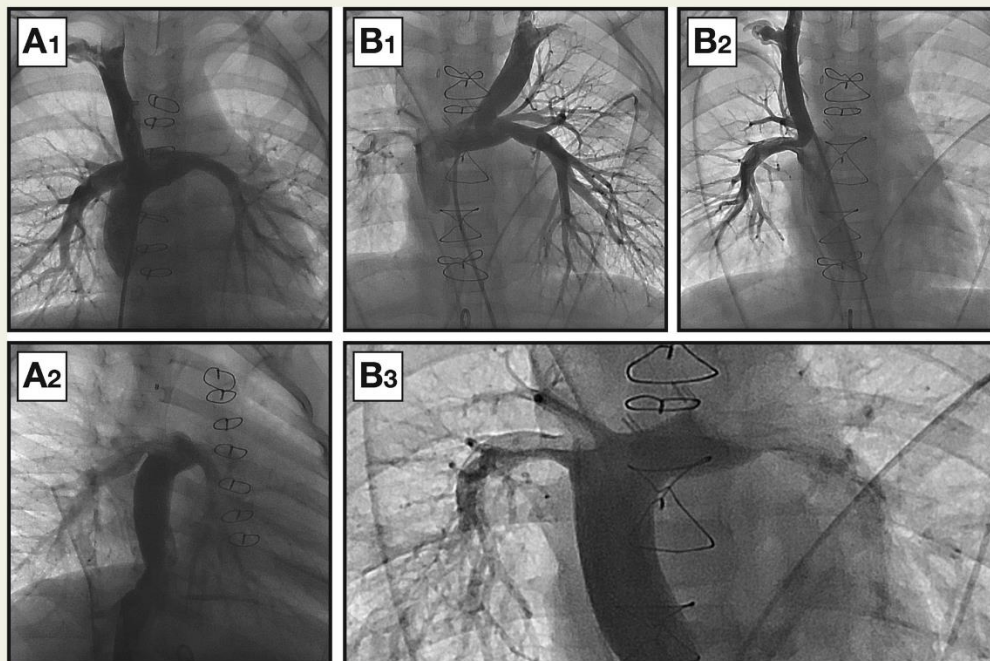


Figure 1 Catheterisation after standard extracardiac Fontan operation demonstrates an unobstructed connection (A1), however, the right pulmonary artery obstruction becomes obvious with rotation (A2). Injection into the left superior vena cava (B1), right superior vena cava (B2) and the conduit (B3) demonstrates unobstructed cavo-pulmonary connections in a patient with T-Fontan operation.

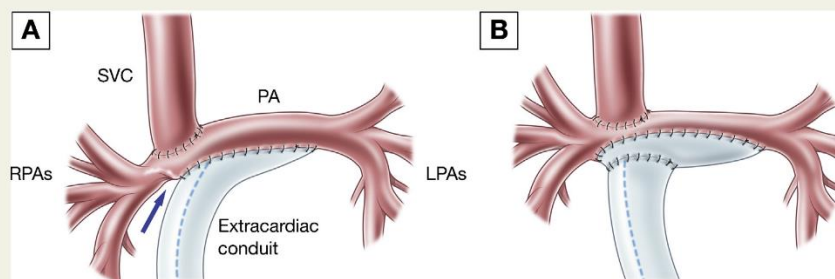


Figure 2 Right pulmonary artery narrowing that may occur in standard extracardiac Fontan operation (A). Modification of end-to-side connection of the conduit in T-Fontan operation (B).

Since September 2013, we have used this technique in 11 patients. It is very simple, reproducible and could add to the armamentarium of surgeons, who perform Fontan operations.

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

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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

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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.

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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,

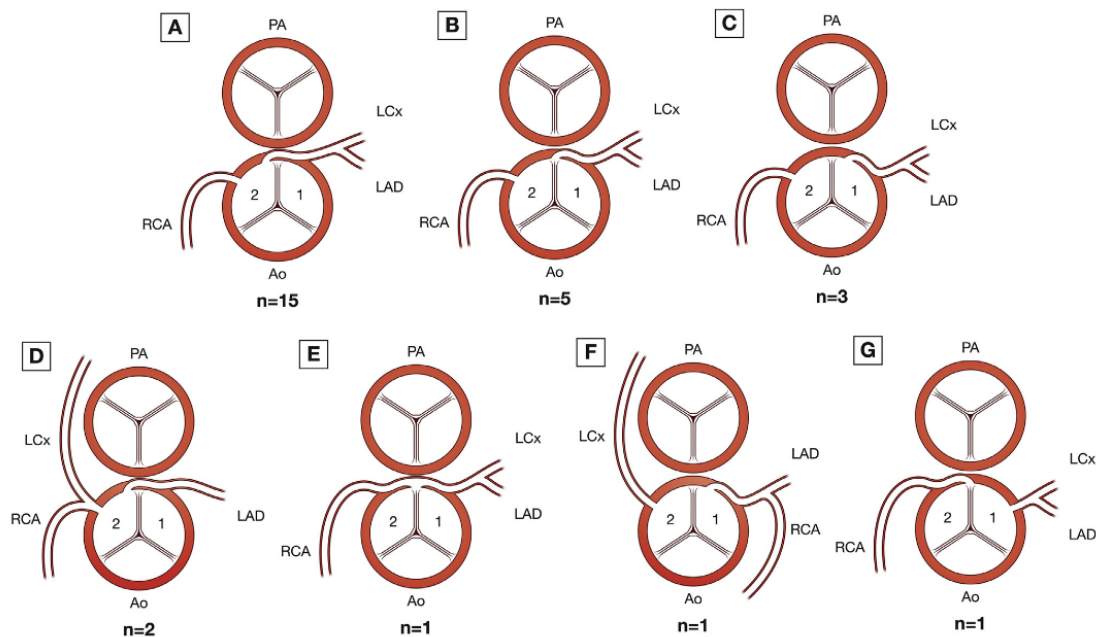


Fig 1. (A–F) Intramural course of the left coronary artery (LCA) was most common ($n = 27$) and in most patients ($n = 17$) the intramural LCA came from sinus 2 (A and D). Intramural right coronary artery (RCA) was encountered in 2 children (E and G). (Ao = aorta; LAD = left anterior descending coronary 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 patient had an angiogram 14 months postoperatively and remained asymptomatic.

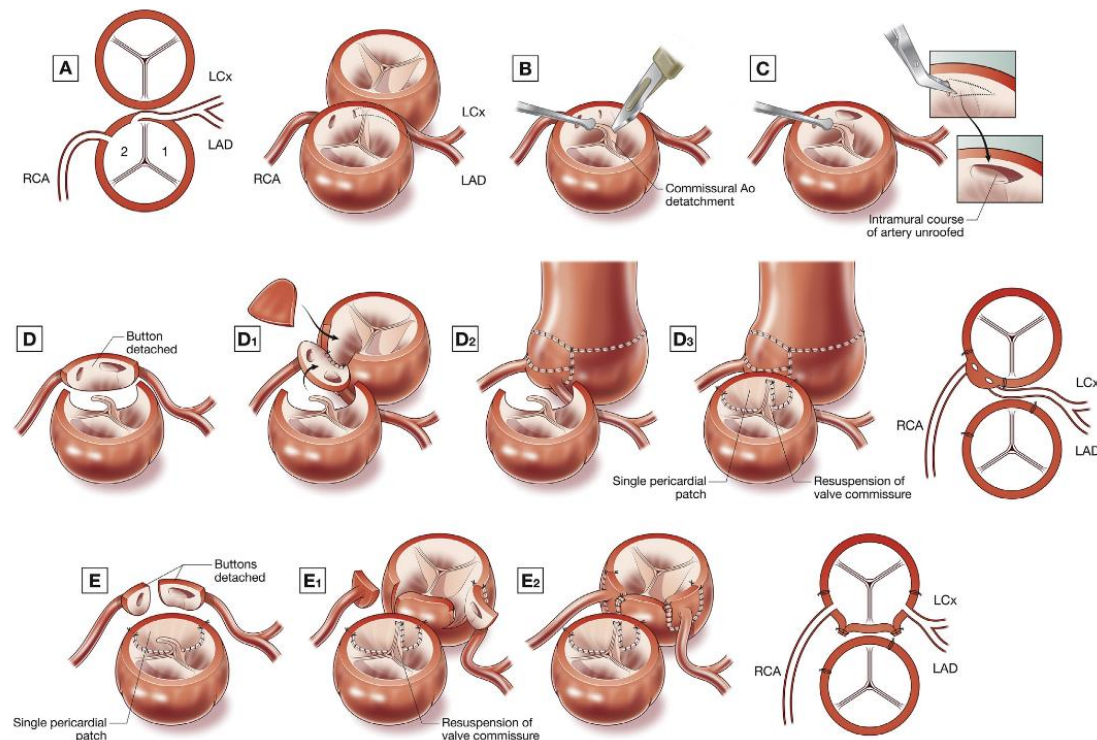


Fig 2. Surgical technique of intramural coronary artery transfer. Following identification of (A) the intramural segment, the detachment of the posterior commissure of (B) the aortic (neopulmonary) valve was performed in most patients ($n = 25$). The unroofing of the (C) intramural coronary artery was done in 16 patients. Then the coronary arteries were detached and transferred either as (D) a single button facilitated with a pericardial hood (D₁–D₃) in the first 3 patients or as (E) two 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 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.

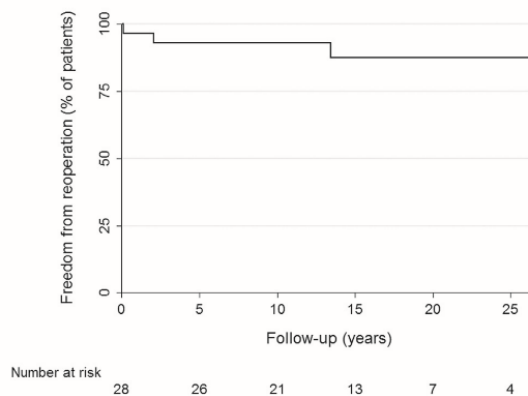


Fig 3. Freedom from reoperation.

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

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

	Mild	Moderate	Severe
Neo-aortic valve regurgitation	9 (32)	0 (0)	0 (0)
Neo-aortic 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 (%).

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.

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AAOC OF LCA FROM RIGHT CORONARY SINUS

of the feeding artery [5]. Meanwhile, systemic artery-to-pulmonary vein fistulae without lung sequestration are rare and are usually diagnosed at an early age [5]. Aberrant vessels originating from the aortic arch and descending aorta have not been reported in adult patients, to our knowledge. Systemic artery-to-pulmonary vein fistulae could be treated with ligation or percutaneous closure of the fistulous tract. Because the two aorta-to-pulmonary vein fistulae in our patient were narrow and tortuous enough to enable the performance of percutaneous procedures, we successfully occluded the fistulae by performing coil embolization.

The diagnosis of multiple systemic artery-to-pulmonary vein fistulae is difficult, and developing a therapeutic strategy is important. Multimodality imaging is crucial for diagnosing multiple fistulae. CT or magnetic resonance imaging is useful in determining the entire course of the tract, the morphologic size and complexities of the fistula, and the presence of associated lung sequestration. The treatment plan for multiple aorta-to-pulmonary vein fistulae should be reasonable and tailored for patient-specific conditions. As a result of the mutual exchange of opinions between the cardiologist, cardiac surgeon, and radiologist, the sequential treatment of the multiple systemic artery-to-pulmonary vein fistulae in our patient was successful.

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Anomalous Aortic Origin of the Left Coronary Artery From the Right Coronary Sinus: Diagnosis and Surgical Repair of Intramural Retrovalvular Coronary Artery

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Anomalous aortic origin of the left coronary artery from the right coronary sinus is a rare congenital anomaly that may cause sudden death. Direct translocation of the left

coronary artery could be difficult due to its intramural course and proximity to the aortic valve. We described the surgical management of a child after sudden hemodynamic collapse and the coronary translocation technique that prevented distortion of the aortic root and allowed successful translocation of the abnormal coronary artery despite its intramural course immediately behind the aortic valve commissure.

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Anomalous aortic origin of a coronary artery (AAOCA) is a rare anomaly that accounts for approximately 0.2% of cardiac malformations [1] and may result in sudden cardiac death [2, 3]. A large proportion of AAOCA also have an interarterial or intramural course, or both [2]. Although an anomalous right CA from the left coronary sinus has been described more often, an anomalous left CA (LCA) from the right coronary sinus has a much greater risk of sudden death [3].

A healthy 10-year-old girl collapsed suddenly while running. She was resuscitated at a peripheral hospital, had ST depression in the inferolateral leads, moderately reduced left ventricular (LV) systolic function and increased lactate (6.3 mmol/L). She was urgently transferred to the intensive care unit of the Royal Children's Hospital with stable vital signs on adrenalin (0.15 µg/kg/min) and O₂ at 4 L/min. Her electrocardiogram showed frequent premature ventricular contractions, short runs of nonsustained ventricular tachycardia, and persistent ischemic changes. A transthoracic echocardiogram demonstrated minimal LV dilatation and preserved systolic function with no obvious wall motion abnormality.

She had cardiac arrest and was emergently placed onto extracorporeal membrane oxygenation support. Cardiac catheterization was performed, right ventricular (RV) biopsy specimen was normal, and the initial coronary angiogram appeared normal, with good flow in all coronary arteries. Owing to elevated troponin and a high index of suspicion of a coronary anomaly, a focused transthoracic echocardiogram was performed on extracorporeal membrane oxygenation and demonstrated the anomalous origin of LCA from the right coronary sinus with an interarterial course. This was confirmed on a cardiac computed tomography angiogram (Fig 1). The intramural segment of the left main CA was too short for unroofing in a way that a neostium could be created far enough into the left coronary sinus to allow commissural resuspension.

Intraoperatively, the intramural LCA was exposed by detaching the aortic valve commissure (Fig 2A and B). The aortic wall of the neoleft coronary sinus was

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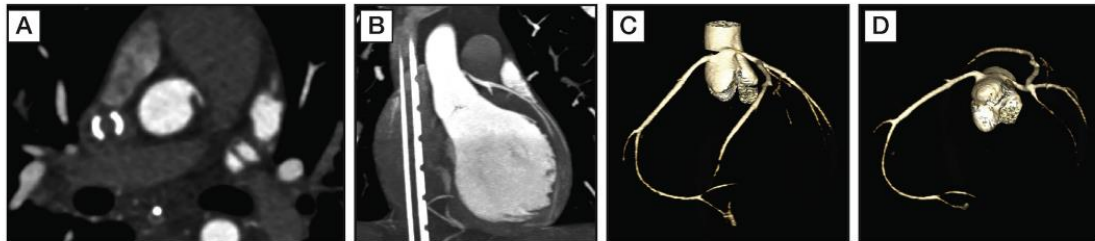


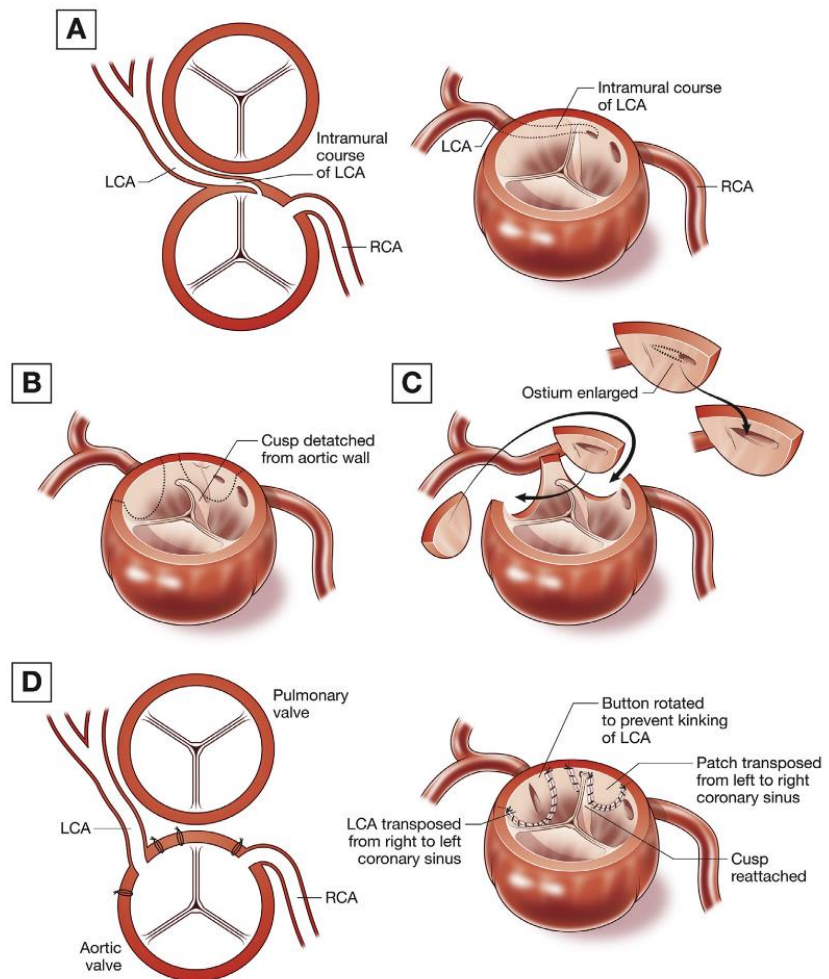
Fig 1. Computed tomography shows (A and B) left coronary artery origin from the right coronary sinus and its proximal interarterial course and (C and D) its intramural course in relation to aortic the valve. (A and B) The venous cannula is in the right atrium.

partially resected and reimplanted into the right coronary sinus after the LCA transfer, and the aortic valve was reattached so that the normal anatomy of the aortic root was preserved (Fig 2C and D). The ostium of the LCA

was enlarged, and the button was rotated to prevent kinking of the LCA.

An intraoperative epicardial echocardiogram confirmed good flow into the LCA after translocation. Owing

Fig 2. (A) Illustration shows the origin and course of the anomalous left coronary artery (LCA) from the right coronary sinus. (B) Intraoperatively, the aortic valve cusp was detached, exposing a retrovalvular intramural course of the LCA. (C) This maneuver allowed unroofing of the intramural LCA. (C and D) The LCA button was then rotated approximately 60 degrees clockwise and was transposed to the left coronary sinus. (RCA = right coronary artery.)



to poor LV function, she was supported with extracorporeal membrane oxygenation, which was weaned off in 2 days after normalization of the LV function. The patient has normal aortic valve function, no aortic insufficiency, is asymptomatic, and after normal results on an exercise test and Holter electrocardiogram monitoring, is involved in competitive swimming at 1 year after the operation.

Comment

The first manifestation of the AAOCA may be sudden death, although many patients may remain asymptomatic [2–4]. Several factors have been proposed to contribute to sudden death, including the intramural course, acute angle of take-off, systolic stretching, and compression of the anomalous CA between the great arteries during exercise [3, 4].

The electrocardiogram is often normal in asymptomatic patients, whereas in only 50% of symptomatic patients it is abnormal [3, 5]. The diagnosis can be made by careful transthoracic echocardiogram, yet is not always easy. A color Doppler examination improves the evaluation by identifying flow within the anomalous CA [6]. A parasternal long-axis sweep between aorta and pulmonary artery can visualize the proximal LCA and increases the accuracy when used in conjunction with parasternal short-axis view [7]. Cardiac computed tomography confirms the diagnosis.

Surgical repair is recommended in all patients with an anomalous LCA from the right coronary sinus due to the increased risk of sudden death [2, 3]. In addition, symptomatic patients with an anomalous right CA from the left coronary sinus should undergo surgical repair, unless it is a nondominant anomalous right CA in an asymptomatic patient [2, 3]. Methods of repairing AAOCA may involve unroofing of the anomalous CA with an intramural course [2–4], direct reimplantation of the anomalous CA [3, 5], CA bypass grafting [2], or pulmonary artery translocation [3]. The unroofing procedure has been reported with good early results (2–4); however, the long-term outcomes are yet to be established.

Experience with surgical repair of the AAOCA in children is limited. Sharma and colleagues [4] described 75 patients (median age, 46 years; range, 13 to 70 years) operated on between 1992 and 2011, all of whom underwent surgical unroofing of an AAOCA, with no early deaths, and 1 late death after mean follow-up of 1.5 years. Similarly, Mainwaring and colleagues [3] described 50 patients (median age, 14 years; range, 5 days to 47 years) operated on between 1999 and 2010, with 35 patients undergoing surgical unroofing. They reported no deaths after mean follow-up of 5.3 years.

Unfortunately, simple unroofing of the intramural CA is not always feasible due to proximity of the aortic valve, as it was in our patient. Such a patient would require reimplantation of the CA after unroofing and reattachment of the aortic valve. The reimplantation is more technically difficult and has a risk of obstruction of the reimplanted CA due to kinking [2]. Reimplantation of

the anomalous CA has been described with good early results [3, 5]. Mainwaring and colleagues [3] described 6 patients who underwent CA reimplantation with no deaths. Similarly, Erez and colleagues [5] described 9 patients (mean age, 12 years; range, 4 months to 23 years) operated on between 2003 and 2005, of whom 7 patients underwent CA reimplantation and 2 patients underwent unroofing of the anomalous CA, with no deaths after a mean follow-up of 1 year.

In the child described in this report, prompt medical attention prevented sudden death, and an echocardiogram was helpful in establishing the diagnosis that was confirmed by computed tomography images. The surgical technique described here allowed successful translocation of the abnormal CA despite its intramural course immediately behind the aortic valve commissure.

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Neonatal Repair in a Patient With Heterotaxy, Truncus Arteriosus, Pulmonary Artery Sling, and Tracheal Stenosis

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We present a newborn with heterotaxy features, multiple congenital anomalies, truncus arteriosus with long segment tracheal stenosis, and a left pulmonary artery sling. The patient had complete neonatal repair with slide