Outcomes of Surgery for the Spectrum of Atrioventricular Septal Defects.

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Abstract

Atrioventricular septal defects (AVSDs) are a spectrum of diseases affecting the atrioventricular septum, junction and valves. Disease severity varies from mild, in the form of partial AVSD, to severe in the form of unbalanced AVSD. Regardless of the severity, all patients require surgery in childhood to improve long-term survival. At each end of the spectrum, research has been relatively limited compared to the amount of attention focused on the commonest form, complete AVSD. Partial AVSD (pAVSD) has been considered a relatively minor defect, often grouped with *secundum* atrial septal defects, but this ignores the fact that pAVSD shares much of the anatomical complexity of other forms of AVSD. Unbalanced AVSD (uAVSD) is frequently not amenable to complete repair, requiring staged palliation resulting in a Fontan circulation. Early results of palliative strategies in these patients were very poor, and there has been relatively little attention paid to the single ventricle palliation strategy in recent years.

This project focuses on these two less studied forms of AVSD, in order to determine current results, and risk factors for poor outcomes. For each condition we have followed the largest series of patients ever reported in the literature, with over 30 years of follow-up.

In children with partial AVSD, we have demonstrated that survival is excellent, yet there is a very high rate of reoperation in the long-term. We found that closing the cleft of the left atrioventricular valve (LAVV) improved outcomes, even when that valve was not incompetent. Reoperation in this group was shown to be mostly due to LAVV regurgitation, and we demonstrated that improved rates of repair could be achieved with a novel patch augmentation technique. While some groups have advocated performing repair in infancy, we demonstrated, in a propensity score matched analysis, that better survival was achieved with repair after one year of age.

In children with unbalanced AVSD, we found that, although there was a high attrition rate, children who achieved Fontan completion had much better outcomes than previously thought possible. We demonstrated that atrioventricular valve (AVV) regurgitation was a major cause of reoperation and morbidity and that outcomes were very poor in children in whom repair failed. Importantly, we found that mechanical prosthetic replacement may be preferable if an adequate repair cannot be achieved.

Finally, we examined the impact of pulmonary artery banding in children with complex AVSD, and demonstrated that it did not worsen AVV regurgitation and allowed the majority of patients to progress to delayed complete repair or Fontan completion.

Declaration

This is to certify that:

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

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

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

Preface

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

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2. Buratto E, Daley M, Ye XT, Radford D, Alphonso N, d'Udekem Y, Brizard CP, Konstantinov IE. Repair of partial atrioventricular septal defect in infancy: is it durable? 97th Annual Meeting of the American Association of Thoracic Surgery. April 29 – May 3, 2017. Boston, MA, USA.

3. Buratto E, Ye XT, Weintraub RG, d'Udekem Y, Brizard CP, Konstantinov IE. Outcomes of univentricular repair in children with unbalanced atrio-ventricular septal defect. 96th Annual Meeting of the American Association of Thoracic Surgery. May 14 – 18, 2016. Baltimore, MD, USA.

4. Buratto E, McCrossan B, Kelly A, Bullock A, d'Udekem Y, Brizard C, Konstantinov IE. Partial atrio-ventricular septal defects: 37 years' experience of surgical repair. 6th World Congress of Paediatric Cardiology and Cardiac Surgery. February 17 – 22, 2013. Cape Town, South Africa.

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List of abbreviations

ASD: atrial septal defect

AVSD: atrioventricular septal defect

AVV: atrioventricular valve

AVVI: atrioventricular valve index

AVVR: atrioventricular valve regurgitation

BCPS: bidirectional cavopulmonary shunt

BiVR/BiVC: biventricular recruitment or conversion

BVR: biventricular repair

cAVSD: complete atrioventricular septal defect

ePTFE: expanded polytetrafluoroethylene

LAR: long axis ratio

LAVV: left atrioventricular valve

LAVVR: left atrioventricular valve regurgitation

LV: left ventricle

LVOT: left ventricular outflow tract

LVOTO: left ventricular outflow tract obstruction

PAB: pulmonary artery band

pAVSD: partial atrioventricular septal defect

RCH: Royal Children's Hospital, Melbourne

RV: right ventricle

SVP: single ventricle palliation

tAVSD: transitional atrioventricular septal defect

uAVSD: unbalanced atrioventricular septal defect

Chapter 1: Introduction and literature review

1.1 Introduction

Atrioventricular septal defects (AVSDs) are a spectrum of diseases, of differing severity, affecting the atrioventricular septum, junction and valves. The incidence of AVSD is approximately 3 - 5 per 10, 000 live births (1 - 4). Although the severity of the different forms of AVSD varies markedly, all share similar developmental origins, common anatomical malformations and require surgery in childhood to improve life expectancy. This family of defects has previously been referred to as atrioventricular canal defects and endocardial cushion defects, the latter name reflecting the putative embryological origin of the atrioventricular septum (5). The current preferred terminology is AVSD, which is used throughout this thesis.

1.2 Anatomy and development of the normal atrioventricular septum

The atrioventricular septum refers to the region of the heart interposed between the normal offset of the tricuspid and mitral valves; it is the septum that separates the right atrium from the left ventricle (6). The atrioventricular junction is characterized by the "figure of eight" structure of the fibrous skeleton of the heart, which surrounds the orifices of the atrioventricular valves providing them with distinct *annuli* (5).

Development of the atrioventricular septum occurs between the 5^{th} and 7^{th} weeks of gestation. In the region of the atrioventricular junction, four mesenchyme filled protrusions form via epithelial to mesenchymal transformation, which are known as the atrioventricular endocardial cushions (7). In the normally developing embryo, the *septum primum* grows caudally from the roof of the common atrium towards the atrioventricular junction (7). The opening between the developing *septum primum* and the endocardial cushions is known as the *foramen primum* and is a site of right to left shunting during this period of development. The leading edge of the *septum primum* is known as the mesenchymal cap (8). An additional septal structure, known as the vestibular spine, protrudes ventrally from the base of the atrium and contributes to development of the interatrial septum. The *foramen primum* is closed when fusion of the endocardial cushions, mesenchymal cap and vestibular spine occurs (7-9). It is

the muscularized vestibular spine, which contributes to the majority of the base of the atrial septum (10).

Septation of the ventricles occurs from the beginning of the 4th week of gestation, with growth of the muscular ventricular septum from the caudal aspect of the developing ventricle, towards the atrioventricular endocardial cushions (10). The muscular septum ceases development prior to reaching the endocardial cushions, leaving an interventricular foramen. Septation of the outflow portions of the interventricular septum occurs due to fusion of the conotruncal swellings, which are protrusions in the outflow tract much like the endocardial cushions. Finally the inlet ventricular septum is formed by fusion of the endocardial cushions, conotruncal swellings, and muscular ventricular septum closing the interventricular foramen (11).

1.3 Anatomy and development of atrioventricular septal defects

The exact mechanism of abnormal development leading to AVSDs has proved elusive for many years. Although traditionally considered "endocardial cushion defects", evidence from limited studies on human embryos demonstrate the mass of endocardial cushion tissue is normal in developing hearts with AVSD (8, 12, 13). It appears instead that failure of the endocardial cushions to properly fuse with the other septal structures is the likely cause of AVSD. It has been shown that the vestibular spine develops abnormally in hearts with AVSD, and as such the current proposed mechanism of AVSD formation is failed fusion of the endocardial cushions due to abnormal development of the vestibular spine (9, 12).

The defining anatomical element of AVSDs is the common atrioventricular junction. (5). There is a deficient ("scooped") inlet ventricular septum and failure of the atrial septum to reach the atrioventricular valves, creating a defect in the interatrial septum adjacent to the atrioventricular valves, known as the *ostium primum* (5, 6). Furthermore, the aorta assumes a more anterior position, as it cannot "wedge" as it normally would between the mitral and tricuspid *annuli*, and there is a disproportionately long outlet portion of the left ventricular mass. This abnormal ratio of inlet to outlet left ventricular mass has been described as the "goose-neck" deformity due to its appearance on cardiac catheterization.

The atrioventricular valves are also abnormal, and it is the relationship of their leaflets to the ventricular septum, which determine the type of AVSD. In all types there are 5 leaflets, two of which are "bridging leaflets" which cross the septum (inferior and superior bridging leaflets, respectively) (5). In the complete form of AVSD (cAVSD), the leaflets have no

attachments to the atrial or ventricular *septae*, hence there is free interatrial and interventricular communication. In the partial form of AVSD (pAVSD) the bridging leaflets are attached to the ventricular septal crest, and although the septal crest remains deficient ("scooped"), there is no interventricular communication (5). It should be noted that this is sometimes referred to as an *ostium primum* atrial septal defect (ASD), however as this belies the abnormalities of the ventricular septum, atrioventricular junction, atrioventricular valves and left ventricular outflow tract (LVOT). As such we prefer the term pAVSD. A third subgroup has some attachments of the leaflets to the ventricular crest, but there remains a restrictive interventricular communication, this form is known as transitional or intermediate AVSD (tAVSD)(8). The most severe form of AVSD results when cAVSD occurs in combination with unbalanced atrioventricular valve orifices over the ventricular septum, a condition known as unbalanced AVSD (uAVSD).

1.4 Partial atrioventricular septal defect

Although pAVSD is the least severe form of AVSD, it carries a poor prognosis if left untreated. A seminal paper by Somerville et al, which followed 122 patients with untreated pAVSD, demonstrated that in a six-year follow-up period, 27% of patients over the age of 30 died, and a further 27% progressed to disability (14). Atrial arrhythmias were the most common cause of deterioration, becoming nearly universal by the age of 50 years. Surgical repair of pAVSD was first performed by Lillehei in 1954 (15), and has been enthusiastically embraced by the surgical community, limiting the number of unrepaired cases described.

Surgical technique

The current approach to repair of pAVSD is via a median sternotomy on cardiopulmonary bypass with aortic and bicaval cannulation. A right atriotomy is performed and the anatomy inspected. In most institutions the cleft in the left atrioventricular valve is closed in its entirety with fine interrupted polypropylene sutures. The LAVV is assessed for regurgitation, and additional valvuloplasty techniques may be employed if necessary. A patch of autologous pericardium is then used to close the *ostium primum* defect, which is anchored with a continuous polypropylene suture along the ventricular septal crest and the margins of the *ostium primum.* The patch may be carried to the left or right of the coronary sinus (16).

Survival

In historical series, early mortality was reported to be in excess of 10% (17 – 21). However, with advances in operative technique and peri-operative management, numerous more recent studies have shown that early mortality following pAVSD repair is very low, ranging from 1 – 3% (22 – 27). Survival at 10-year has been reported in the range of 87% - 98% and 30-year survival has been reported from 78% - 94% (25 – 27).

Multiple studies have analysed risk factors for early and late mortality in these patients. Although there is a degree of heterogeneity between studies, the most consistently reported risk factors for death are age below one year at the time of repair, congestive heart failure at the time of repair, moderate to severe left atrioventricular valve regurgitation (LAVVR) at the time of repair and more complex LAVV pathology (24, 26, 28 – 30). Although it is not a consistent finding in all studies, improved long-term survival with closure of the LAVV cleft has been demonstrated (26).

Reoperation

While major advances have been made in early mortality and long-term survival in more recent years, the high rate of reoperation has remained a problem, albeit somewhat underappreciated in the surgical community. The requirement for reoperation following repair of pAVSD is relatively high, and has been reported to be 8 - 19% at 10-years, and 17 – 25% at 30-years (25 – 27). The most frequent reasons for reoperation are regurgitation through the LAVV and LVOT obstruction (LVOTO), with a smaller number of reoperations required for residual septal defects (31).

The most frequently reported risk factors for reoperation following pAVSD repair are age less than 1 year, moderate or greater preoperative LAVVR, moderate or greater early postoperative LAVVR and failure to close the cleft (24 – 26, 30, 32). Most of these factors relate to reoperation for LAVVR, as this is the most common cause for reoperation.

Quality of life

As health outcomes, such as survival, have improved dramatically since the early days of pAVSD repair, attention should be given to quality of life in these patients as they progress into adulthood (33). This is a topic, which has not been subject to extensive study, and the limited literature available includes small patient numbers and conflicting findings. Welke et al reported quality of life outcomes for 35 patients, who had undergone pAVSD repair as children and were at least 15 years old at the time of the study, finding there was no difference

between these patients and age adjusted norms for physical and mental components of their quality of life (27).

Conversely, Bowman et al (24), in 20 children who had prior pAVSD repair, found that 20% were at risk of impaired quality of life in the emotional domain, while 5% were at risk in the physical domain. They also assessed quality of life in 28 adults, identifying 23.4% as having troubles in the physical domain, while 4.8% described difficulties in social domain (24). This study did not provide a comparison with age matched population norms so it is difficult to interpret the degree of impairment associated with the pAVSD repair itself.

The small number of patients, inconsistent findings, and use of different measures of quality of life make it difficult to ascertain the level of physical and social functioning these patients have as they progress into adult life. Furthermore, up to 20% of patients have Down syndrome, and these patients are typically excluded from such quality of life assessments. These difficulties are not limited to pAVSD but have been found in the entire literature on quality of life outcomes following correction of congenital heart disease (33).

Timing of surgery

There remains some controversy regarding the optimal timing of surgery for patients with pAVSD. Most groups proceed to surgery in the preschool years, between the ages of 2 and 4 years, in stable patients. Surgery is performed earlier in cases of cardiac failure or significant LAVVR (34).

Some groups have advocated performing routine repair in asymptomatic patients prior to the preschool years. Agny et al (35) operated on 38 patients at a median age of 1.8 years between 1981 and 1997 and found a very low rate of long-term LAVVR in their cohort (0.9%), attributing this to earlier repair. However, they reported an early mortality of 7.9%, substantially higher than other contemporary studies. Similarly, the group of Minich et al (36) reporting 87 repairs performed between 2004 and 2006 at a median age of 1.8 years, found lower rates of LAVVR and an earlier return to normal age-matched weight in patients who underwent pAVSD repair, and on this basis advocated earlier surgery.

Conversely, the group of Bowman et al (24), reporting 105 cases performed between 1995 and 2011 at a median age of 7.9 years, demonstrated a significantly lower level of LAVVR in patients who had surgery at an older age, and as such, advocated delaying surgery until after 5 years of age.

The retrospective nature of these studies subjects them to significant risk of bias, and as such they must be interpreted carefully. Age at time of repair is often influenced by other

factors such as degree of pre-operative LAVVR and heart failure, and although Agny et al (35) confined their study to elective cases and Minich et al (36) used multivariable regression in an attempt to address confounding variables, they may not have fully accounted for selection bias.

Approach to the LAVV cleft

The approach to the LAVV has changed over the several decades since pAVSD repair was first performed. In the early years, several groups, most notably the groups of Carpentier et al (37) and Rastelli et al (38), advocated a trifoliate approach to the repair, leaving the LAVV cleft unsutured. More recently most groups advocate routine closure of the LAVV cleft, assuming it can be done without creating stenosis, regardless of the degree of LAVV regurgitation (25, 26). Several studies have shown that closure of the LAVV cleft is associated with lower rates of LAVVR, reoperation on the LAVV and even mortality (26, 27, 39). At reoperation for LAVVR, tearing through of a cleft repair or incomplete initial cleft closure are frequently reported as the reason for LAVVR. In the absence of prospective data, most groups practice routine cleft closure.

Controversy has remained mainly in the approach to the cleft in patients with minimal LAVV regurgitation at operation. The group of Al Hay et al (40) most recently suggested that the cleft between the superior and inferior leaflets should be left unsutured in cases of minimal regurgitation. However, this recommendation was based on a series of only 24 children with pAVSD who did not have cleft closure, so it is unclear how generalisable these results would be.

1.5 Complete atrioventricular septal defect

The natural history for children with unrepaired cAVSD is not entirely clear, as there has never been a longitudinal study following children who have not had surgery. Berger et al (41) combined data from several sources and estimated that in unrepaired patients with cAVSD, 1-year survival was only 35% and 2-year survival was 15%. One of the major contributors to mortality in these children is the early development of pulmonary vascular disease, with irreversible disease occurring in 35% of children in the first year of life (42). Surgical repair in infancy is now routine and associated with excellent results.

Surgical technique

There are three predominant techniques used to repair cAVSD, no single technique has been definitively demonstrated to provide superior results.

The two-patch technique typically utilizes a patch of synthetic material (eg expanded polytetrafluoroethylene) to close the ventricular component of the defect. The bridging leaflets are then anchored to the patch. A separate patch, either synthetic or of autologous pericardium, is then used to close the *ostium primum* defect (43, 44).

The traditional single patch technique requires the surgeon to divide the bridging leaflets at the point where they meet. A single large patch is sutured around the rim of the ventricular defect either with interrupted mattress sutures or as a continuous suture. The bridging leaflets are sutured to the patch, and the patch is then sutured around the *ostium primum* defect with a continuous suture (45).

A simplified single patch technique involves directly closing the ventricular component of the defect by displacing the bridging leaflets apically and suturing them to the ventricular septal crest. Mattress sutures are placed in the ventricular septal crest, through the bridging leaflets and then through the pericardial patch. Tying these sutures closes the ventricular portion. The *ostium primum* defect is then closed with an autologous pericardial patch (46).

Survival

Historical results of repair of cAVSD demonstrated substantial early mortality of greater than 10% (47 – 49). More recently, survival has been much improved, with early mortality reported in the range of 1.5 - 4 % in large series (43, 47, 48, 50 – 55).

There are multiple reports of long-term survival following cAVSD repair. Generally, survival at 10-years has been 85 - 90% (43, 47, 48, 56), while survival at 20-years has been in the range of 80 – 90% (48, 52), with no differences observed with different techniques of repair.

Several studies have analysed risk factors for long-term survival. The most commonly observed risk factors are older age at time of surgery, earlier era of surgery, significant preoperative LAVV regurgitation, additional major cardiovascular malformation, preoperative congestive heart failure, presence of an accessory LAVV orifice and severe post-operative LAVV regurgitation (47, 48, 57, 58).

Reoperation

Similarly to pAVSD, despite considerable gains in early and late survival following cAVSD repair, there remains a considerable risk of reoperation, particularly on the LAVV. Large series estimate freedom from reoperation on the LAVV at 10-years to be 80 – 90 % (43, 47 – 49, 52).

Risk factors for reoperation include incomplete cleft closure, dysplastic LAVV, deficient lateral leaflet, post-operative moderate or greater LAVV regurgitation and additional cardiovascular malformations (47, 52, 53, 55).

Timing of surgery and the use of pulmonary artery banding

Historically the results of complete repair of cAVSD in infancy were poor, with hospital mortality as high as 20% (57). However, in recent years, outcomes have improved markedly, and surgery in infancy has become routine in most centres (43, 49, 51, 54, 56, 59). It has been shown that surgery less than 6 months of age is associated with both improved survival and reduced risk of reoperation (43, 60). It appears that surgery below 3 months of age increases the risk of late reoperation, and as such elective repair between 3 and 6 months of age may provide optimal results (43).

However, there is a challenging group of patients who present with heart failure at less than 3 months of age or with cAVSD associated with additional complex cardiovascular malformations who may not be suitable for immediate complete repair. In these children a pulmonary artery band (PAB) may be used to protect the pulmonary circulation against the development of irreversible pulmonary vascular disease, while allowing complete repair to be deferred, thus permitting the child to grow (61 – 64). However, there is concern that PAB in these children may increase the risk of LAVV regurgitation (64), and it has been unclear what proportion of children would eventually progress to complete repair.

1.6 Unbalanced atrioventricular septal defect

Unbalanced AVSD is the most severe end of the spectrum of AVSD, constituting approximately 10% of all children with AVSD (65). In these patients the inflow of the common AVV is directed preferentially into one of the ventricles, resulting in ventricular imbalance, with a variable degree of hypoplasia of the other ventricle. It is frequently associated with hypoplasia of the outflow structures of the non-dominant ventricle, and multiple other cardiac and extracardiac abnormalities, including a particularly high frequency

of heterotaxy syndromes (66). The optimal approach to this group of patients has proven controversial, with some groups favouring single ventricle palliation (SVP), and others attempting biventricular repair (BVR), depending on the degree of ventricular hypoplasia (65). Generally, results for patients with uAVSD have been much poorer than those with balanced ventricles.

Single ventricle palliation

The traditional surgical approach to uAVSD has been three-stage SVP culminating in the Fontan circulation. In this strategy, staged palliation is performed to allow patients to tolerate total cavopulmonary connection, a functional univentricular circulation in which blood flow passively returns to the pulmonary arteries, while the dominant ventricle supplies the systemic blood flow (67). In large series reporting results for the overall population undergoing Fontan completion, survival at 10-years is 77 - 91% (68 – 73). However, there have been relatively few series examining the outcomes of SVP in patients with uAVSD.

The earliest series describing SVP in patients with uAVSD reported dismal results, with essentially universal mortality (57, 74). More recent reports have demonstrated improved outcomes, but still substantial rates of mortality and morbidity. Drinkwater et al (75) reported 45 patients with uAVSD who underwent SVP between 1986 and 1996. Most patients had RV dominance (25/45, 55.6%). They followed a strategy of pulmonary artery banding (PAB), followed by bidirectional cavopulmonary shunt (BCPS) and Fontan completion. However, only 16 of 45 patients (35.6%) progressed to Fontan completion. Of patients who underwent Fontan operation, 37.5% (6/16) had died at a mean follow-up of 2.5 years.

Owens et al (66) reported 44 patients with uAVSD who presented between 1998 and 2003, of whom 79.5% (35/44) underwent SVP. The majority of patients had right ventricular dominance (39/44, 88.6%). Survival was 51% at a mean follow-up of 25 months. Only 16 of 44 patients (36.4%) progressed to Fontan completion. They reported significantly poorer mid-term survival for SVP in patients with uAVSD when compared with patients with hypoplastic left heart syndrome.

Nathan et al (76) described 83 patients with uAVSD who underwent SVP between 2000 and 2016. They demonstrated a 10-year survival of approximately 60% in children undergoing SVP, while freedom from reoperation was less than 40% at 10-years. The majority of re-operations were on the AVV.

Biventricular strategies

In recent times, several groups have attempted BVR in patients with uAVSD and varying degrees of ventricular imbalance. This requires complex decision making regarding the potential for the non-dominant ventricle to support either the pulmonary or systemic circulation, respectively (77). To date, it remains unclear which patients would benefit from BVR. However, several different thresholds have been described to aid decision making, one of the more commonly used methods is the atrioventricular valve index (AVVI) which is the ratio of the cross-sectional area of the non-dominant ventricle to the dominant ventricle (78). An AVVI<0.67 has been associated with poor outcomes in BVR. One of the challenges in attempting BVR, is that changing strategy to SVP after failed BVR is associated with particularly poor outcomes (77). Nonetheless, several groups have reported mid-term results of modest sized series of patients undergoing BVR with uAVSD.

De Oliviera and colleagues (79) performed biventricular repair on 32 patients with unbalanced AVSD and small RV between 1989 and 2003. Early mortality was 9%, while 10-year survival was 87%. They found that patients with an AVVI <0.5 were at increased risk of early death, and suggested that a 4mm interatrial fenestration may be beneficial in these patients.

Delmo Walter et al (80) described 19 children with uAVSD and a small left ventricle who underwent biventricular repair between 1988 and 2005. They defined uAVSD as an LV/RV long axis ratio (LAR) < 1.1. Early mortality was 10.5%, while 10-year survival was 89.5%. They found LAR <0.65 to be a risk factor for death.

Foker et al (81) reported 23 children with uAVSD who underwent biventricular repair between 1990 and 2005. They defined ventricular hypoplasia as a ventricular volume z score of -2.0. They demonstrated that all patients exhibited catch up growth to normal ventricular size at a mean follow-up of 12 years, while midterm survival was 87%.

Nathan et al (76) studied 212 patients with uAVSD from 2000 to 2016. Three different surgical strategies were used: SVP (82/212), BVR (67/212) and biventricular conversion or recruitment (BiVC/BiVR)(63/212). They reported significantly better survival with both BVR and BiVC/BiVR strategies, compared with SVP. However, this study was biased against SVP, as all patients who were not suitable for BVR, BiVC/BiVR or who died before either strategy could be implemented, were included in the SVP group.

Atrioventricular valve function

Dysfunction of the common atrioventricular valve (AVV) is a major contributor to morbidity and mortality in patients with uAVSD. In published series of patients undergoing SVP, the rate of AVV surgery is approximately 30% (66, 75). The need for AVV surgery in these patients has been shown to be associated with a significantly increased risk of mortality (66). Although biventricular repair may be expected to stabilize the annulus and reduce the risk of AVV regurgitation, in patients receiving BVR or BiVC/BiVR strategies, the rate of AVV reoperation appears similarly high (76).

When AVV regurgitation is present in these patients it is difficult to obtain a competent repair. Early strategies to repair the common AVV were limited to de Vega type annuloplasty, yet the results of this technique were not durable (82). In more recent times, annuloplasty was supplemented by an "edge-to-edge" repair, where the midpoints of the inferior and superior bridging leaflet were approximated with a suture to create a double orifice valve (83). However, this strategy was associated with a substantial rate of late failure (84, 85) The latest technique to be employed in repair of the common AVV is an edge-to-edge repair re-enforced with a strip of expanded polytetrafluoroethylene (ePTFE), a so-called "Goretex bridge." It is hoped that this strategy will stabilize the annulus, reinforce the edge-to-edge repair and allow for growth of the annulus (84, 85). The long-term results of this strategy have yet to be determined.

1.7 Thesis outline

Aims and scope of thesis

This thesis aims to investigate the outcomes of the two less studied forms of AVSD, partial and unbalanced AVSDs. Each of these conditions is the subject of a large retrospective review to determine long-term outcomes and the factors associated with improved survival and freedom from reoperation.

For partial AVSD, particular areas of interest are the rate of reoperation, as well as the controversies surrounding the timing of surgery and approach to the LAVV cleft.

For unbalanced AVSD, we focus on the outcomes of single ventricle palliation as well as the management of complications of the AVV.

Finally, we examine the impact of pulmonary artery banding on patients with AVSD, as it is a potentially important adjunct in the management of complicated forms of complete and unbalanced AVSD.

Chapter objectives

Chapter 2: Determine the short- and long-term outcomes of repair of pAVSD. Particular emphasis is placed on the long-term rate of reoperation and the impact of closure of the LAVV cleft on outcomes.

Chapter 3: Determine the causes of reoperation following repair of pAVSD, with particular focus on the mechanism of failure of the LAVV.

Chapter 4: Evaluate the impact of pAVSD repair in infancy on long-term outcomes using propensity score matching.

Chapter 5: Determine the long-term outcomes of a strategy of single ventricle palliation to treat children with uAVSD.

Chapter 6: Evaluate the outcomes of AVV surgery in patients with uAVSD undergoing single ventricle palliation.

Chapter 7: Evaluate the impact of PAB on the outcomes of children with uAVSD, with particular attention to AVV function and progression to complete repair or Fontan completion.

Chapter 2: Repair of partial atrioventricular septal defect: a 37-year experience

2.1 Introduction

Partial AVSD is the least severe form of AVSD, and repair in childhood has been demonstrated to have excellent short-term and long-term survival in the modern era (25 – 27). The success of operative treatment for pAVSD has led to it being relatively less well studied than other forms of AVSD, and it is often considered a simple form of congenital heart disease, much like *ostium secundum* ASD.

However, the anatomical abnormalities present in pAVSD are more extensive than simply an ASD, and as such a more complicated long-term course is predicted (5). Nevertheless, previous reports have included relatively small numbers of patients and have not included detailed analysis of the risk factors for death and reoperation. Furthermore, there remains controversy about how best to manage the LAVV cleft, with some advocating routine closure (26), while others argue it should not be closed if there is minimal LAVV regurgitation (40).

In order to establish the local outcomes of pAVSD repair and predictors of survival and reoperation, a review was conducted of all patients to have ever had pAVSD repair at the Royal Children's Hospital (RCH). In the period from 1975 to 2012, a total of 249 patients underwent repair of pAVSD. In order to ensure survival data were accurate, matching was performed with the Victorian Registry of Births, Deaths and Marriages.

This study demonstrated very low early mortality and excellent long-term survival following repair of pAVSD. Furthermore, closure of the LAVV cleft was found to be associated with improved survival, even in children without significant LAVV regurgitation.

However, it also identified a high rate of reoperation approaching 25% at 30-years. Most of these reoperations were related to failure of the LAVV. This high rate of reoperation has previously been under appreciated in this population.

Another important finding of this study was the relatively low rate of cardiology specialist follow-up of adult survivors of pAVSD repair. Less than half of adult patients

had recent cardiology follow-up, which is of particular concern given the high rate of reoperation.

Taken together, this study suggested that closer follow-up, particularly for monitoring of the LAVV is warranted in patients with repaired pAVSD.

2.2 Buratto E, et al. Eur J Cardiothorac Surg. 2015;47:796-802.

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ORIGINAL ARTICLE

CONGENITAL

Repair of partial atrioventricular septal defect: a 37-year experience

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Abstract

OBJECTIVES: Partial atrioventricular septal defect (pAVSD) is routinely repaired with a low mortality. However, limited data are available on the long-term follow-up of these patients. The current study was designed to determine long-term survival and morbidity of a large cohort of patients operated on at a single institution.

METHODS: From 1975 to 2012, 249 consecutive patients underwent pAVSD repair at the Royal Children's Hospital. The follow-up data were obtained from hospital records, correspondence with cardiologists and primary care physicians, patient surveys and the state death registry.

RESULTS: The early mortality rate was 1.2% (3/249), while the long-term survival rate was 96% (95% CI: 93–98%) at 10 years and 94% (95% CI: 89–97%) at 30 years. Freedom from reoperation was 84% at 10 years and 75% at 30 years. The most common reoperations were left atrioventricular valve surgery (30/249, 12.1%), resection of left ventricular outflow tract obstruction (12/249, 4.8%) and closure of residual atrial septal defects (5/249, 2.0%). Implantation of a permanent pacemaker was required in 3.2% (8/249) of patients. Despite a substantial reoperation rate, only 43% of patients older than 18 years of age were seen by a cardiologist within the most recent 2 years of the study period, compared with 80% of those younger than 18 years ($P < 0.001$).

CONCLUSIONS: Repair of pAVSD is performed with a low mortality and excellent long-term survival. However, a substantial reoperation rate warrants close follow-up into adulthood.

Keywords: Congenital heart disease • Septal defects • Outcomes

INTRODUCTION

The spectrum of atrioventricular septal defects makes up 7–17% of congenital heart disease [1], of which partial atrioventricular septal defects (pAVSDs) constitute ~25% [2]. Typically, pAVSD is repaired in the preschool years, or earlier if signs of heart failure develop. An operative mortality rate of 1.6–13% [3–10] and a long-term survival rate of 78–85% at 30-years follow-up [3, 5] have been reported. The reoperation rate ranges from 17 to 20% at 30-years follow-up [3, 5]. Here, we review our results with an emphasis on long-term follow-up.

MATERIALS AND METHODS

Patients

Between January 1975 and January 2012, 249 consecutive patients underwent surgical correction of a pAVSD at the Royal Children's Hospital, Melbourne, and were included in the present retrospective review. Ethics approval was granted by the Royal Children's Hospital Human Research Ethics Committee.

Data were obtained by retrospective review of patient records and follow-up was obtained by correspondence with the patient's cardiologist or general practitioner. Patients were contacted by telephone and asked to complete a questionnaire if no current medical practitioner could be identified. For patients who were lost to follow-up, the Victorian registry of Birth Deaths and Marriages was searched for death records.

Definitions

Left atrioventricular valve regurgitation (LAVVR) was evaluated by echocardiography and its severity was graded according to the American Society of Echocardiography criteria [11].

Early postoperative LAVVR was defined as LAVVR as measured on postoperative transthoracic echocardiography during the initial admission.

Left atrioventricular valve (LAVV) stenosis was defined as a left atrium to left ventricular diastolic pressure gradient >5 mmHg or operation for LAVV stenosis.

Left ventricular outflow tract obstruction (LVOTO) was defined as a gradient of >20 mmHg across the LVOT or surgery for LVOTO [12].

Early mortality was defined as death occurring prior to hospital discharge or within 30 days of operation.

Complete LAVV cleft closure was defined as direct closure of the entire cleft of the left atrioventricular valve to the chordal attachment. Partial cleft closure was defined as any degree of incomplete closure of the cleft.

Clinically significant arrhythmia was defined as any arrhythmia on discharge from the hospital that required medication or implantation of a permanent pacemaker or implantable cardiac defibrillator.

Complete cardiology follow-up was considered to have occurred when a patient had been reviewed by a cardiologist on or after 1 January 2012.

Operative procedure

The repair of pAVSD was performed through a median sternotomy with bicaval cannulation and cardiopulmonary bypass with hypothermic cardioplegic arrest. The decision to close the cleft in the LAVV was made at the surgeon's discretion, depending on the degree of LAVVR on preoperative echocardiogram and as assessed at surgery with normal saline infusion. The ostium primum defect was repaired with an autologous pericardial patch. In a small number of patients prior to 1990 Dacron (7 patients) or Teflon felt (2 patients) patches or direct suture closure (2 patients) were used to repair the ostium primum defect. Hypothermic circulatory arrest was used only in 10 patients operated on prior to 1990.

Statistical analysis

Data were analysed with STATA version 12 (Stata Corp., College Station, TX, USA). Unless stated to the contrary, continuous data were summarized as mean ± standard deviation. The time-dependent end-points investigated were: all-cause mortality, the first cardiac reoperation, the first reoperation for LAVV regurgitation and the first reoperation for LVOTO. For all end-points, time was measured starting from repair for pAVSD. Reoperation times were considered to have been censored in the event of death (but not other types of reoperation). Kaplan–Meier analysis was used to estimate survival and freedom from reoperation. Cox proportional hazards regression was used to examine risk factors for mortality, first reoperation and first reoperation for LAVVR. The risk factors examined were: age, sex, trisomy 21 status, presence of associated congenital heart defects, previous operation, congestive heart failure (CHF), degree of pre-operative LAVVR, decade of operation, cleft closure and additional surgical procedures and degree of early post-operative LAVVR. Where appropriate, for analysis continuous variables were converted to *z*-scores to allow better comparison of estimated hazard ratios between continuous and binary factors. For mortality, univariable analysis only was performed due to the small number of deaths (12 in total). For the reoperation end-points, factors with large effect size (HR >2.0 or HR <0.5) together with moderate evidence against the null hypothesis ($P < 0.25$) upon univariable analysis were considered for inclusion in the multivariable model. Owing to the small number of first reoperations and first reoperations for LAVV regurgitation among patients with complete covariate data (29 and 19 in total, respectively), these multivariable models were restricted to three and two factors, respectively. Test of the proportional hazards assumption was based on Schoenfeld residuals. For patients known to be alive at the end of the study, completeness of cardiology follow-up between patients younger than 18 years and patients older than 18 years on 1 January 2012 was compared using a χ^2 test.

RESULTS

Patient demographics

Demographic data are summarized in Table 1. The mean age of patients at operation was 4.1 ± 3.8 years; 49.0% (122/249) were male and 51.0% (127/249) were female. Trisomy 21 was diagnosed in 20.9% of the cohort (52/249). At the time of complete repair, 16.8% (42/249) had CHF and 28.1% (70/249) had moderate or severe LAVVR. A total of 219 associated defects occurred in 134 patients (53.8%), which are detailed in Table 2.

Intraoperative details

Intraoperative data are summarized in Table 1. The mean cardiopulmonary bypass time was 78.9 ± 30.0 min, while the mean aortic cross-clamp time was 50.3 ± 22.0 min. The cleft in the LAVV was completely closed in 66% (164/249), partially closed in 15% (37/249) and not closed in 19% (48/249).

Additional concurrent procedures were performed on 139 (55.8%) patients who underwent a total of 183 additional procedures, which are detailed in Table 2. Briefly, the most common were

Table 1: Demographics and intraoperative data

Total	249
Age at pAVSD repair in years (median [IQR] [range])	2.9 [1.4–5.1] [0.05–18.1]
Sex	
Male, number (%)	122 (49.0)
Female, number (%)	127 (51.0)
Down syndrome, number (%)	52 (20.9)
Weight at pAVSD repair in kg (median [IQR] [range])	12.5 [8.6–17] [2.9–62]
Preoperative CHF, number (%)	42 (16.9)
LAVV regurgitation moderate or severe, number (%)	70 (28.1)
Associated defects, number (%)	134 (53.8)
Prior operations, number (%)	17 (6.8)
Bypass time (min)	78.9 ± 30.0
Cross-clamp time (min)	50.3 ± 21.9
Associated procedure, number (%)	139 (55.8)
Cleft, number (%)	
Not closed	48 (19.3)
Partially closed	37 (14.9)
Completely closed	164 (65.9)
Primum ASD, number (%)	
Direct closure	2 (0.8)
Pericardial patch	237 (95.2)
Dacron patch	7 (2.8)
Teflon felt patch	3 (1.2)

paAVSD: partial atrioventricular septal defect; ASD: atrial septal defect; CHF: congestive heart failure; IQR: interquartile range.

Table 2: Associated congenital heart disease and additional procedures

	Number (%) of patients
Associated CHD	
Secundum ASD/PFO	88 (35.3)
PDA	26 (10.4)
VSD[a]	29 (11.6)
Coarctation	14 (5.6)
LSVC	13 (5.2)
Double orifice LAVV	10 (4.0)
Pulmonary hypertension	7 (2.8)
Left atrial isomerism	3 (1.2)
Right-sided aortic arch	2 (0.8)
Other[b]	9 (3.6)
Additional procedure	
Secundum ASD/PFO closure	88 (35.3)
VSD closure	27 (10.8)
Additional LAVV procedure	22 (8.8)
PDA ligation	18 (7.2)
LVOTO resection	6 (2.4)
Lung biopsy	6 (2.4)
Additional RAVV procedure	5 (2.0)
LSVC ligation	5 (2.0)
Other[c]	6 (2.4)

ASD/PFO: atrial septal defect/patent foramen ovale; CHD: congenital heart disease; LAVV: left atrioventricular valve; LSVC: left superior vena cava; PDA: patent ductus arteriosus; RAVV: right atrioventricular valve; VSD: ventricular septal defect; LVOTO: left ventricular outflow tract obstruction.
[a]VSD in the muscular septum, not adjacent to atrioventricular valves.
[b]Absent RAVV septal cusp ($n = 1$), anomalous left carotid arising from left pulmonary artery ($n = 1$), coronary sinus atresia ($n = 1$), abnormal papillary muscles ($n = 1$), double orifice RAVV ($n = 1$), right ventricular outflow tract obstruction ($n = 1$), dextrocardia ($n = 1$), pulmonary stenosis ($n = 1$) and cor tritriatum ($n = 1$).
[c]Unroofing of the coronary sinus common pulmonary vein channel ($n = 1$), ligation of anomalous right carotid ($n = 1$), baffling of superior vena cava to the right atrium ($n = 1$), resection of right ventricular outflow tract obstruction ($n = 1$), cor triatriatum repair ($n = 1$) and coarctation repair ($n = 1$).

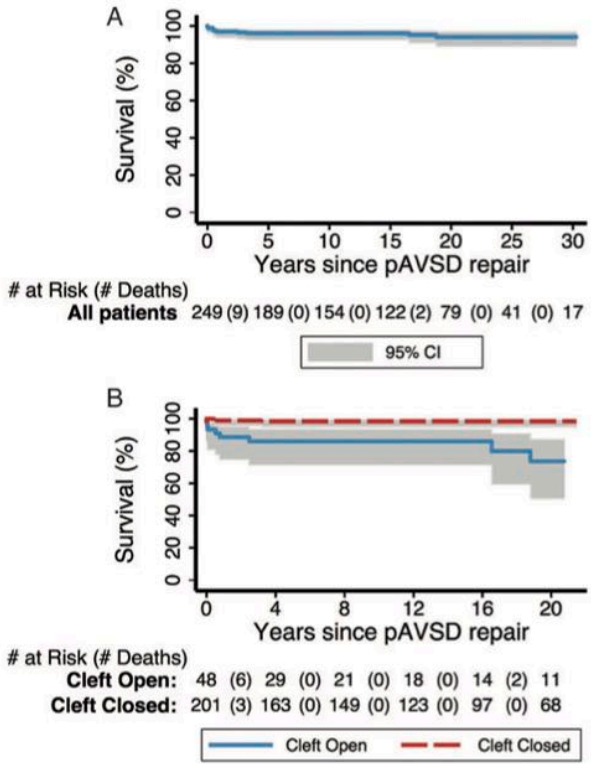

Figure 1: Kaplan–Meier survival curve for (**A**) entire cohort and (**B**) patients stratified by whether cleft was left open or closed.

patent foramen ovale or secundum atrical septal defect (ASD) closure in 35.3% (88/249), ventricular septal defect (VSD) closure in 10.8% (27/249), additional procedures on the LAVV in 8.8% (22/249) and patent ductus arteriosus ligation in 7.2% (18/249).

Survival

The mean follow-up for patients was 15.1 ± 9.8 years spanning 1 day to 37.5 years, with 204 patients (82%) having complete follow-up (last follow-up for survivors occurred on or after 1 January 2012).

Three patients died in the hospital, making the early mortality rate 1.2% (3/249). The first patient was a 3-week old girl operated on in 1987, transferred from a peripheral hospital *in extremis*. She had a double orifice LAVV, multiple muscular VSDs, severe right atrioventricular valve regurgitation and pulmonary hypertension. On the first day after complete repair the patient had a cardiac arrest and could not be resuscitated. The second patient was a 3-week old boy operated on in 1993, with a severely regurgitant, dysplastic LAVV. He was ventilator dependent following subclavian flap repair for aortic coarctation. Following complete repair of pAVSD, multiple attempts to wean off inotropes resulted in severe pulmonary congestion. Mitral valve replacement was performed but the patient could not be weaned off bypass and treatment was withdrawn. The third patient was a 4-month old boy operated on in 2007, with pAVSD, down syndrome, secundum ASD, pulmonary hypertension and chronic lung disease. The child had a cardiac arrest preoperatively, was rushed to the operating room and placed on cardiopulmonary bypass. After complete repair of the pAVSD, the patient was brought to the ICU with extracorporeal membrane oxygenator (ECMO) support. The patient developed sepsis and persistent pulmonary hypertension. The ECMO was withdrawn on the 11th postoperative day and the patient died.

The late mortality rate among hospital survivors was 3.6% (9/246). Survival is illustrated in Fig. 1 and Table 3. The survival rate at 10 and 30 years was 96% (95% CI: 93–98%) and 94% (95% CI: 89–97%), respectively. By univariable analysis (Table 4), higher age at pAVSD repair (HR = 0.22; 95% CI: 0.1–0.5) and closure of the LAVV cleft (HR = 0.08; 95% CI: 0.02–0.29) were the factors most likely to be associated with decreased risk of mortality, while preoperative CHF (HR = 14; 95% CI: 3.9–53) was associated with an increased risk of mortality. As noted in the statistical methods, multivariable analysis to separate the effects of these factors was not feasible due to the small number of deaths.

When patients with trivial to mild preoperative LAVVR were analysed as a separate group, older age at pAVSD repair (HR = 0.25; 95% CI: 0.1–0.6; $P = 0.003$) and closure of the cleft (HR = 0.12; 95% CI: 0.1–0.5; $P = 0.003$) remained predictors of better long-term survival, while preoperative CHF (HR = 22; 95% CI: 4.6–106; $P < 0.001$) and early postoperative moderate-to-severe LAVV regurgitation (HR = 8.2; 95% CI: 1.6–45; $P = 0.011$) were associated with increased risk of mortality.

Table 3: Outcomes by decade of pAVSD

Item	Decade			
	1975–1984	1985–1994	1995–2004	2005 onwards
Number of patients	35	88	84	42
Age at pAVSD repair (median [IQR])	4.3 [2.5–5.4]	2.3 [1.4–5.0]	2.5 [1.1–5.0]	3.5 [1.5–5.4]
Cleft closed, *n* (%); *P*-value*	23 (66%)	78 (89%); *P* = 0.003	72 (86%); *P* = 0.013	28 (67%); *P* = 0.93
Early mortality, *n* (%)	0 (0%)	2 (2.2%)	0 (0%)	1 (2.4%)
5-year survival [% (95% CI)]	91% (75–97%)	98% (91–99%)	97% (89–99%)	95% (82–99%)
10-year survival [% (95% CI)]	91% (75–97%)	98% (91–99%)	97% (89–99%)	–
5-year freedom from reoperation [% (95% CI)]	82% (65–92%)	85% (75–92%)	92% (83–96%)	87% (72–94%)
10-year freedom from reoperation [% (95% CI)]	82% (65–92%)	79% (68–86%)	89% (78–94%)	–

paAVSD: partial atrioventricular septal defect; IQR: interquartile range.
*P-value is derived from the χ^2 test of the given decade compared with the 1975–84 decade.

Table 4: Univariable analysis of risk factors for mortality following pAVSD repair

Factor	*n*	HR	*P*-value	95% CI	
Preoperative congestive heart failure	249	14.30	<0.001	3.9	53.1
Left AV valve cleft was closed	249	0.08	<0.001	0.0	0.3
Age at pAVSD repair (in years)	249	0.22	<0.001	0.1	0.5
Early postoperative moderate to severe LAVV regurgitation	183	4.62	0.064	0.9	23.4
Presence of associated congenital heart defects	249	4.10	0.069	0.9	18.7
Patient had prior operation	244	2.73	0.199	0.6	12.7
Sex (0 = male; 1 = female)	249	2.19	0.204	0.7	7.3
Date of pAVSD procedure (on *z*-score scale)	249	0.87	0.669	0.5	1.6
Patient had concomitant surgical procedure	249	1.24	0.713	0.4	4.0
Preoperative moderate to severe left AV valve (LAVV) regurgitation	249	0.89	0.866	0.2	3.3

AV: atrioventricular; paAVSD: partial atrioventricular septal defect; LAVV: left atrioventricular valve.

Table 5: Reoperations

Procedure	Number (%) of reoperations
LAVV surgery	39 (58.2)
LVOTO resection	16 (23.9)
Residual ASD closure	6 (9.0)
Residual VSD closure	2 (3.0)
Other[a]	4 (6.0)

ASD: atrial septal defect; LAVV: left atrioventricular valve; LVOTO: left ventricular outflow tract obstruction; VSD: ventricular septal defect.
[a]RAVV repair (*n* = 1), sub-pulmonary resection (*n* = 1), orthotopic heart transplant (*n* = 1), left ventricular assist device implantation (*n* = 1).

Reoperations

A total of 67 reoperations were performed on 43 patients (18.7%), which are summarized in Table 5. Freedom from reoperation is shown in Fig. 2. Freedom from reoperation at the 10- and 30-year follow-up was 84% (95% CI: 78–88%) and 75% (95% CI: 67–81%), respectively. By univariable analysis (Table 6), preoperative CHF (HR = 4.3; 95% CI: 2.3–8.0), cardiovascular surgery prior to pAVSD repair (HR = 3.2; 95% CI: 1.4–7.3), moderate-to-severe early postoperative LAVVR (HR = 7.3; 95% CI: 3.3–16) and older age at pAVSD repair (HR = 0.8; 95% CI: 0.7–0.96) were the factors most likely to be associated with reoperation. Under multivariable analysis, moderate to severe early postoperative LAVV regurgitation, preoperative CHF and cardiovascular surgery prior to pAVSD repair remained independently associated with increased risk of reoperation (Table 6).

Reoperation for LAVVR was performed in 12.1% (30/249) of patients, who underwent a total of 39 LAVV procedures. By univariable analysis, preoperative CHF (HR = 4.4; 95% CI: 2.1–9.3), preoperative moderate to severe LAVV regurgitation (HR = 2.6; 95% CI: 1.2–5.4), younger age at pAVSD repair (in years) (HR = 0.8; 95% CI: 0.7–0.95) and moderate to severe early postoperative LAVVR (HR = 14.6, 95% CI: 5.9–36) were the factors most likely to be associated with later reoperation for LAVV regurgitation. Under multivariable analysis, both early postoperative LAVV regurgitation and preoperative CHF remained independently predictive of the need for repeat LAVV surgery (Table 6).

Reoperation for LVOTO was performed in 12 patients (5.2%) who underwent a total of 16 LVOTO resections. Six reoperations for residual ASD were performed in 4 patients (2.0%), while 2 patients had reoperation for residual VSD (0.8%).

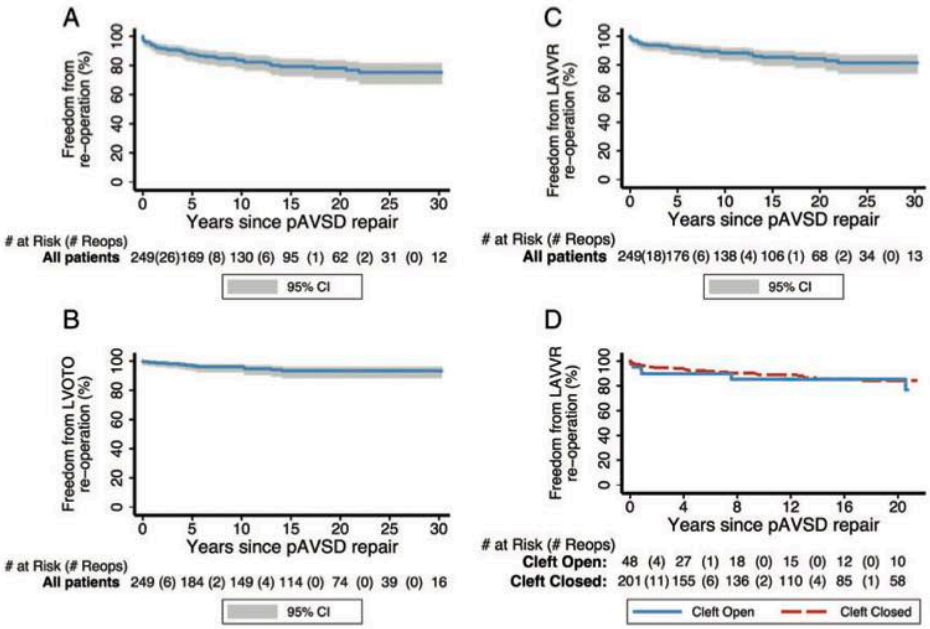

Figure 2: Kaplan–Meier curves for (**A**) freedom from reoperation, (**B**) freedom from first reoperation for left ventricular outflow tract obstruction, (**C**) freedom from first reoperation for left atrioventricular valve regurgitation for the entire cohort and (**D**) freedom from first reoperation for LAVVR stratified by whether the cleft was left open or closed.

Table 6: Risk factors associated with reoperation following pAVSD repair

Factor	Univariable					Multivariable[a]			
	n	HR	*P*-value	95% CI		HR	*P*-value	95% CI	
Risk factors for first reoperation						*n* = 180 (29 first reops)			
Early postoperative moderate to severe LAVV regurgitation	182	7.3	<0.001	3.3	16.0	8.2	<0.001	3.3	18.1
Preoperative congestive heart failure	246	4.3	<0.001	2.3	8.0	2.5	0.02	0.9	4.6
Patient had prior operation	241	3.2	0.005	1.4	7.3	3.7	0.015	1.2	10.0
Age at pAVSD repair (in years)	246	0.8	0.006	0.7	1.0				
Preoperative moderate to severe left AV valve (LAVV) regurgitation	246	1.8	0.06	1.0	3.4				
Sex (0 = male; 1 = female)	246	1.5	0.19	0.8	2.8				
Date of pAVSD procedure (on *z*-score scale)	246	0.8	0.22	0.6	1.1				
Presence of associated congenital heart defects	246	1.2	0.60	0.6	2.2				
Left AV valve cleft was closed	246	0.9	0.73	0.4	2.0				
Patient had concomitant surgical procedure	246	1.0	0.89	0.6	1.9				
Risk factors for first reoperation for LAVVR						*n* = 171 (19 first reops)			
Early postoperative moderate to severe LAVV regurgitation	171	14.6	<0.001	5.9	36.2	13.5	<0.001	5.4	33.9
Preoperative congestive heart failure	231	4.4	<0.001	2.1	9.3	2.8	0.034	1.1	7.2
Preoperative moderate to severe left AV valve (LAVV) regurgitation	231	2.6	0.013	1.2	5.4				
Age at pAVSD repair (in years)	231	0.8	0.020	0.7	1.0				
Patient had prior operation	231	2.1	0.165	0.7	6.1				
Date of pAVSD procedure (on *z*-score scale)	231	0.8	0.186	0.5	1.1				
Sex (0 = male; 1 = female)	231	1.3	0.439	0.6	2.8				
Patient had concomitant surgical procedure	231	0.9	0.693	0.4	1.8				
Presence of associated congenital heart defects	231	1.1	0.731	0.5	2.4				
Left AV valve cleft was closed	231	0.8	0.737	0.3	2.2				

AV: atrioventricular; paAVSD: partial atrioventricular septal defect; LAVV: left atrioventricular valve: LLVR: left atrioventricular valve regurgitation.
[a]The number of factors entered into each model was limited according to the number of observed first reoperations for that outcome.

Left atrioventricular valve dysfunction

Follow-up on LAVV status by echocardiography was available for 199 patients. LAVV regurgitation was as follows: 65% (130/199) of patients had mild or trivial LAVV regurgitation, 20% (39/199) of patients had moderate or severe LAVV regurgitation but had not had an operation. Surgery for LAVV regurgitation was performed in 15% (30/199) of patients. Regarding LAVV stenosis, 95% (189/199) of patients were free of LAVV stenosis 3.5% (7/249) of patients had mild LAVV stenosis, 0.5% (1/199) of patients had moderate LAVV

stenosis. Surgery for LAVV stenosis was performed in 2 patients (1.0%) both of whom had mixed LAVV stenosis and regurgitation.

Left ventricular outflow tract obstruction

Information on the status of the LVOT was available for 200 patients (84%): 173 patients were free of LVOTO (86%), 15 patients (8%) had LVOTO that had not required surgery and 12 patients (6%) had LVOTO resection.

Arrhythmias

Documented information on arrhythmias was available for 202 patients, of whom 13 patients (6.4%) had a clinically significant arrhythmia. Arrhythmias identified were atrial fibrillation in 1.5% (3/202), supraventricular tachycardia in 1.5% (3/202), sick sinus syndrome in 1.5% (3/202) and heart block in 2.0% (4/202). Permanent pacemakers were implanted in 3.2% of the patients (8/249), for heart block (Mobitz type II, $n = 1$ and complete heart block, $n = 3$) and for sick sinus syndrome ($n = 4$).

Cardiology follow-up for local patients

Of the 235 local patients, there were 200 patients for whom the date of their last visit to a cardiologist was known. The median duration of cardiology follow-up for these patients was 10.6 years (interquartile range: 5.3–17.3 years). Among these 200 patients, 177 were known to be alive at the end of the study on 1 January 2012, with 98 patients (55%) under 18 years of age. For patients under 18 years of age, 78 (80%) were seen by a cardiologist after 1 January 2012, compared with 34 patients (43%) over 18 years of age ($P < 0.001$).

COMMENT

Complete repair of pAVSD was first performed at the Royal Children's Hospital in 1975. The current study was designed to review the long-term outcomes for pAVSD repair at a single institution.

The operative mortality rate of 1.2% in our study was lower compared with other studies, which have generally reported an early mortality rate in the range of 1.6–5% for pAVSD repair performed in children [3–8]. In contrast, Baufreton *et al.* [9] in a cohort of 100 patients operated on from 1989 to 1993 reported an early mortality rate of 13%, but included both partial and intermediate AVSD repair, while Agny *et al.* [10] in a cohort of 51 patients undergoing pAVSD repair from 1981 to 1997, with a relatively lower mean age of 22 months, reported an early mortality rate of 7.9%.

The long-term survival rate was 96% at 10 years and 94% at 30 years, respectively. This compared favourably with other studies, which have demonstrated survival rates of 93–98% at the 10-year and 78–85% at the 30-year follow-up, respectively [3–5]. Older age at time of operation and closure of the LAVV cleft were predictors of better long-term survival, while preoperative CHF was a risk factor for death.

The present study found reoperation rates of 16% at 10 years and 25% at 30 years, which were somewhat higher than in previous studies, which have varied by 17 to 20% at the 30-year follow-up [3, 5]. It is unclear from the current study whether the improved survival of our patients resulted in more patients surviving long enough to require a reoperation or if a more aggressive reoperation strategy resulted in improved survival. This improved survival of our patients is, however, consistent with the findings of Stulak *et al.* [13], who, in a cohort of 96 patients undergoing reoperation following pAVSD between 1962 and 2006, demonstrated that reoperation following pAVSD repair could be performed with good long-term survival.

Freedom from LAVV reintervention was 77% at 30 years. Reoperation for LAVV surgery was strongly associated with the presence of early postoperative moderate to severe LAVV regurgitation. Freedom from surgery for LVOTO was 92% at the 30-year follow-up. LVOTO requiring surgery has previously been described to occur in 10% of patients at the 10-year follow-up [4] and is multifactorial, related to intrinsic narrowing and elongation of the LVOT, malalignment of the aorta, squeezing of the LVOT by its muscular walls and anomalous insertion of the LAVV tension apparatus [14].

Interestingly, in our cohort the year of operation did not influence the outcomes. This is in contrast to the findings of El-Najdawi *et al.* [3], describing 334 patients undergoing pAVSD from 1955 to 1995, and Najm *et al.* [4], who presented 180 patients undergoing pAVSD repair between 1982 and 1996, demonstrating a decrease in mortality in more recent years of their cohorts. Decreasing mortality over time is also demonstrated by comparing these more recent cohorts with historical results presented by Losay *et al.* [15] in a cohort of 92 patients operated on between 1955 and 1975. The present study enrolled patients from 1975 to 2011 inclusive, which represents a relatively more recent cohort, with approximately three-quarters of patients operated on after 1990. It is possible that many of the advancements in treatment that were introduced during the enrolment periods of other studies were present for the majority of cases included in this study. For example throughout the study period we have operated on patients at a younger age, compared with the series of Welke *et al.* [5], and El-Najdawi *et al.* [3], where in the earlier decades the mean patient age was 9–10 years. Likewise, there was no consistent trend to increasing rates of cleft closure over time, unlike in the cohort of Welke *et al.* [5], where in more recent decades the rates of cleft closure were significantly higher.

An ongoing topic of contention has been whether the cleft in the LAVV should be closed in patients without significant LAVVR [16]. In the present study, as in other reports [3, 5, 6], the decision to close the cleft was made by the surgeon based on the intraoperative examination of the valve. We have demonstrated that cleft closure is associated with improved survival, whether or not patients had significant preoperative LAVVR. This is in contrast to Al Hay *et al.* [6], who, describing a cohort of 126 patients with pAVSD and trivial to mild LAVVR repaired between 1983 and 2003, concluded that the cleft should be left open if the LAVV is competent. It should be noted that they did not analyse long-term survival, probably due to their smaller cohort and shorter follow-up. Conversely, our results are consistent with other groups who analysed cohorts with LAVVR ranging from trivial to severe [3, 5]. Owing to the retrospective nature of the study we cannot prove causation, but this would seem to further support routine cleft closure as advocated by other groups [4, 16].

Given the excellent survival, but higher reoperation rate found in our study, we believe that further improvement lies in thorough follow-up and reduction of long-term morbidity. A key component of this approach should be the maintenance of regular cardiology follow-up after transition to adult cardiology service. While patients tended to have good follow-up to the age of 18 years, thereafter follow-up fell to around 40%. This is consistent with the report by Mackie *et al.* [17], who found that cardiology follow-up falls away with increasing age. Our current practice is to follow the

patients with stable, repaired pAVSD in the cardiology clinic at two yearly intervals with transfer of care to an adult congenital clinic at the age of 18 years. We believe that, given the high level of reintervention, continuing up to 20 years postoperatively, it is important for an adult patients to continue regular follow-up to allow timely diagnosis and treatment of any long-term complications. This approach is consistent with up-to-date published guidelines [18, 19].

The major limitation of this study is its retrospective nature. Furthermore, a low event rate, especially for mortality, may have reduced the accuracy of statistical analysis.

In conclusion, repair of pAVSD continues to be performed with low operative mortality and excellent long-term survival. There is a substantial need for late reoperation continuing up to 20 years postoperatively. This necessitates regular ongoing cardiology follow-up into adulthood.

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Chapter 3: Long-term outcomes of reoperations following repair of partial atrioventricular septal defect

3.1 Introduction

In chapter 2, we demonstrated that although the early and long-term survival following repair of pAVSD are excellent, there is a high rate of reoperation, up to 25% at 30 years. The majority of these reoperations are related to LAVV regurgitation and LVOTO. However, the high rate of reoperation is a relatively under recognized late complication of pAVSD repair. Furthermore, the anatomical mechanisms of LAVV regurgitation and LVOTO have not been investigated in detail. As such, we reviewed all reoperation following pAVSD repair in order to understand how to reduce the rate of late reoperation.

During the study period of 1975 to 2012, 40 patients had undergone reoperation following primary repair of pAVSD at the RCH. The most common cause for reoperation in this study was regurgitation of the LAVV, followed by LVOTO. Analysis of the mechanism of LAVV demonstrated that most cases were related to the LAVV cleft, either rupture of a previous cleft closure, or failure to adequately close the cleft at the first operation.

Importantly, in most cases of LAVVR, it was possible to repair the valve. It was also demonstrated that the rate of successful repair increased following the introduction of a strategy of cleft augmentation with pericardial patch, a technique developed in our institution.

This study highlighted the importance of a secure and complete closure of the LAVV cleft at primary operation as well as the potential benefit of the patch augmentation strategy of LAVV repair.

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CONGENITAL

Long-term outcomes of reoperations following repair of partial atrioventricular septal defect

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Abstract

OBJECTIVES: Partial atrioventricular septal defect (pAVSD) is repaired with excellent long-term survival. However, up to 25% of patients require reoperations. This study reviews results of reoperation following pAVSD repair at a single institution.

METHODS: From 1975 to 2012, 40 patients (16%, 40/246) underwent reoperation following pAVSD repair at the study institution. The data were retrospectively reviewed.

RESULTS: The mean time to reoperation was 5.4 ± 5.8 years. The most common reoperations were left atrioventricular valve (LAVV) surgery (78%, 31/40) and resection of left ventricular outflow tract obstruction (20%, 8/40). The most common cause for LAVV surgery was regurgitation through the cleft (58%, 18/31), followed by central regurgitation (29%, 9/31). Most cases of LAVV regurgitation were treated by repair (77%, 24/31), rather than replacement (23%, 7/31). Since the introduction of a patch augmentation technique for LAVV repair in 1998, the rate of repair has increased from 54 to 94% ($P = 0.012$). The early mortality rate was 2.5% (1/40). The survival rate was 90% (95% CI: 76–96) at 10 years and 83% (95% CI: 60–94) at 20 years. The rate of freedom from further reoperation was 66% (95% CI: 46–80) at 10- and 20-year follow-up.

CONCLUSIONS: The most common cause for reoperation following pAVSD repair was LAVV regurgitation through the LAVV cleft. Reoperation is performed with survival comparable to that of primary pAVSD repair, yet the rate of further reoperations remains high. The patch augmentation technique for LAVVR has significantly increased the rate of successful LAVV repair.

Keywords: Congenital heart disease • Septal defects • Outcomes

INTRODUCTION

The spectrum of atrioventricular septal defect affects 3–5 per 10 000 live births, with partial atrioventricular septal defects (pAVSDs) constituting ~25% of these [1–4]. Current practice is to surgically correct pAVSD in the preschool years or earlier if heart failure develops. While early mortality is low and long-term survival excellent, up to 25% of these patients require reoperation at 30 years follow-up [5–13]. The most common causes of reoperation are left atrioventricular valve regurgitation (LAVVR) and left ventricular outflow tract obstruction (LVOTO) [4, 14]. We performed a retrospective review of all reoperations performed following repair of pAVSD at a single institution.

PATIENTS AND METHODS

Patients

Between January 1975 and January 2012, 249 consecutive patients underwent surgical correction of pAVSD at the Royal Children's Hospital (RCH), Melbourne. Of these, 40 underwent a cardiac re-operation and were included in the present study. The study was approved by the RCH Human Research Ethics Committee.

Data were obtained by retrospective review of patient records and follow-up was obtained by correspondence with the patient's cardiologist or general practitioner. Patients were contacted by telephone and asked to complete a questionnaire if no current

medical practitioner could be identified. For patients who were lost to follow-up, the Victorian Registry of Births, Deaths and Marriages was searched for death records.

Operative approach

Our approach to repair of pAVSD has previously been described in detail [13]. Decision to close the LAVV cleft is made intraoperatively based on a combination of direct inspection and echocardiographic assessment. In cases of trivial or less LAVVR, practice has changed over the study period; currently, it is routinely closed unless contraindicated.

Reoperations were performed via a median sternotomy on cardiopulmonary bypass with mild hypothermia. A single case was performed under hypothermic circulatory arrest.

Our institutional approach to LAVV regurgitation following repair of partial and complete AVSD has been previously described in detail [15, 16]. Patients are referred for reoperation when they have moderate or greater LAVVR; however, consideration is given to the age of the patient and the feasibility of repair on echocardiographic evaluation. In all cases, LAVV repair is preferred to LAVV replacement. Prior to 1998, repair was undertaken in a conventional manner including closure of the cleft between the superior and inferior bridging leaflets and annuloplasty, depending on the cause of the regurgitation as seen on echocardiography and intraoperatively. Following 1998, a patch augmentation technique was applied to those patients with normal papillary muscles. In this technique, the thickened edges of the superior and inferior bridging leaflets adjacent to the cleft are resected, leaving only pliable tissue. Subsequently, a thin strip of autologous pericardium treated with 0.625% glutaraldehyde is inserted into the defect, patching the area of the cleft and, thus, augmenting the leaflet. The free edge of the patch is then suspended either with Goretex neochordae or chordal transfer. The technique for creating neochordae has been previously described [16]; their length is determined from the adjacent normal chordae and a plastic template is used to ensure that they are tied to the correct length. In a limited number of patients, an annuloplasty is also performed, consisting of commissuroplasty with pledgetted mattress sutures [15].

For relief of LVOTO, all patients underwent myomectomy via an aortotomy. In cases where accessory LAVV tissue was seen to contribute, this was resected. In one of these cases, a left atriotomy was also performed to allow adequate resection of the accessory subvalvular tissue.

Statistical analysis

Data were analysed with STATA version 12 (Stata Corp, College Station, TX, USA). Unless stated to the contrary, continuous data were summarized as mean ± standard deviation. The time-dependent endpoints investigated were: mortality, second cardiac reoperation, second reoperation for LAVV regurgitation and second reoperation for LVOTO. For all endpoints, time was measured starting from the time of first reoperation following pAVSD repair. Kaplan–Meier analysis was used to estimate survival and freedom from reoperation. Statistical analysis of the impact of the patch augmentation on outcomes was performed as follows: the Fisher's exact test was used to compare proportions of valves repaired prior to and after the introduction of the technique; conversely, a Cox proportional hazards test was used to compare freedom from reoperation between the patch augmentation technique and the traditional repair. The threshold for statistical significance was taken as $P < 0.05$.

Table 1: Baseline data

Total number	40
Age (years)	8.1 ± 6.7
Gender number (%)	
Male	23 (57.5)
Female	17 (42.5)
Down syndrome (%)	6 (15)
Time to reoperation (years)	5.4 ± 5.8
Cleft closed at original operation (%)	33 (82.5)
Cross-clamp time (min)	74.3 ± 38.7
Bypass time (min)	104.1 ± 47.8
Nature of reoperation	
LAVV procedure	27
LVOTO relief	8
ASD repair	1
LAVV + LVOTO	2
LAVV + ASD	1
LAVV + VSD	1

ASD: atrial septal defect; LAVV: left atrioventricular valve; LVAD: left ventricular assist device; LVOTO: left ventricular outflow tract obstruction; VSD: ventricular septal defect.

Table 2: LAVV reoperation details

	n (%)
Aetiology of LAVVR	
Cleft	18 (58.1)
Central regurgitation	9 (29.0)
Combination	2 (6.5)
Other[a]	2 (6.5)
LAVV surgical approach	
Repair	24 (77.4)
Patch augmentation technique	13 (41.9)
Annuloplasty + cleft closure	4 (12.9)
Cleft closure alone	7 (22.6)
Replacement	7 (22.6)

LAVV: left atrioventricular valve; LAVVR: left atrioventricular valve regurgitation.
[a]One case of deficient left mural leaflet and one case of deficient inferior bridging leaflet.

RESULTS

Operative details

A total of 40 patients underwent reoperation, with demographic data presented in Table 1. The most common procedures were LAVV repair or replacement (31/40, 77.5%) and relief of LVOTO (10/40, 25%). Four patients underwent more than one concomitant procedure (4/40, 10%).

Details on LAVV surgery are presented in Table 2. The most common cause for reoperation on the LAVV was regurgitation through the cleft (18/31, 58%), followed by central regurgitation

Table 3: LVOTO reoperation details

	n (%)
Aetiology of LVOTO	
Fibromuscular subaortic membrane	10 (100.0)
Accessory LAVV tissue	3 (30.0)
LVOTO techniques	
Myomectomy	10 (100.0)
Resection accessory LAVV tissue	3 (30.0)

LVOTO: left ventricular outflow tract obstruction; LAVV: left atrioventricular valve.

(9/31, 29%). Of the 18 cases of regurgitation through the cleft, 7 were due to rupture of the cleft closure, while the remaining 11 cases were due to a residual cleft (not closed, *n*= 6 and incomplete closure, *n* = 5). Of the cases of central regurgitation, 5 were due to annular dilatation, while the remaining 4 were due to dysplastic or deficient leaflets. In the majority of cases, the LAVV was repaired (24/31, 77.4%). In the remaining patients, the LAVV was replaced (7/31, 22.6%). Of the repairs, the patch augmentation technique was used in addition to this technique (2/13, 15%). Prior to 1998, 7 of 13 patients underwent repair (7/13, 53.8%) compared with 17 of 18 after the introduction of the technique (17/18, 94.4%), representing a significant increase in the proportion of valves successfully repaired ($P = 0.012$). The patch augmentation repair was introduced in 1998 [15].

Details on patients undergoing surgery for LVOTO are presented in Table 3. In all patients, a subaortic membrane was present (10/10, 100%), in 3 of these patients there was also accessory LAVV tissue (3/10, 30%). These cases were managed either with myomectomy in isolation or myomectomy with excision of redundant LAVV tissue. In 1 patient, the superior bridging leaflet was approached from the left atrium and detached to facilitate resection of fibrous tissue with subsequent reattachment.

The remaining 3 patients had residual atrial septal defect ($n = 2$) and residual VSD ($n = 1$) repairs.

Survival

There was a single death in the early postoperative period, giving an early mortality rate of 2.5% (1/40). This patient was a 3-week old boy, who presented in 1993 with coarctation of the aorta and pAVSD, with a severely dysplastic LAVV, but balanced ventricles and normal biventricular function. He initially underwent subclavian flap repair of the coarctation, but could not be weaned off the ventilator due to heart failure, and so was brought forward for pAVSD repair. Following pAVSD repair, multiple attempts to wean off inotropes resulted in severe pulmonary congestion. LAVV replacement with a 16-mm Carbomedics valve was performed, but the patient could not be weaned off bypass despite maximal inotropic support. A second attempt to replace the valve with a 10-mm pulmonary homograft was performed, despite an initial improvement in haemodynamics, bypass could not be weaned, and with rising pulmonary pressures despite maximal inotropic therapy, treatment was withdrawn.

Long-term survival is demonstrated in Fig. 1. The survival rate at 10 years was 90.2% (CI: 75.9–96.2%), while at 20 years it was 83.2% (CI: 60.2–93.6%). Of interest, all of the deaths occurred in patients whose first reoperation was on the LAVV.

Reoperation

Long-term freedom from a second reoperation is shown in Fig. 2. The rate of freedom from reoperation was 66% (CI: 46–80%) at both 10 and 20 years. Eleven patients underwent a further reoperation (11/40, 28%), while 5 patients underwent a third reoperation (5/40, 13%). Details of these procedures are provided in Table 4. There were 4 reoperations on the LAVV; 3 of these were in patients who had previous repairs and required late reoperation for severe LAVVR. At reoperation, the mechanisms of regurgitation were: annular dilatation ($n = 1$) deficient lateral leaflet in a patient with a single papillary muscle ($n = 1$) and LAVV endocarditis associated with rupture of a transposed chorda ($n = 1$). Of these 3 patients, 1 had undergone the patch augmentation technique for the initial LAVV repair.

There were no patients whose initial reoperation was for LAVVR who subsequently required relief of LVOTO and *vice versa*. There were no patients who underwent a fourth reoperation.

DISCUSSION

It has been well documented that complete repair of pAVSD is associated with a low early mortality rate in the range of 1.2–5% in recent studies [5–13]. However, there is a relatively high requirement for reoperation, up to 25% at 30 years of follow-up [5, 7, 13]. This requirement for reoperation represents a target for potential reduction in morbidity and improvement in the quality of life in patients with pAVSD, and prompted the current review. Previously, there has only been a single review evaluating outcomes following reoperation for pAVSD reported in the literature [14], while several groups have reviewed outcomes of combined cohorts with partial, transitional and complete AVSD undergoing reoperation [15–22].

The indication for reoperation in our cohort was predominantly LAVV regurgitation or LVOT obstruction, which is consistent with previous reports [5, 7, 14]. At our institution, we have previously identified risk factors for reoperation on the LAVV to be preoperative congestive heart failure and moderate or greater LAVVR on discharge echocardiogram [13]. In examining LAVV regurgitation, the majority of cases were due to regurgitation through the cleft, and it is interesting to note that almost half of these cases were due to rupture of an initial cleft repair, with the remaining cases being due to a residual cleft. This finding emphasizes the importance of secure cleft closure at initial correction of a pAVSD.

The majority of patients with LAVVR in our study underwent repair (77.4%). This is a higher rate of repair when compared with Stulak *et al.* [14] who described a LAVV repair rate of 52% in their cohort of 92 patients. However, our results are consistent with other groups who have analysed LAVV reoperation on partial and complete AVSD patients and recommended repair over replacement [18–22].

A recent paper by our group described the patch augmentation technique in patients undergoing reoperation for LAVVR following either complete or partial AVSD [15]. It demonstrated that there was improved freedom from reoperation in the patch augmentation group. In the present study, there was no statistically significant difference in freedom from reoperation between the groups, likely due to the small number of patients. However, the rate of

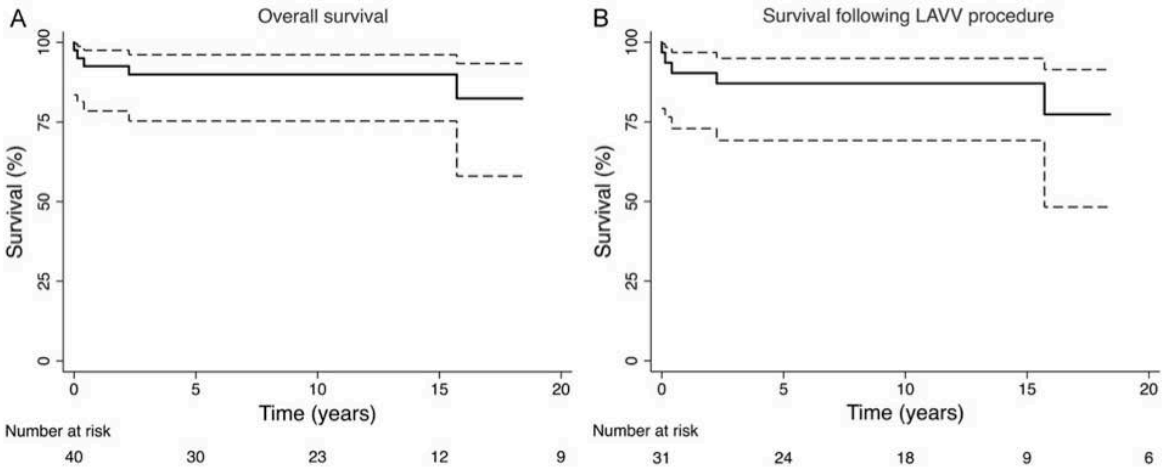

Figure 1: (**A**) Kaplan–Meier survival curve and (**B**) Kaplan–Meier survival curve for the post-LAVV procedure group. LAVV: left atrioventricular valve.

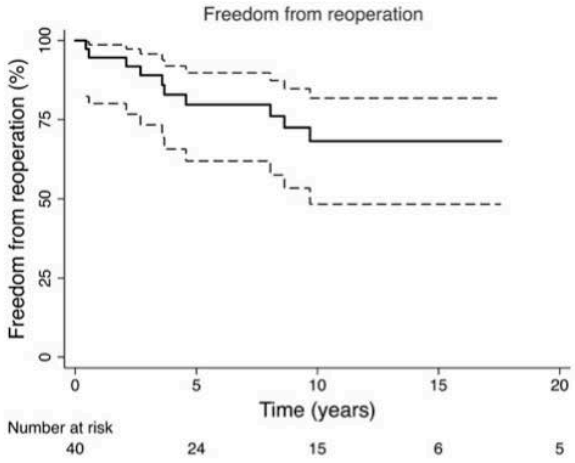

Figure 2: Kaplan–Meier curve for freedom from further reoperation.

Table 4: Details of further reoperations

	Second reoperation, *n* (%)	Third reoperation, *n* (%)
LAVV surgery	4 (36.4)	3 (60.0)
Repair	2	0
Replacement	2	3
LVOTO	4 (36.4)	1 (20.0)
Residual ASD	2 (18.2)	0
Transplant	1 (9.1)	0
LVAD (Thoratec paracorporeal)	0	1 (20.0)

LAVV: left atrioventricular valve; LVOTO: left ventricular outflow tract obstruction; ASD: atrial septal defect; LVAD: left ventricular assist device.

successful repair has significantly increased, since the introduction of this technique in 1998, from 54 to 94%. This may reflect the fact that this technique increases the range of valve pathologies that can be repaired.

LVOTO requiring surgery occurs in up to 10% of patients at 10 years and is multifactorial, related to intrinsic narrowing and elongation of the LVOT, malalignment of the aorta and anomalous insertion of LAVV chordae [23]. In our series, the indication for reoperation for LVOTO was mostly a fibromuscular subaortic membrane, with additional contribution of a redundant LAVV tension apparatus in approximately one-third of patients.

We have demonstrated an early postoperative mortality rate of 2.5%, which is consistent with the early mortality reported for initial pAVSD repair, and less than a previously reported result for reoperation following pAVSD repair of 5.2% [14]. Long-term survival at 20 years of follow-up was 83%, similar to the long-term survival following initial repair of pAVSD [5–7]. All deaths occurred in patients who underwent LAVV surgery; however, this may simply reflect the fact that it is by far the most common procedure.

The requirement for further reoperation in our cohort was relatively high with a 10-year freedom rate from a second reoperation of 66%. Interestingly, all reoperations occurred in the first 10 years and the rate remained unchanged at 20 years. This is a higher proportion of reoperations than seen in the group reviewed by Stulak *et al.* [14], who reported 10-year freedom rate from reoperation of 83%. It is, however, in line with other groups who had a similar rate of LAVV repair to our cohort [18–22]. The pattern of further reoperation is similar to that of the initial reoperation, dominated by procedures on the LAVV and LVOT. Interestingly, patients retained their pattern of pathology, with no patient who had LAVV reoperation subsequently requiring relief of LVOTO, and *vice versa*.

The time to reoperation in our cohort was 5.8 years, shorter than described by Stulak *et al.* [14]. This may represent a more aggressive strategy of reintervention on the LAVV. However, it is similar to that reported by Sojak *et al.* [24], who argued that early repair of the LAVV may prevent dysplastic changes which render it unrepairable. The fact that they achieved a similar rate of repair to our group would seem to support this contention.

CONCLUSION

The most common cause for reoperation following pAVSD repair was LAVV regurgitation through the LAVV cleft. Reoperation is performed with survival comparable to that of primary pAVSD repair,

yet the rate of further reoperations remains high. The patch augmentation technique for LAVVR has significantly increased the rate of successful LAVV repair.

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Chapter 4: Propensity score matched analysis of partial atrioventricular septal defect repair in infancy

4.1 Introduction

Repair of pAVSD has traditionally been undertaken electively in the preschool years, between 2 and 4 years of age (25, 26). This is in contrast to cAVSD, which is typically repaired between 3 and 6 months of age, as these children are at higher risk of developing heart failure (43). There has been a recent trend in some units to repair pAVSD under 1 year of age electively, with the hope that early repair would result in early stabilization of the LAVV annulus and leaflets, and prevent progressive degeneration of the LAVV (36, 86). However, there is very published little data on outcomes of children under 1 year of age undergoing pAVSD repair to support this hypothesis.

Early reports of pAVSD repair under 1 year of age included mostly children with early heart failure, and demonstrated very poor outcomes (87, 88). However, these are not likely to reflect the outcomes of pAVSD performed electively under 1 year of age. Some recent papers have demonstrated promising results for pAVSD repair in younger age groups, but they have very small cohorts.

We performed a multicenter analysis, including children from 3 paediatric cardiac surgery centres in Australia, in order to analyse the long-term outcomes of pAVSD repair in infants compared to older children. As there are inherent biases in the selection of children who underwent repair under 1 year of age, such as heart failure, failure to thrive and LAVV regurgitation, we performed propensity score matching to generate two well-matched cohorts.

This study demonstrated that despite matching for risk factors, pAVSD repair in infancy was associated with worse long-term survival and no benefit in terms of reoperation rate. As such, it suggests that elective repair should continue to be performed after 1 year of age.

4.2 Buratto E et al. Heart. 2017 (*in press*).

Congenital heart disease

ORIGINAL RESEARCH ARTICLE

Propensity score matched analysis of partial atrioventricular septal defect repair in infancy

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ABSTRACT

Objective Partial atrioventricular septal defect (pAVSD) is usually repaired between 2 and 4 years of age with excellent results. Repair in infancy has been associated with poorer outcomes. However, most infants in reported series had heart failure or significant left atrioventricular valve (LAVV) regurgitation. The impact of surgery in infancy on outcomes remains unclear.

Methods All children at three institutions who underwent repair of pAVSD from 1975 to 2015 were included. Infants (aged <1 year) were compared with older children in a propensity score matched analysis. Variables used to generate propensity scores were: failure to thrive, congestive heart failure, preoperative LAVV regurgitation, associated congenital heart disease.

Results pAVSD repair was performed on 430 children, 17.9% (75/420) were infants. Infants (mean age 0.5±0.3 years) had higher rates of LAVV regurgitation, heart failure and additional cardiac malformations than older children (mean age 4.7±3.5 years). At 30 years, survival for infants was 82.1% (95% CI 70.1% to 89.6%) compared with 95.7% (95% CI 91.3% to 97.9%) in older children (P<0.001). Propensity score matching yielded 52 well-matched pairs. Survival at 30 years was 87.9% (95% CI 75.0% to 94.4%) for infants compared with 98.1% (95% CI 87.1% to 99.7%) for older children (P=0.04). There was no significant difference in freedom from reoperation between the groups.

Conclusions Despite matching for risk factors, survival after repair of pAVSD in infancy is lower than that when repair is performed in older children, with no difference in reoperation rates. This suggests that elective repair of pAVSD should be deferred until after infancy.

INTRODUCTION

Elective repair of partial atrioventricular septal defect (pAVSD) is typically performed in the preschool years, usually between 2 and 4 years of age.[1–4] Early and long-term results are excellent, however, the rate of reoperation approaches 25% at 20 years.[1] Operation in infancy is usually required due to failure to thrive. Thus, the true impact of early surgery has been difficult to define, and the ideal age of elective surgery remains controversial.[5–8] Recently, there has been a trend to perform elective repair in infants, who would otherwise have repair later in life,[7 8] with a view to reducing long-term adverse events. We, therefore, performed a multicentre retrospective study, with risk adjustment using propensity score matching, of children undergoing pAVSD repair to determine the impact of surgery in infancy on outcomes.

METHODS

Patients

Three major Australian paediatric cardiac surgery units enrolled patients to this study: The Royal Children's Hospital, Melbourne (n=277), The Prince Charles Hospital, Brisbane (n=111) and the Lady Cilento Hospital in Brisbane (n=42). All children who underwent repair of pAVSD at these centres between 1975 and 2015 were included in the study. Ethics approval was obtained (HREC32047E and HREC/14/QPCH/45). As the study was a retrospective chart review and patient contact was not required, the relevant ethics committees waived the requirement for patient consent. Follow-up data were obtained by review of medical records, and correspondence with cardiologists and general practitioners. Survival status was ascertained by matching all patients with the Australian National Death Index registry.

Infants were defined as children who were aged 1 year or younger at the time of pAVSD repair. Early death was defined as death prior to discharge or within 30 days of the procedure. Significant LAVV regurgitation was defined as moderate or greater LAVV regurgitation as assessed by echocardiography.

Operative technique

The surgical technique used for repair of the pAVSD has been previously described in detail.[1] All operations were performed via a median sternotomy using cardiopulmonary bypass with standard aortic and bicaval venous cannulation with moderate hypothermia and blood cardioplegia. Surgery was performed through a right atriotomy in all cases. Closure of the cleft of the LAVV was performed at the surgeon's discretion, on the basis of echocardiographic assessment and saline testing. Closure of the ostium primum was performed using a patch.

Statistical methods

Data were analysed with STATA V.13 (StataCorp, College Station, Texas, USA). All continuous variables are expressed as mean±SD, unless otherwise specified. Categorical variables are expressed as frequency and percentage. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Pearson's χ^2 test, unless

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Table 1 Baseline characteristics comparing infants and children aged over 1 year

	Infant	>1 year	Standardised difference	P value
n	75	355		
Age (years)	0.50±0.29	4.7±3.5		
Male, n (%)	36 (48.0)	167 (47.0)	1.9	0.88
Trisomy 21	20 (26.7)	76 (21.4)	11.8	0.34
Significant preoperative AVVR	27 (36.0)	113 (31.8)	8.7	0.50
CHF	41 (54.7)	28 (7.9)	117.3	<0.001
Failure to thrive	47 (62.7)	68 (19.2)	96.0	<0.001
Associated CHD	49 (65.3)	108 (30.4)	75.0	<0.001
Cleft closed (%)	52 (69.3)	306 (86.2)	−41.3	<0.001
Concomitant procedures	50 (66.7)	144 (40.6)	54.0	<0.001

AVVR, atrioventricular valve regurgitation; CHD, coronary heart disease; CHF, congestive heart failure; FTT, failure to thrive.

group size was <10, in which case the Fisher's exact test was used. Time-dependent variables were analysed using the Kaplan-Meier survival method. Infants and patients aged >1 year were compared using the log-rank test. The threshold for statistical significance was taken as $P<0.05$. Univariable risk factors for mortality and reoperation were determined using the Cox proportional hazards test.

Propensity score matched analysis was performed to account for clinical necessity to perform pAVSD repair in infancy. Variables used to generate the propensity score were the risk factors for mortality and reoperation following pAVSD identified in univariable analysis (failure to thrive, congestive heart failure, preoperative LAVV regurgitation, associated congenital heart disease). Furthermore, it was decided a priori to include sex and the presence of trisomy 21 into the model to ensure balance, as it was suspected that these variables could influence the decision to operate. Matching on the generated propensity scores was performed in a one-to-one fashion with calliper width equal to twice the SD of the logistic regression of the mean of propensity scores (0.044). The degree of balance of baseline characteristics between groups was assessed using standardised differences, where a difference of <10% was considered to reflect high degree of balance. Kaplan-Meier analysis was performed to estimate time-dependent end points. To account for the matched nature of the data, an adjusted log-rank test stratified by quintiles of propensity scores was used to assess differences between groups for time-dependent outcomes .[9 10]

RESULTS

Baseline data

A total of 430 children underwent repair of pAVSD during the study period. Infants constitute 17.4% (75/430) of the cohort. Preoperative characteristics, comparing infants and patients aged over 1 year, are shown in table 1. The two groups differ substantially; infants have a significantly greater proportion with failure to thrive (62.7% vs 19.2%, $P<0.001$), congestive heart failure (CHF) (54.7% vs 7.9%, $P<0.001$) and associated cardiovascular defects (65.3% vs 30.4%, $P<0.001$).

Operative data

The two groups also differ in terms of operative characteristics: infants had a greater proportion of additional concomitant procedures (66.7% vs 40.6%, $P<0.001$), cleft closure was performed less frequently in infants (69.3% vs 86.2%, $P<0.001$) and infants also had longer mean bypass times (92.7±41.4 vs 77.4±27.6 min, $P<0.001$). Early mortality was higher in the infants compared with older children (5.3% (4/75) vs 0% (0/355), $P=0.001$).

Long-term outcomes

Mean follow-up time was 16.7±11.0 years (median: 16.9, IQR: 7.7–25.3). Kaplan-Meier curves comparing long-term survival between infants and children aged over 1 year are shown in figure 1A. Survival for infants was 84.6% (95% CI 73.9% to 91.2%) at 10 years and 82.1% (95% CI 70.1% to 89.6%) at 20 and 30 years. Survival for children aged over 1 year was 98.7% (96.5%–99.5%) at 10 years, 97.4% (95% CI 94.5% to 98.7%) at 20 years and 95.7% (95% CI 91.3% to 97.9%) at 30 years. The difference in survival was statistically significant ($P<0.001$).

Kaplan-Meier curves comparing freedom from reoperation between infants and children aged over 1 year are shown in figure 1B. Freedom from reoperation for infants was 67.0% (95% CI 53.2% to 77.5%) at 10 years and 54.1% (95% CI 36.3% to 67.0%) at 20 years. Freedom from reoperation for older children was 86.0% (95% CI 81.0% to 89.8%) at 10 years and 76.8% (95% CI 69.8% to 82.3%) at 20 years. The freedom from reoperation was significantly greater in the older group ($P<0.001$).

Freedom from reoperation for LAVV regurgitation for infants was 78.5% (95% CI 65.5% to 87.1%) at 10 years and 69.0% (95% CI 50.6% to 81.7%) at 20 years. For children older than 1 year, freedom from reoperation for LAVV regurgitation was 89.5% (95% CI: 84.5% to 93.0%) at 10 years and 81.9% (95% CI 74.7% to 87.2%) at 20 years. Freedom from reoperation for

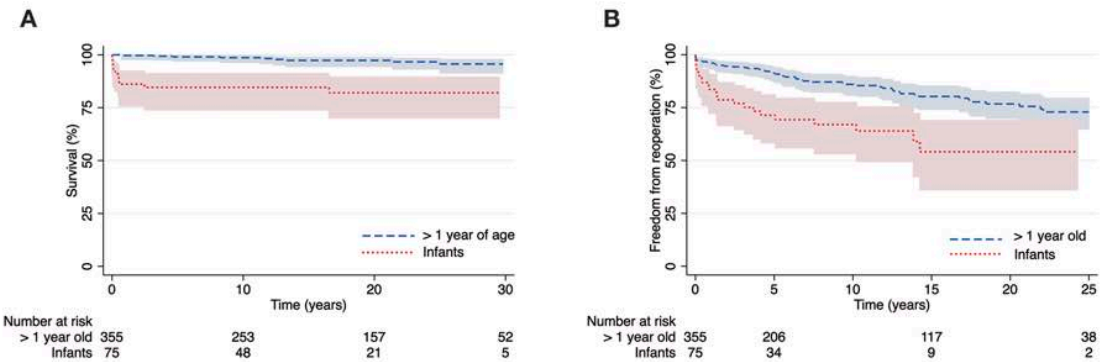

Figure 1 Kaplan-Meier curves for (A) survival and (B) freedom from reoperation.

Table 2 Univariable predictors of mortality and reoperation following repair of pAVSD

Univariable risk factor	Mortality		Reoperation	
	HR (95% CI)	P value	HR (95% CI)	P value
Additional CHD	3.1 (1.3 to 7.5)	0.01	1.0 (0.6 to 1.5)	0.90
Cleft closure	0.2 (0.1 to 0.5)	<0.001	0.8 (0.4 to 1.5)	0.49
Failure to thrive or CHF	5.0 (1.9 to 12.7)	0.001	2.6 (1.7 to 4.1)	<0.001
Infant	6.9 (2.9 to 16.0)	<0.001	2.7 (1.7 to 4.5)	<0.001
LAVVR≥moderate	1.0 (0.4 to 2.4)	0.95	2.3 (1.4 to 3.7)	<0.001
Trisomy 21	1.7 (0.7 to 4.1)	0.27	0.6 (0.3 to 1.1)	0.08
Year of procedure	1.0 (0.9 to 1.0)	0.78	1.0 (1.0 to 1.0)	0.68

LAVVR, left atrioventricular valve regurgitation; CHD, coronary heart disease; CHF, congestive heart failure; pAVSD, partial atrioventricular septal defect.

Table 3 Multivariable predictors of mortality and reoperation following repair of pAVSD

Risk factor	HR (95% CI)	P value
Mortality		
Additional CHD	1.7 (0.7 to 4.4)	0.25
CHF or FTT	2.3 (0.78 to 6.6)	0.13
Cleft closure	0.3 (0.15 to 0.82)	0.02
Infant	3.2 (1.2 to 8.5)	0.02
Reoperation		
CHF or FTT	2.6 (1.5 to 4.4)	<0.001
Infant	1.8 (1.0 to 3.1)	0.05
LAVVR≥moderate	2.3 (1.5 to 3.7)	<0.001

LAVVR, leftatrioventricular valve regurgitation; CHD, coronary heart disease; CHF,congestiveheartfailure; FTT, failure to thrive; pAVSD, partial atrioventricular septal defect.

LAVV regurgitation was significantly greater in the older group (P=0.005).

Cause of death following pAVSD repair

Survival information was available for all patients from the NDI, however, for three patients cause of death information could not be obtained. The majority of recorded deaths (76.1%, 17/21) were cardiovascular in nature. In NDI reporting, cardiovascular deaths were attributed to heart failure (13/21, 61.9%), surgical complications (2/21, 9.5%), stroke (1/21, 4.8%) and respiratory failure (1/21, 4.8%). Non-cardiovascular causes of death were due to malignancy (3/21, 14.3%) and motor vehicle accident (1/21, 4.8%).

Cause of reoperations following pAVSD repair

A total of 73 patients underwent 101 reoperations following repair of pAVSD. The causes of reoperation were LAVV repair or replacement (68%, 68/101), relief of left ventricular outflow tract obstruction (17%, 17/101), repair of residual septal defect (12%, 12/101), right AVV repair (1%, 1/101), subpulmonary resection (1%, 1/101), left ventricular assist device implantation (1%, 1/101) and orthotopic heart transplantation (1%, 1/101).

Univariable predictors of death and reoperation

Univariable predictors of mortality and reoperation following repair of pAVSD are shown in table 2. The risk factors for mortality were surgery in infancy (HR=6.9, P<0.001), CHF or failure to thrive (HR=5.0, P=0.001) and the presence of additional coronary heart disease (HR=3.1, P=0.01). Conversely, cleft closure was associated with a decreased risk of mortality (HR=0.2, P<0.001).

The univariable risk factors associated with reoperation were infancy (HR=2.7, P<0.001), significant preoperative LAVV regurgitation (HR=2.3, P<0.001) and CHF or failure to thrive (HR=2.6, P<0.001).

Multivariable predictors of death and reoperation

Multivariable predictors of mortality and reoperation are shown in table 3. The only factor independently associated with mortality was surgery in infancy (HR=3.2, P=0.02), while cleft closure was associated with improved survival (HR=0.3, P=0.02).

The independent predictors of the risk of reoperation were the presence of CHF or failure to thrive (HR=2.6, P<0.001), moderate or greater LAVV regurgitation (HR=2.3, P<0.001) and surgery in infancy (HR=1.8, P=0.05).

Propensity score matched cohort

To ensure that infants and older children were in a comparable clinical status preoperatively, these two groups were matched for the baseline characteristics described in table 1. Propensity score matching yielded 52 matched pairs, with demographic data summarised in table 4. After matching there were no significant differences between infants and older children in terms of sex distribution, trisomy 21 status, rates of failure to thrive, congestive heart failure, preoperative LAVV regurgitation, associated congenital heart disease, cleft closure, concomitant cardiovascular procedures.

After matching, the early mortality was 3.8% (2/52) for infants, while there were no early deaths in the group aged over 1 year (P=0.3). Kaplan-Meier curves for survival for the matched cohort are shown in figure 2A. Long- term survival for infants was 87.9% (95% CI 75.0% to 94.4%) at 10, 20 and 30 years follow-up. For children aged over 1 year, survival was 98.1% (95% CI 87.1% to 99.7%) at 10, 20 and 30 years of age. This difference was statistically significant (P=0.04). Kaplan-Meier curves for reoperation for the matched cohort are shown in figure 2B. Long-term freedom from reoperation was 75.2% (95% CI 58.5% to 86.0%) at 10 years and 63.7% (95% CI 41.7% to 79.3%) at 20 years for infants. For children aged over 1 year freedom from reoperation was 82.8% (95% CI 68.5% to 91.1%) at 10 and 20 years of follow-up. Freedom from reoperation was not significantly different between the groups (P=0.28).

Table 4 Baseline characteristics of the propensity score matched cohorts

	Infant	>1 year	Standardised difference	P value
n	52	52		
Age (years)	0.51±0.29	3.8±3.1		
Male, n (%)	25 (48.1)	25 (48.1)	0.0	1.0
Trisomy 21	11 (21.2)	10 (19.2)	4.5	0.81
Significant preoperative AVVR	18 (34.6)	17 (32.7)	4.0	0.84
CHF	18 (34.6)	19 (36.5)	4.8	0.84
Failure to thrive	28 (55.7)	29 (55.8)	−4.3	0.85
Associated CHD	31 (59.6)	31 (59.6)	0.0	1.0
Cleft closed (%)	39 (75.0)	37 (71.2)	9.5	0.66
Concomitant procedures	33 (63.5)	35 (67.3)	−8.0	0.68

AVVR, atrioventricular valve regurgitation; CHD, coronary heart disease; CHF, congestive heart failure.

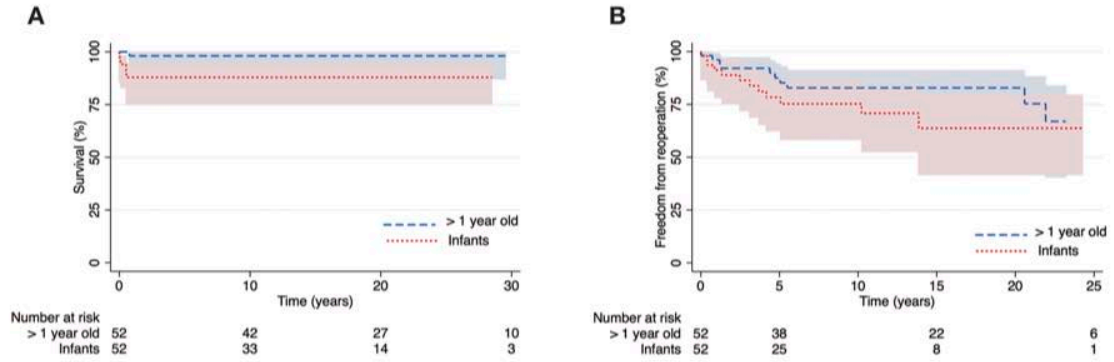

Figure 2 Kaplan-Meier curves for the propensity score matched cohorts for (A) survival and (B) freedom from reoperation.

Long-term freedom from reoperation for LAVV regurgitation in infants was 88.4% (95% CI 74.0 to 95.0) at 10 years and 81.6% (95% CI 59.4% to 92.3%) at 20 years. For the children aged over 1 year, freedom from reoperation for LAVV regurgitation was 91.7% (95% CI 79.2% to 96.8%) at 10 and 20 years follow-up. There was no significant difference between the two groups (P=0.47).

DISCUSSION

pAVSDs form the least severe end of the spectrum of AVSDs. It has been well established that early mortality is low and the long-term survival is excellent.[1–4] However, we have recently shown that there is a substantial reoperation rate, approaching 25% at 25 years,[1] suggesting pAVSD may not be as benign as previously thought. Furthermore, there has recently been renewed interest in defining the optimal timing of elective surgery for pAVSD.[5–8] The majority of reoperations following pAVSD repair are for LAVV regurgitation.[11 12] Therefore, it was proposed that early repair might prevent progressive annular dilatation and degeneration of the LAVV leaflets and, thus, decrease the risk of later reoperation.[6 8 13]

However, historical reports of repair of pAVSD in infancy have shown poor outcomes, with early mortality in the range of 9%–36% .[3 14 15] Yet, all of these studies included small numbers of patients, and repair was performed in infancy mainly due to heart failure or failure to thrive.

Several recent reports have addressed the impact of early surgery on outcomes of pAVSD repair. Minich *et al*[6] reported results from the multicentre Pediatric Heart Network Database. This study included 87 children who had pAVSD repairs performed between 2004 and 2006 at a median age of 1.8 years. In hospital mortality was 1.1% (1/87). Children who had pAVSD repair between 3 and 18 months had an earlier return to normal age-matched weight. Furthermore, children who were over 4 years of age had a much higher degree of LAVV regurgitation. However, the mean follow-up in this study was only 6 months.

In contrast, Bowman *et al*[7] reported 105 children who had pAVSD repair at the Mayo Clinic between 1995 and 2011, at a median age of 7.9 years. Early mortality was 1.0% (1/105). They demonstrated better 5-year survival and decreased rate of LAVV regurgitation in patients who had pAVSD repair over the age of 18 months.

Most recently, Devlin *et al*[8] reported a series of 86 children who underwent pAVSD repair between 1990 and 2014 at a median age of 1.5 years. They reported no early deaths and identified no difference in rates of reoperation when comparing children by quartiles of age. They concluded that repair of pAVSD under the age of 18 months was safe, and recommended that repair should be performed under 2 years of age.

In the context of these results, our study is important as it is the largest cohort of patients with pAVSD reported so far, has a multi-institutional design with 40 years of follow-up. In addition to thorough matching, our study includes the largest cohort of infants undergoing pAVSD repair ever reported.

On simple direct comparison of infants and older children undergoing pAVSD repair, infants had poorer outcomes. However, they also had much higher rates of heart failure, failure to thrive, LAVV regurgitation and associated cardiac abnormalities at the time of surgery, all of which were risk factors for poorer survival. This is likely to represent a bias in patient selection, as patients with heart failure, LAVV regurgitation and failure to thrive required earlier surgery. Furthermore, the presence of additional congenital heart defects may necessitate earlier surgery, and this may have also contributed to increased surgical risk. In this context, it is not surprising that children operated in infancy had a higher early mortality (5.6% vs 0%) significantly lower 20-year survival (79% vs 97%) and lower freedom from reoperation at 20 years (52% vs 75%). Indeed, univariable analysis demonstrated that heart failure, failure to thrive and presence of additional congenital heart defects were all associated with increased mortality. However, it is misleading to simply interpret outcomes of surgery in infancy without considering the fact that children with heart failure, failure to thrive and LAVV regurgitation were much more likely to have surgery in infancy.

In order to address this bias, we performed a propensity score matched analysis, based on risk factors for mortality and reoperation after pAVSD repair. This generated two groups of patients who were well matched in terms of the risk factors for death following pAVSD repair, differing only in terms of age at the time of surgery. In this analysis, survival of infants was significantly lower than older children (88% compared with 98%) at 20 years. Most of this difference was due to deaths occurring in the first year after surgery.

Furthermore, the risk of reoperation was also higher in the infant group. Freedom from reoperation at 20 years was only 64% in infants compared with 83% in older children. Although this difference was not statistically significant, it casts doubt on the hypothesis that earlier surgery may reduce the risk of late LAVV reoperation by preventing progressive degeneration of the leaflets and dilatation of the ventricle.

Thus, it appears that in our study that in well-matched cohorts, infants have a higher rate of mortality in the first year following repair. Although survival plateaus for infants at that time, they never catch up to the survival of older children. Furthermore, there is a steady rate of reoperation in both groups, and earlier repair does not seem to prevent progression of LAVV dysfunction.

There is still a group of patients with pAVSD who develop early heart failure or failure to thrive who will require early surgery, even in infancy, in order to control their symptoms and prevent progressive heart failure. These patients should not have their surgery delayed, as doing so is likely to be harmful. However, for children who are stable without signs of heart failure or failure to thrive, we believe elective repair should be delayed until the preschool years.

LIMITATIONS

This study is limited by its retrospective nature. Furthermore, the operations were performed over a 40-year period, and as such improvements in safety of surgery in infancy in more recent years may have mitigated some of the increased risk we have observed.

CONCLUSIONS

Despite matching for risk factors, survival after repair of pAVSD in infancy is lower than when repair is performed in older children, with no difference in reoperation rates. Our findings suggest that elective repair of pAVSD should be deferred until after infancy.

Key questions

What is already known about this subject?
Partial atrioventricular septal defect (pAVSD) is repaired with very low risk in preschool-aged children. Repair in infancy has previously been associated with very poor outcomes. Recently, there has been a move to repair pAVSD in infancy, with the hope of preventing deterioration of the left atrioventricular valve.

What does this study add?
This is the largest cohort of infants undergoing repair of pAVSD reported, and the only propensity matched study comparing infants and older children. Repair in infancy is associated with poorer survival and no reduction in the risk of reoperation on the left atrioventricular valve.

How might this impact on clinical practice?
Our study suggests that elective repair of pAVSD should be deferred until after infancy.

Contributors EB was responsible for designing the study, collecting the data, analysing data and writing the manuscript. MD was responsible for data collection, writing the paper and revising the paper. XTY was responsible for data collection, and contributed to writing the manuscript. DJR was responsible for study design, data collection and revision of manuscript. NA was responsible for study design, data collection and revision of manuscript. CPB was responsible for study design and revision of the manuscript. Y'U was responsible for study design and revision of the manuscript. IEK did the study design, drafting and revision of the manuscript.

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Competing interests Y'U is a consultant for Actelion and MSD. CPB serves on the advisory board of Admedus.

Ethics approval Royal Children's Hospital Melbourne HREC.

Provenance and peer review Not commissioned; externally peer reviewed.

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Chapter 5: Long-term outcomes of single-ventricle palliation for unbalanced atrioventricular septal defects: Fontan survivors do better than previously thought.

5.1 Introduction

Unbalanced AVSD represents the most severe end of the spectrum of AVSDs. These patients usually have complex anatomy, with one hypoplastic ventricle, and frequently additional malformations such as heterotaxy.

Early attempts at SVP produced very poor results (66, 75). In response to these poor outcomes, some units have favoured strategies of direct BVR or biventricular conversion whereby the hypoplastic ventricle is "trained" to facilitate eventual BVR (76, 80, 81). These strategies are still considered to be experimental, and it remains unclear which patients would benefit from this technique.

At RCH, children with uAVSD usually undergo SVP. We performed a review of all 139 patients who underwent SVP for uAVSD from 1976 to 2015. This study demonstrated that there was a substantial rate of mortality, with less than 60% of patients surviving at 25-years follow-up. There was also a very high rate of reoperation on the common AVV, with approximately one third of patients requiring at least one operation for AVV regurgitation.

An important finding of this study was the relatively positive outlook for patients who achieved Fontan completion. These patients had greater than 80% survival at 25-years, which is much better than had previously been reported, and similar to the overall population of children undergoing Fontan completion.

The message of this study is that Fontan completion produces satisfactory results in patients with uAVSD, but deterioration of the common AVV continues to be a major cause of reoperation and morbidity.

5.2 Buratto E, et al. J Thorac Cardiovasc Surg. 2017;153:430-438.

CONGENITAL: FONTAN

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Long-term outcomes of single-ventricle palliation for unbalanced atrioventricular septal defects: Fontan survivors do better than previously thought

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ABSTRACT

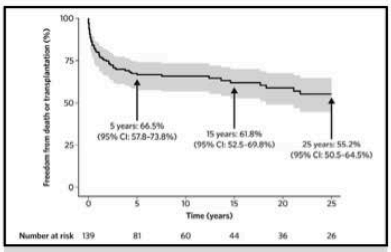
Background: Single-ventricle palliation (SVP) for children with unbalanced atrioventricular septal defect (uAVSD) is thought to carry a poor prognosis, but limited data have been reported.

Methods: We performed a retrospective review of children with uAVSD who underwent SVP at a single institution. Data were obtained from medical records and correspondence with general practitioners and cardiologists.

Results: Between 1976 and 2016, a total of 139 patients underwent SVP for uAVSD. A neonatal palliative procedure was performed in 83.5% of these patients (116 of 139), and early mortality occurred in 11.2% (13 of 116). Ninety-four patients underwent stage II palliation, with an early mortality of 6.4% (6 of 94). Eighty patients (57.6%) underwent Fontan completion, with an early mortality of 3.8% (3 of 80). Interstage mortality was 11.7% (12 of 103) between stages I and II and 17.0% (15 of 88) between stage II and Fontan.

Long-term survival was 66.5% (95% confidence interval [CI], 57.9%-73.9%) at 5 years, 64.4% (95% CI, 55.5%-72.0%) at 15 years, and 57.8% (95% CI, 47.5%-66.8%) at 25 years. Survival post-Fontan was 94.9% (95% CI, 86.9%-98.0%) at 5 years, 92.0% (95% CI, 80.6%-96.8%) at 15 years, and 82.4% (95% CI, 61.5%-92.6%) at 25 years. Risk factors associated with death or transplantation were aortic atresia (hazard ratio [HR], 5.3; $P = .03$) and hypoplastic aortic arch (HR, 2.5; $P = .02$). Atrioventricular valve operations were required in 31.7% of the patients (44 of 139), with 31.8% of them (14 of 44) requiring a further operation.

Conclusions: Children undergoing SVP for uAVSD have substantial mortality, with <60% survival at 25 years. However, survival of children who achieve Fontan completion is better than has been reported previously. (J Thorac Cardiovasc Surg 2017;153:430-8)



Freedom from death or transplantation for patients with uAVSD undergoing single ventricle palliation.

Central Message

Patients with unbalanced atrioventricular septal defects who achieve Fontan completion have better survival than was previously thought.

Perspective

Single ventricle palliation for unbalanced atrioventricular septal defects is associated with substantial mortality, with <60% survival at 25 years. However, in those who achieve Fontan completion, survival is similar to that of the general Fontan population. Management of the atrioventricular valve (AVV) remains a challenge, with almost one-third of patients requiring AVV surgery.

See Editorial Commentary page 439.

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Children with unbalanced atrioventricular septal defect (uAVSD) constitute approximately 10% of all patients with atrioventricular septal defect (AVSD).[1,2] The majority of these children undergo single-ventricle palliation (SVP). Children undergoing SVP for uAVSD have been shown to have a particularly poor prognosis.[2-5]

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Abbreviations and Acronyms

AVSD = atrioventricular septal defect
AVV = atrioventricular valve
AVVR = atrioventricular valve regurgitation
BCPS = bidirectional cavopulmonary shunt
HLHS = hypoplastic left heart syndrome
LV = left ventricle
PA = pulmonary artery
PDA = patent ductus arteriosus
SVP = single-ventricle palliation
TAPVD = total anomalous pulmonary venous drainage
uAVSD = unbalanced atrioventricular septal defect

In series published to date, only one-third of patients with uAVSD achieved Fontan completion, and nearly 40% of those who achieved Fontan completion died by 2.5 years of follow-up.[2,3] Furthermore, reports on the long-term follow-up of this challenging group of patients are limited.[3] We retrospectively reviewed our experience of SVP in children with uAVSD.

METHODS

Patients

All patients with uAVSD who underwent SVP at the Royal Children's Hospital, Melbourne between January 1, 1976, and January 1, 2016, were included in the study. Ethics approval was granted by the Royal Children's Hospital's Human Research Ethics Committee (HREC 32047E). International patients were excluded, because follow-up data were not available for this group.

Here uAVSD was defined as a complete AVSD, as confirmed on echocardiography, which in the opinion of the treating team was not suitable for biventricular repair (ie, the ventricles could not be septated), owing to either a hypoplastic ventricle or a straddling atrioventricular valve (AVV). Baseline data were collected by retrospective chart review. Follow-up data were obtained by correspondence with the patients' general practitioners and cardiologists. Follow-up was considered complete if the last confirmed patient contact occurred within 2 years of the end of the study period. Early death was defined as death occurring within 30 days after surgery or before discharge from the hospital. Significant AVV regurgitation was defined as moderate or greater AVV regurgitation as assessed on echocardiography.

Stage I palliation was defined as either the Norwood procedure or other procedures. These other procedures included pulmonary artery band, Damus–Kaye–Stansel connection, repair of total anomalous pulmonary venous drainage (TAPVD), ligation of a patent ductus arteriosus (PDA), pulmonary valvuloplasty, or right ventricle–to–pulmonary artery conduit. All Norwood procedures were performed after the year 2000. Stage II procedures were bidirectional cavopulmonary shunt (BCPS) operations. Stage III was Fontan completion.

Statistical Methods

All data were analyzed using Stata version 13 (StataCorp, College Station, Tex). All continuous data are expressed as mean ± standard deviation unless specified otherwise. Continuous data were compared between groups using the Mann–Whitney *U* test. Discrete variables were compared between groups using the χ^2 test, unless group size was <10, in which case the Fisher exact test was used. Time-dependent endpoints, specifically survival and freedom from death and transplantation, were analyzed using the Kaplan–Meier method, with time commencing at the initial palliation for analysis of the overall cohort and at the individual stages for analyses of each stage of palliation. Risk factors evaluated in a univariable Cox regression were age, moderate or greater atrioventricular valve regurgitation (AVVR), heterotaxy syndrome, double-outlet right ventricle, year of operation (in days since 1976, scaled to years), aortic atresia, aortic arch hypoplasia, hypoplastic pulmonary arteries (PAs), chromosomal abnormality, hypoplastic left ventricle (LV), and Norwood procedure as stage I palliation.

Variables with at least moderate evidence against the null hypothesis ($P < .10$) were included in a multivariable model. Specifically, for stage I and stage II procedures, a competing risks model was used for survival analysis, where follow-up time was defined as the interval between the relevant stage and last follow-up, death, transplantation, or progression to the next stage. Furthermore, for stage I and II, a competing risks regression was performed with a Fine and Gray proportional subhazards model, using the same univariable predictors and threshold for inclusion in a multivariable model as in the Cox model described above. The threshold for statistical significance was $P < .05$.

RESULTS

A total of 139 patients underwent SVP for uAVSD at the study institution between January 1, 1976, and January 1, 2016. Follow-up was complete for all patients. The mean follow-up time was 12.2 ± 14.4 years (median, 8.4 years; interquartile range [IQR], 1.1-21.1 years). The baseline demographic data are summarized in Table 1. The procedures are summarized in Figure 1.

Stage I Procedures

Of the 139 children, 16.5% (23 of 139) did not undergo a stage I procedure, including 12.2% (17 of 139) who proceeded directly to stage II and 4.3% (6 of 139) who proceeded directly to Fontan. The remaining 83.5% of patients (116 of 139) underwent a stage I procedure (Table 2). The median age at the time of stage I palliation was 11.5 days (IQR, 4.0-63.9 days; mean, 112.8 ± 378.0 days). The mean age at stage I was 233.6 ± 545.7 days in those operated on before the year 2000, but decreased to 18.3 ± 31.8 days in those operated on from 2000 onward ($P = .002$). At least one additional concomitant cardiovascular procedure was performed in 50.0% of the patients (58 of 116). The most common concomitant procedures were PDA ligation (23.3%; 27 of 116), PA reconstruction (8.6%; 10 of 116), aortic arch repair (7.8%; 9 of 116), and TAPVD repair (6.9%; 8 of 116). Early mortality was 11.2% (13 of 116). The Norwood procedure was associated with a significantly greater risk of early mortality compared with other stage I procedures (45.5% vs 7.5%; $P = .003$). Early mortality was more frequent in patients who underwent additional concomitant procedures compared with those who did not, but the difference was not statistically significant (17.2% vs 5.2%; $P = .07$). Hypoplastic LV ($P = 1.0$), age at time of

CONG

TABLE 1. Demographic data

Variable	Value
Total number of patients	139
Sex, n (%)	
Male	79 (56.8)
Female	60 (43.2)
Ventricular dominance, n (%)	
Left	30 (21.6)
Right	94 (67.6)
Balanced	15 (10.8)
Additional cardiac anomalies, n (%)*	
Heterotaxy	102 (73.4)
DORV	72 (51.8)
Additional VSD (not inlet)	69 (49.6)
Bilateral SVC	59 (42.4)
Right atrial isomerism	48 (34.5)
Right aortic arch	45 (32.4)
Secundum ASD	45 (32.4)
Pulmonary atresia	43 (30.9)
Interrupted IVC	41 (30.2)
Left atrial isomerism	38 (27.3)
TGA	38 (27.3)
TAPVD	37 (26.6)
Dextrocardia	29 (20.9)
Aortic arch hypoplasia	21 (15.1)
Pulmonary artery hypoplasia	17 (12.2)
Aortic coarctation	16 (11.5)
MAPCAs	8 (5.8)
Aortic atresia	4 (2.9)
Moderate or greater AVVR at stage I, n (%)	20 (14.4)
Gastrointestinal malrotation, n (%)	31 (23.0)
Chromosomal abnormality, n (%)	11 (7.9)
Trisomy 21	4 (2.9)
Other	7 (5.0)

DORV, Double-outlet right ventricle; *VSD*, ventricular septal defect; *SVC*, superior vena cava; *ASD*, atrial septal defect; *IVC*, inferior vena cava; *TGA*, transposition of the great arteries; *TAPVD*, total anomalous pulmonary venous drainage; *MAPCAs*, major aortopulmonary collateral arteries; *AVVR*, atrioventricular valve regurgitation.
*All conditions with more than 2% of the cohort affected.

operation ($P = .11$) and surgery before 2000 ($P = .38$) were not predictive of early mortality.

Another 11.7% of patients (12 of 103) who survived stage I died before stage II palliation. Age at the time of stage I ($P = .45$), presence of hypoplastic LV ($P = 1.0$), additional procedures at the time of stage I ($P = .54$), and initial surgery before 2000 ($P = 1.0$) were not significantly predictive of the risk of interstage death.

Stage II Procedures

A stage II procedure was performed in 94 patients (Table 2). The median patient age at the time of stage II was 10.3 months (IQR, 4.4-20.3 months; mean, 19.2 ± 32.3 months), and the median interval between stage I and stage II procedures was 10.7 months (IQR, 3.96-20.4 months; mean, 16.7 ± 22.7 months). The mean age at the time of stage II decreased significantly after 2000 (9.5 ± 9.4 months vs 33.6 ± 46.1 months; $P < .001$). An additional concomitant procedure was performed in 71.3% of the patients (67 of 94). The most frequently performed concomitant procedures were AVV repair (13.8%; 13 of 94), TAPVD repair (12.8%; 12 of 94), main PA division (12.8%; 12 of 94), and PA patch enlargement (9.6%; 9 of 94). Early mortality was 6.4% (6 of 94). Moderate or greater AVVR at the time of stage II was associated with increased early mortality (15.4% vs 2.9%; $P = .048$). Hypoplastic LV ($P = 1.0$), age at the time of stage II ($P = .13$), additional concomitant procedures ($P = .18$), and having undergone initial surgery before 2000 ($P = .68$) were not associated with increased risk of early mortality.

Among the patients who survived stage II palliation, another 17.0% (15 of 88) died without progressing to Fontan. Interstage mortality was less frequent after 2000, but this did not reach statistical significance (11.3% vs 25.7%; $P = .09$). Age at the time of stage II ($P = .37$), hypoplastic LV ($P = .55$), and additional procedures at the time of stage II ($P = 1.0$) did not predict an increased risk of interstage mortality.

Fontan Procedure

Eighty patients underwent Fontan completion, the details of which are summarized in Table 2. The median age at the time of Fontan completion was 5.8 years (IQR, 4.3-7.9 years; mean, 7.1 ± 5.5 years). The mean age at the time of Fontan has deceased in recent years, from 8.7 ± 6.9 years in those who underwent initial surgery before 2000 to 5.2 ± 2.1 years in those who underwent initial surgery from 2000 onward ($P = .004$). Additional procedures were performed in 40.0% of the patients (32 of 80), most frequently AVV surgery (15.0%; 12 of 80) and main pulmonary artery division (7.5%; 6 of 80). The median interval between the stage II procedure and Fontan completion was 4.3 years (IQR, 3.5-5.4 years; mean, 4.3 ± 3.5 years). Early mortality was 3.8% (3 of 80). Age at the time of Fontan ($P = .41$), hypoplastic LV ($P = .21$), significant AVVR before Fontan ($P = .45$), concomitant procedure ($P = .56$), type of Fontan ($P = 1.0$), and have undergone initial surgery before 2000 ($P = 1.0$) were not predictive of early mortality after Fontan completion.

Survival for the Whole Cohort

For the overall cohort, survival was 66.5 % (95% CI, 57.9%-73.9%) at 5 years, 64.4% (95% CI, 55.5%-72.0%) at 15 years, and 57.8% (95% CI, 47.5%-66.8%) at 25 years. There were 5 orthotopic cardiac transplantations (5 of 139; 3.6%). Freedom from death and transplantation was 66.5% (95% CI, 57.8%-73.8%) at 5 years, 61.8% (95% CI, 52.5%-69.8%) at 15 years, and

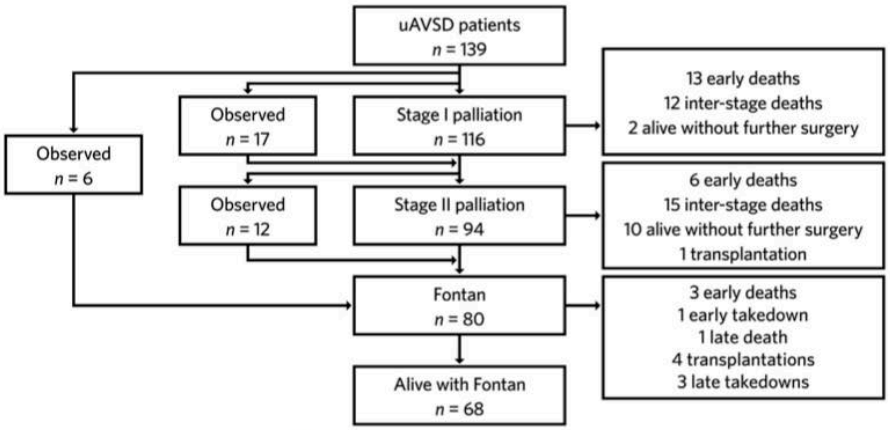

FIGURE 1. Procedures and outcomes.

55.2% (95% CI, 50.5%-64.5%) at 25 years (Figure 2, *A*). Univariable predictors of death or transplantation are summarized in Table 3. Aortic atresia (HR, 8.5; $P < .001$), hypoplastic aortic arch (HR, 3.2; $P < .001$), Norwood procedure (HR, 2.9; $P = .01$), and more recent initial surgery (HR, 1.03; $P = .04$) were associated with adverse outcomes. The factors entered into a multivariable model are listed in Table 4. Aortic atresia (HR, 5.3; $P = .03$) and hypoplastic aortic arch (HR, 2.5; $P = .02$) were independently associated with increased risk of death or transplantation.

TABLE 2. Type of procedure and early mortality by stage of palliation

Procedure	Number of procedures	Early mortality, n (%)
Stage I		
MBT	51	1 (2.0)
Isolated PAB	28	3 (10.7)
Central shunt	13	1 (7.7)
Norwood	11	5 (45.5)
DKS	7	2 (28.6)
PDA ligation	2	0 (0)
Isolated TAPVD repair	1	0 (0)
RV-PA shunt	1	1 (100)
Pulmonary valvuloplasty	2	0 (0)
Total	116	13 (11.2)
Stage II		
BCPS	41	4 (9.8)
Bilateral BCPS	31	2 (6.5)
Kawashima	22	0 (0.0)
Total	94	6 (6.4)
Stage III (Fontan)		
Extracardiac conduit	49	2 (4.1)
Lateral tunnel	21	1 (4.8)
Atriopulmonary connection	10	0 (0.0)
Total	80	3 (3.8)

In cases where more than 1 operation was performed concomitantly, the dominant procedure is listed. *MBT*, Modified Blalock–Taussig shunt; *PAB*, pulmonary artery band; *DKS*, Damus–Kaye–Stansel connection; *PDA*, patent ductus arteriosus; *TAPVD*, total anomalous pulmonary venous drainage; *RV-PA*, right ventricle to pulmonary artery shunt; *BCPS*, bidirectional cavopulmonary shunt.

Survival Following Stage I

The competing risk model of outcomes following stage I palliation is shown in Figure 2, *B*. Univariable predictors of death or transplantation are listed in Table 3. In univariable analysis, aortic arch hypoplasia (HR, 3.1; $P = .01$) and Norwood procedure (HR, 3.2; $P = .03$) were predictive of death or transplantation, whereas hypoplastic PAs (HR, 0.11; $P = .03$) was predictive of decreased risk. In a multivariable model, significant AVVR at the time of stage I was predictive of decreased transplantation-free survival (HR, 2.5; $P = .03$) (Table 4).

Survival Following Stage II

The competing risk model of outcomes following stage II palliation is shown in Figure 2, *C*. Univariable predictors of death or transplantation are listed in Table 3. Aortic atresia was associated with increased risk of death or transplantation (HR, 10.6; $P < .001$). Because no other factors approached statistical significance, multivariable analysis was not performed.

Survival Following Fontan Operation

The mean follow-up time after Fontan completion was 12.3 ± 9.7 years (median, 9.3 years; IQR, 4.2-21.8 years). In the patients who underwent Fontan completion, survival was 94.9% (95% CI, 86.9%-98.0%) at 5 years, 92.0% (95% CI, 80.6%-96.8%) at 15 years, and 82.4% (95% CI, 61.5%-92.6%) at 25 years. Freedom from death, Fontan takedown, and transplantation was 89.7% (95% CI, 80.4%-94.7%) at 5 years, 83.5% (95% CI, 69.7%-91.3%) at 15 years, and 77.3% (95% CI,

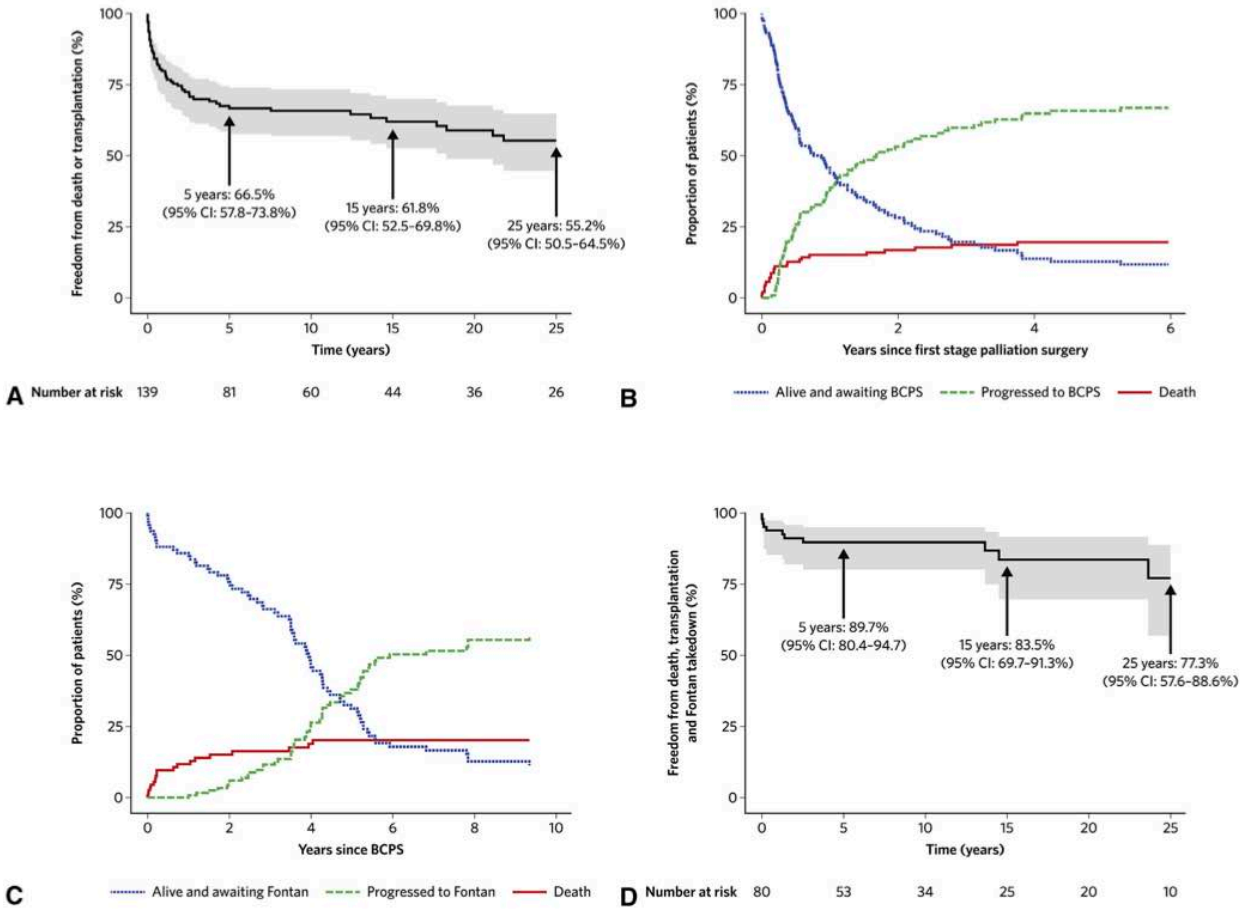

FIGURE 2. Kaplan–Meier freedom from death and transplantation for the entire cohort (A), competing risk model for stage I (B), competing risk model for stage II (C), and freedom from death, transplantation, and Fontan takedown in patients who underwent Fontan (time in years after Fontan completion) (D). *CI*, Confidence interval; *BCPS*, bidirectional cavopulmonary shunt.

57.6%-88.6%) at 25 years (Figure 2, *D*). In univariable analysis, only older age at the time of Fontan approached statistical significance as a predictor of death or transplantation (HR, 1.1; $P = .06$). Although chromosomal abnormalities were not predictive of adverse outcome, only 1 of 4 patients (25%) with trisomy 21 survived to Fontan.

At the end of the study period, 85.0% of the patients (68 of 80) were alive with a Fontan circulation. Late death occurred in 6.3% of these patients (5 of 80). Fontan takedown was performed in 5.0% of the patients (4 of 80), 1 of whom (1.3%) was still alive at last follow-up. Orthotopic cardiac transplantation was performed in 4 patients following the Fontan procedure (4 of 80; 5.0%), 2 of whom (2.5%) were alive at last follow-up. New York Heart Association (NYHA) functional class could be determined for 97.1% of the Fontan survivors (66 of 68) at their most recent follow-up; 83.3% (55 of 66) were in NYHA class I, 12.1% (8 of 66) were in NYHA class II, and 4.5% (3 of 66) were in NYHA class III. Late complications at the last follow-up included dysrhythmia in 35.0% (28 of 80), hepatic dysfunction in 13.8% (11 of 80), protein-losing enteropathy in 5.0% (4 of 80), and plastic bronchitis in 2.5% (2 of 80).

AVV Procedures

Additional procedures on the AVV were performed in 31.7% of the patients (44 of 139) because of AVVR. Of the initial procedures, 6.8% (3 of 44) were replacements, and the remaining 93.2% (41 of 44) were repairs. The timing of the initial AVV procedure based on the stage of palliation is shown in Table 5. Early mortality for initial AVV operations was 18.2% (8 of 44). Of those who underwent an AVV operation, 31.8% (14 of 44) required a second AVV operation, of which 64.3% (9 of 14) were repairs and 35.7% (5 of 14) were replacements. Another

TABLE 3. Univariable predictors of death or transplantation for the whole cohort, and each stage of palliation (Fontan take-down is included as failure in the Fontan group)

	Whole cohort		Stage I		Stage II		Fontan	
Variable	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.0 (0.95-1.1)	.80	0.1 (0.00-3.6)	.20	0.94 (0.74-1.2)	.62	1.1 (1.0-1.1)	.06
Aortic atresia†	**8.5 (3.0-24.4)**	**<.001**	3.5 (1.3-17.5)	.13	**10.6 (4.3-26.3)**	**<.001**	*	*
Arch hypoplasia	**3.2 (1.7-6.0)**	**<.001**	**3.1 (1.4-7.1)**	**.01**	1.8 (0.59-5.2)	.32	*	*
Chromosomal abnormality	0.88 (0.32-2.4)	.81	0.91 (0.21-3.9)	.90	2.4 (0.56-10.6)	.24	*	*
DORV	0.82 (0.49-1.4)	.64	0.56 (0.25-1.3)	.16	1.1 (0.47-2.6)	.84	1.6 (0.48-5.3)	.46
Heterotaxy	0.84 (0.48-1.5)	.55	0.78 (0.34-1.8)	.57	0.93 (0.33-2.6)	.89	0.81 (0.24-2.7)	.73
Hypoplastic LV	0.92 (0.53-1.6)	.78	1.1 (0.47-2.5)	.84	0.73 (0.31-1.7)	.48	0.95 (0.28-3.2)	.94
Hypoplastic PAs	0.62 (0.31-1.2)	.17	**0.11 (0.01-0.84)**	**.03**	1.1 (0.44-2.8)	.83	0.85 (0.23-3.8)	.85
Moderate or greater AVVR	1.8 (0.92-3.5)	.09	**2.5 (0.99-6.3)**	**.05**	1.7 (0.72-4.2)	.22	0.57 (0.07-4.5)	.59
Norwood procedure	**2.9 (1.3-6.5)**	**.01**	**3.2 (1.1-9.3)**	**.03**	1.4 (0.32-6.4)	.65	*	*
Year of procedure	**1.03 (1.0-1.06)**	**.04**	1.02 (0.99-1.1)	.15	0.97 (0.92-1.02)	.29	0.99 (0.92-1.1)	.71

Bold indicates the variable reaches statistical significance. *HR*, Hazard ratio; *CI*, confidence interval; *DORV*, double-outlet right ventricle; *LV*, left ventricle; *PA*, pulmonary artery; *AVVR*, atrioventricular valve regurgitation. *An insufficient number of patients survived to Fontan completion, precluding analysis. †Only 4 patients in total.

9.1% of patients (4 of 44) required a third AVV operation, which included 1 valve closure and 3 re-replacements. No patient required a fourth AVV operation.

Overall freedom from intervention on the AVV was 72.7% (95% CI, 62.7%-80.4%) at 5 years, 63.4% (95% CI, 52.8%-72.7%) at 15 years, and 63.4% (95% CI, 52.8%-72.7%) at 25 years. The risk of undergoing an intervention on the AVV was significantly lower in patients who underwent Fontan completion compared with those who did not (HR, 0.28; $P < .001$) (Figure 3, *A*). From the time of Fontan completion, freedom from AVV operation was 95.5% (95% CI, 86.7%-98.5%) at 5 years, and remained stable at 92.7% (95% CI, 80.8%-97.4%) at 15 and 25 years (Figure 3, *B*).

DISCUSSION

Unbalanced AVSD occurs in approximately 10% of patients with AVSD.[1,2] A biventricular repair in children with uAVSD might not be feasible owing to either hypoplasia of 1 ventricle, with or without override of the AVV, or straddling of the subvalvular apparatus, with 2 well-developed ventricles. The outcomes of SVP in children with uAVSD are rarely reported and generally have been poor.[2-5] Early attempts at Fontan completion in the setting of uAVSD had poor results.[4,5] More recently, only small series of patients with uAVSD undergoing SVP have been reported.[2,3]

Drinkwater and colleagues[2] reported 45 patients with uAVSD who underwent SVP between 1986 and 1996. Only 16 of 45 patients (35.6%) progressed to Fontan completion. Of the patients who underwent the Fontan operation, 37.5% (6 of 16) had died at a mean follow-up of 2.5 years. More recently, Owens and colleagues[3] reported 44 patients with uAVSD who presented between 1998 and 2003, 79.5% of whom (35 of 44) underwent SVP. Survival was 51% at a mean follow-up of 25 months. Only 16 of 44 patients (36.4%) progressed to Fontan completion. The authors did not report the long-term outcomes of patients who survived to Fontan.

In recent large reports of SVP outcomes, the subgroup with uAVSD constituted only a small proportion of the

TABLE 4. Multivariable predictors of death or transplantation

Multivariable predictor	HR (95% CI)	*P* value
Overall		
Aortic atresia	5.3 (1.2-23.0)	.03
Aortic arch hypoplasia	2.5 (1.1-5.5)	.02
≥Moderate AVVR	1.8 (0.84-4.0)	.13
Year of procedure	1.0 (0.98-1.0)	.39
Norwood procedure	0.82 (0.24-2.8)	.80
Stage I		
≥Moderate AVVR	2.5 (1.1-5.9)	.03
Hypoplastic PAs	0.17 (0.02-1.3)	.09
Aortic arch hypoplasia	2.1 (0.84-5.4)	.11
Norwood procedure	1.8 (0.6-5.5)	.32

HR, Hazard ratio; *CI*, confidence interval; *AVVR*, atrioventricular valve regurgitation; *PA*, pulmonary artery.

TABLE 5. Timing of AVV operations in relation to stage of SVP

Stage of SVP	n (%)
Total	44
Before stage I	1 (2.3)
At the time of stage I	1 (2.3)
Between stages I and II	4 (9.1)
At the time of stage II	17 (38.6)
Between stage II and Fontan	9 (20.4)
At the time of Fontan	10 (22.7)
After Fontan	2 (4.5)

SVP, Single-ventricle palliation.

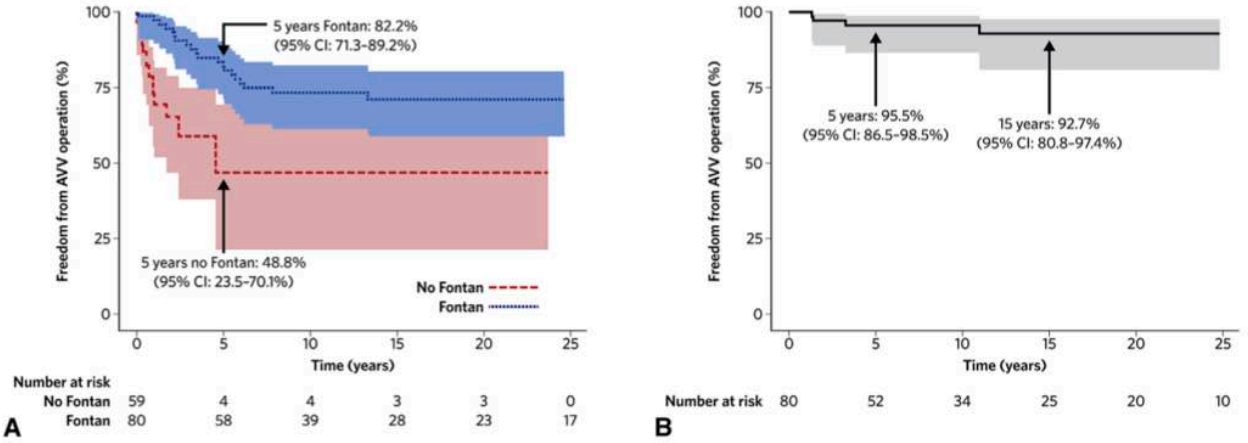

FIGURE 3. Freedom from AVV operation in patients who underwent Fontan and those who did not (A) and freedom from AVV operation after Fontan completion (B). *CI*, Confidence interval; *AVV*, atrioventricular valve.

cohorts. A previous report from our institution described 499 patients who underwent SVP between 1990 and 2008, 14% of whom (72 of 499) had uAVSD.[6] Children with uAVSD had worse overall survival and a higher risk of mortality after stage I and stage II procedures in univariable analysis. Rogers and coworkers[7] reported 771 children who underwent Fontan palliation between 1992 and 2009, of whom 11.4% (88 of 771) had uAVSD. In multivariable analysis, uAVSD independently predicted death or Fontan takedown within 30 days of operation. Lee and colleagues[8] reported 557 patients undergoing stage II palliation between 1998 and 2010, of whom 10.2% had uAVSD. They identified uAVSD as an independent risk factor for failure to achieve Fontan completion. Other recent large reports of Fontan outcomes did not analyze the impact of uAVSD on survival.[9-14]

Overall, there is substantial mortality associated with uAVSD, much of which occurs in the first 5 years, so that only 66.5% of our patients were alive at 5 years after their first surgery, regardless of the stage of palliative procedure. After this, survival stabilized, with only a minor further decrease to 57.8% at 25 years. In our patients, aortic arch hypoplasia, and particularly aortic atresia, were independently associated with death or transplantation in multivariable analysis. In univariable analysis, the Norwood operation as the stage I procedure was associated with poorer outcomes, but this lost significance in the multivariable model. This likely occurred because the majority of these patients had aortic atresia or aortic arch hypoplasia, both of which are known risk factors for mortality following the Norwood procedure[15,16] and were predictors of poor outcome in our multivariable model. Of further interest, LV hypoplasia itself was not associated with poor outcomes in our cohort. In large studies of SVP, hypoplastic left heart syndrome (HLHS) has been associated with significantly poorer outcomes[6,7,12]; however, in patients with hypoplastic LV with aortic atresia or arch hypoplasia, which are known to be higher-risk morphologies of HLHS,[15,16] survival was indeed worse.

Another point of interest is the high rate of interstage mortality, with 11.7% of patients dying between stage I and stage II and 17.0% dying between stage II and Fontan. This is an interesting finding, considering that traditionally the majority of deaths have been thought to occur before BCPS.[6] The age of our patients at Fontan operation was similar to that reported by other groups.[6,9,14] Our previous results for the overall Fontan population,[6] who were of a similar age as our uAVSD cohort, showed a much lower interstage mortality (just over 7% for both interstage periods). This finding suggests that the risk of interstage death may be specific to patients with uAVSD rather than to the age at which Fontan operation was performed. Furthermore, our findings are consistent with those of Lee and colleagues,[8] who identified uAVSD as an independent risk factor for failure to progress from stage II palliation to Fontan.

Age at each stage of palliation decreased after the year 2000. After 2000, we tended to perform stage II palliation at the younger age of 3 months to try to minimize interstage mortality, as has been described previously.[6] Other groups have shown that early BCPS is safe and have advocated its beneficial effects on pulmonary and coronary circulation and in reducing volume load on the systemic ventricle.[17,18] We did not observe an improvement in survival over time; however, this may reflect the fact that patients with more complex disease underwent surgery in more recent years. For example, all Norwood procedures were performed after 2000, and these patients represent a particularly high-risk group.

Survival of our patients who achieved Fontan completion was 94.9% at 5 years and 82.4% at 25 years. These rates compare favorably with long-term survival in large outcome studies of the Fontan procedure, which reported 20-year survival of 71% to 77% in all patients after Fontan completion.[6,11] Furthermore, cumulative freedom from death, Fontan takedown, or transplantation was 82.4% at 15 years after Fontan completion. This finding is consistent with results of recent studies of the entire Fontan population, which found 15-year freedom from Fontan failure in the range of 77% to 91%.[10,12-14] In fact, this is slightly better than the results of the Fontan procedure in patients with HLHS, in whom we previously reported a 10-year freedom from failure of 79%.[6] In addition, more than 80% of Fontan survivors were in NYHA functional class I at last follow-up. Hirsch and colleagues[12] also reported that approximately 80% of survivors in the general Fontan population were in NYHA class I. Thus, outcomes of patients with uAVSD who achieved Fontan completion are not different from those of the general population of patients with Fontan circulation. These results are in contrast to previous reports showing poor outcomes for patients with uAVSD undergoing Fontan.[2-5]

Heterotaxy has been previously described as a risk factor for the Fontan operation.[9,19,20] Despite the associated challenges, there is evidence of recent improved outcomes in patients with heterotaxy syndrome undergoing the Fontan operation.[20,21] The majority of our patients (73%; 102 of 139) had heterotaxy, making it difficult to assess the true impact of heterotaxy per se in patients with uAVSD. Because of the frequent association of heterotaxy and uAVSD, it has been suggested that these 2 factors may interact with each other on multiple regression analysis in these patients.[8] Indeed, heterotaxy was not a risk factor for adverse outcomes in our patients, likely owing to the fact that the majority of our patients had this.

Surgery on the AVV was performed in nearly one-third of our patients. The operative mortality associated with the initial operation on the AVV was 18.2%, and another approximately one-third of patients underwent reoperation on the AVV. AVVR was previously identified as a risk factor for poor outcomes in SVP.[2,6,22,23] Owens and coworkers[3] reported that 30% of their uAVSD patients required operation for AVVR. They identified undergoing an operation on the AVV as a significant risk factor for death, with 75% of patients who underwent an AVV operation deceased at a mean follow-up of 25 months. In our cohort, significant AVVR before initial palliation was associated with poorer long-term outcomes. Conversely, significant AVVR at the time of stage II palliation was associated with early death, but not with poorer long-term survival. This may reflect the fact that few AVV repairs were performed at stage I, when unrepaired AVVR may contribute to late death. Surgery for AVVR was commonly performed at stage II, which might increase surgical risk but may mitigate the risk of late death. These findings are consistent with previous reports indicating that AVVR is a significant risk factor for poor outcomes following stage II.[8,24] In fact, it has been shown that failure to achieve a successful repair of an AVV with significant regurgitation at the time of stage II is associated with mortality.[8] In our patients, it appears that the AVV of those who survived to Fontan completion was of better quality, as demonstrated by a lower rate of AVV operations (Figure 3, *A*). Moreover, it was uncommon for patients to require an AVV operation following Fontan completion (Figure 3, *B*). Taken together, the foregoing findings emphasize the importance of a competent AVV in patients with uAVSD; however, for those patients with uAVSD and significant AVVR, achieving such competence is particularly challenging.

Unfortunately, simple annuloplasty and "edge-to-edge" repair are often unreliable.[25,26] In an attempt to address this issue, our group has adopted the "bridging technique" for AVV repair in children with a single ventricle, as described previously.[26-28] This technique has shown promising early results, but its long-term outcomes remain to be established.[25] We are hopeful that this technique can reduce some of the burden associated with AVVR in this cohort.

This study is limited by its retrospective nature. Although this is the largest study of patients with uAVSD who underwent SVP reported to date, our relatively limited sample size precluded further detailed analysis. This might have affected our ability to demonstrate the significance of some postulated risk factors.

CONCLUSIONS

Children with uAVSD undergoing univentricular repair have high mortality, with <60% of patients alive at 25 years after initial palliation. Furthermore, AVVR is a major problem in this group, with nearly one-third of patients requiring AVV surgery, of whom a further one-third required AVV reoperations. However, survival of patients who achieve Fontan completion is better than has been reported previously, and not different from that in the general Fontan population.

Conflict of Interest Statement

Dr d'Udekem is a consultant for MSD and Actelion. Dr Brizard serves on the advisory board of Admedus. Dr Weintraub serves on the advisory board of Actelion. All other authors have nothing to disclose with regard to commercial support.

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Key Words: Fontan, single-ventricle palliation, unbalanced atrioventricular septal defect

Chapter 6: Successful atrioventricular valve repair improves long-term outcomes in children with unbalanced atrioventricular septal defect

6.1 Introduction

In chapter 5, it was demonstrated that SVP for uAVSD can achieve satisfactory results, especially for those who progress to Fontan completion. However, one of the major causes of morbidity and mortality is the high rate of AVV regurgitation and the need for repeated operations.

Several strategies for surgery on the common AVV have been used over time, none of which have proven particularly successful. There have only been relatively small studies of AVV surgery in patients with uAVSD in the past, which have demonstrated disappointing results with AVV repair (89, 90). In this study we reviewed all patients who underwent AVV surgery at the RCH who had a diagnosis of uAVSD.

During the study period, 44 patients with uAVSD underwent AVV surgery. Just over half of patients survived to 20-years of follow-up. Repair of the AVV was achieved in the majority of cases, however at 20-years just over half of patients were free from AVV reoperation. The presence of moderate or greater AVV regurgitation at discharge was a predictor of much higher risk of mortality and reoperation, especially in infants. There was no single technique of AVV repair, which was found to be associated with superior outcomes.

The important message from this study is that patients with residual AVV regurgitation have very poor outcomes. These patients should be considered for early re-repair or replacement of the valve, preferably during the same procedure or admission, even if they are infants.

6.2 Buratto E, et al. J Thorac Cardiovasc Surg. 2017;154:2019-2027

Successful atrioventricular valve repair improves long-term outcomes in children with unbalanced atrioventricular septal defect

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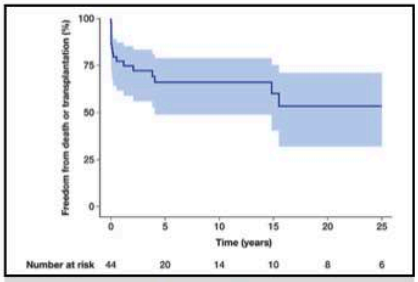
ABSTRACT

Background: Atrioventricular valve regurgitation is a significant cause of morbidity and mortality in patients with unbalanced atrioventricular septal defect. However, knowledge of the outcomes of atrioventricular valve repair in children with unbalanced atrioventricular septal defect and univentricular physiology is limited.

Methods: We conducted a retrospective review of all patients with unbalanced atrioventricular septal defect treated with single-ventricle palliation who underwent atrioventricular valve surgery at The Royal Children's Hospital.

Results: Between 1976 and 2016, 139 children with unbalanced atrioventricular septal defect underwent single-ventricle palliation, of whom 31.7% (44/139) required atrioventricular valve surgery. Repair of the atrioventricular valve was attempted in 97.7% (43/44) of patients, of whom 4.7% (2/43) were converted to replacement during the initial operation. Replacement of the atrioventricular valve without attempted repair was performed in 2.3% (1/44) of patients. Early mortality was 18.2% (8/44). Freedom from death or transplantation at 10 years was 66.0% (95% confidence interval, 49.1-78.5) and at 20 years was 53.3% (95% confidence interval, 32.1-70.6). In multivariable analysis, significant predischarge atrioventricular valve regurgitation (hazard ratio, 6.4; $P = .002$), age less than 1 year (hazard ratio, 8.3; $P = .01$), and repair before stage II palliation (hazard ratio, 3.4; $P = .04$) were associated with death. Freedom from reoperation at 10 years was 61.9% (95% confidence interval, 41.9-76.8) and at 20 years was 56.3% (95% confidence interval, 35.3-72.8). Moderate or greater atrioventricular valve regurgitation at discharge was associated with an increased risk of reoperation (hazard ratio, 1.8; $P = .03$). Of transplant-free survivors, atrioventricular valve regurgitation was less than moderate in 60.0% (15/25) at the most recent follow-up.

Conclusions: Atrioventricular valve surgery in patients with unbalanced atrioventricular septal defect is associated with substantial mortality and a high rate of reoperation. Successful atrioventricular valve repair is associated with better survival and freedom from reoperation. (J Thorac Cardiovasc Surg 2017;■:1-9)



Freedom from death or transplantation after AVV repair in children with uAVSD.

Central Message

AVV surgery in children with uAVSD is challenging, with a high risk of mortality and reoperation. However, successful repair is associated with better outcomes.

Perspective

Children with uAVSD who require AVV surgery have high rates of reoperation and death, with only half of patients surviving at 20 years. Successful AVV repair is associated with better survival, whereas significant residual regurgitation is associated with a poor prognosis, and these patients may benefit from AVV replacement.

See Editorial Commentary page xxx.

CONG

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Abbreviations and Acronyms

AVSD = atrioventricular septal defect
AVV = atrioventricular valve
AVVR = atrioventricular valve regurgitation
CI = confidence interval
ePTFE = expanded polytetrafluoroethylene
SHR = subhazard ratio
SVP = single-ventricle palliation
uAVSD = unbalanced atrioventricular septal defect

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CONG

Unbalanced atrioventricular septal defect (uAVSD) constitutes approximately 10% of all atrioventricular septal defects (AVSDs).[1] When biventricular repair is not feasible, these children require single-ventricle palliation (SVP), which is associated with substantial mortality and morbidity.[2,3] Atrioventricular valve (AVV) regurgitation (AVVR) is a major cause of morbidity in these patients, with up to one third requiring an AVV procedure.[2,3] In the setting of SVP, AVVR is a recognized risk factor for death.[4-6] Furthermore, achieving an adequate, durable AVV repair in patients with single-ventricle physiology is challenging.[7-10] However, reports of AVV repair in patients with uAVSD have been limited to a few small series.[11,12]

MATERIALS AND METHODS

Patients

All patients with uAVSD who underwent SVP and required at least 1 AVV operation at The Royal Children's Hospital, Melbourne from January 1, 1976, to January 1, 2016, were included in this study. Ethics approval was granted by The Royal Children's Hospital Human Research Ethics Committee (32047E). International patients were excluded because follow-up data were not available for this group.

Unbalanced AVSD was defined as a complete AVSD, as confirmed on echocardiography, which in the opinion of the treating team was not suitable for biventricular repair (ie, the ventricles could not be septated). The reasons for this were a hypoplastic ventricle or a straddling AVV.

Baseline data were collected by retrospective chart review. Follow-up data were obtained by correspondence with the patients' general practitioners and cardiologists. Follow-up was complete if the last confirmed patient contact occurred within 2 years of the end of the study period. Early death was defined as death occurring within 30 days of surgery or before discharge from hospital.

The degree of AVVR was graded by echocardiography on an ordinal scale (0 = none, 1 = trivial, 2 = mild, 3 = moderate, 4 = severe). Significant AVVR was considered to be present when AVVR was moderate or greater.

Ventricular dysfunction was defined as moderate or greater dysfunction of the dominant ventricle as reported on echocardiography immediately before AVV repair. The mechanism of AVVR was determined by reviewing preoperative and intraoperative echocardiography reports.

Operative Technique

The techniques used to perform AVV repair were chosen by the operating surgeon at the time of the procedure on the basis of operative findings and echocardiography. Three primary techniques have been adopted over the study period. The earliest repairs were performed using a suture annuloplasty (de Vega type). During the intermediate period, repairs were performed using the "edge-to-edge" technique. In this procedure, the central facing edges of the superior and inferior bridging leaflets were approximated with interrupted Prolene sutures, creating a double orifice valve. More recently, a bridging strip of expanded polytetrafluoroethylene (ePTFE) (Gore-Tex Inc, Flagstaff, Ariz) was used to facilitate edge-to-edge repair. This technique has been described and illustrated in detail.[9,10] The central facing parts of the superior and inferior bridging leaflets were approximated with interrupted Prolene sutures. The distance from the base of the inferior bridging leaflet to the base of the superior bridging leaflet was measured. A strip of ePTFE was then cut to size and sutured to the annulus with interrupted ePTFE sutures and to the leaflets using interrupted Prolene stitches. Additional repair techniques including the insertion of ePTFE neochordae and closure of accessory clefts were performed as required, using techniques previously described in detail.[13]

Statistical Methods

All data were analyzed using STATA version 13 (StataCorp LP, College Station, Tex). All continuous data are expressed as mean ± standard deviation unless otherwise specified. Continuous data were compared between groups using the Mann–Whitney *U* test. Discrete variables were compared between groups using the chi-square test, unless group size was less than 10, in which case the Fisher exact test was used. The degrees of preoperative and postoperative AVVR were compared using the paired 2-tailed Student *t* test. Time-dependent end points, survival, and freedom from death and transplantation were analyzed using the Kaplan–Meier method, with time commencing at the time of AVV surgery. In addition, a competing risk analysis was performed for survival (with transplantation as a competing risk) and reoperation (with death and transplantation as competing risks). Univariable regression analysis of risk factors for death or reoperation was performed using a Fine and Gray's proportional subhazard model to account for competing risk. The factors entered into the model were age less than 1 year, significant preoperative AVVR, significant AVVR at discharge, AVV surgery before stage II palliation, dominant right ventricle, AVV repair with the ePTFE bridge technique, requirement for permanent pacemaker in the early postoperative period, total anomalous pulmonary venous drainage, edge-to-edge repair technique (including both patients with conventional edge-to-edge repair and ePTFE bridge), ventricular dysfunction, and year of operation (measured in days after the first AVV repair in this series, scaled to years). Factors with moderate evidence against the null hypothesis ($P < .10$) were entered into a multivariable model. The variables included in the multivariable analysis were significant predischarge AVVR, age less than 1 year, and repair before stage II palliation.

RESULTS

Demographics

A total of 44 patients underwent AVV surgery during the study period (Figure 1). Baseline demographics are shown in Table 1. Infants accounted for 34.1% (15/44) of patients, including 3 neonates (6.8%, 3/44). There was a high rate of associated defects, particularly heterotaxy (29/44, 65.9%) and double-outlet right ventricle (23/44, 52.3%).

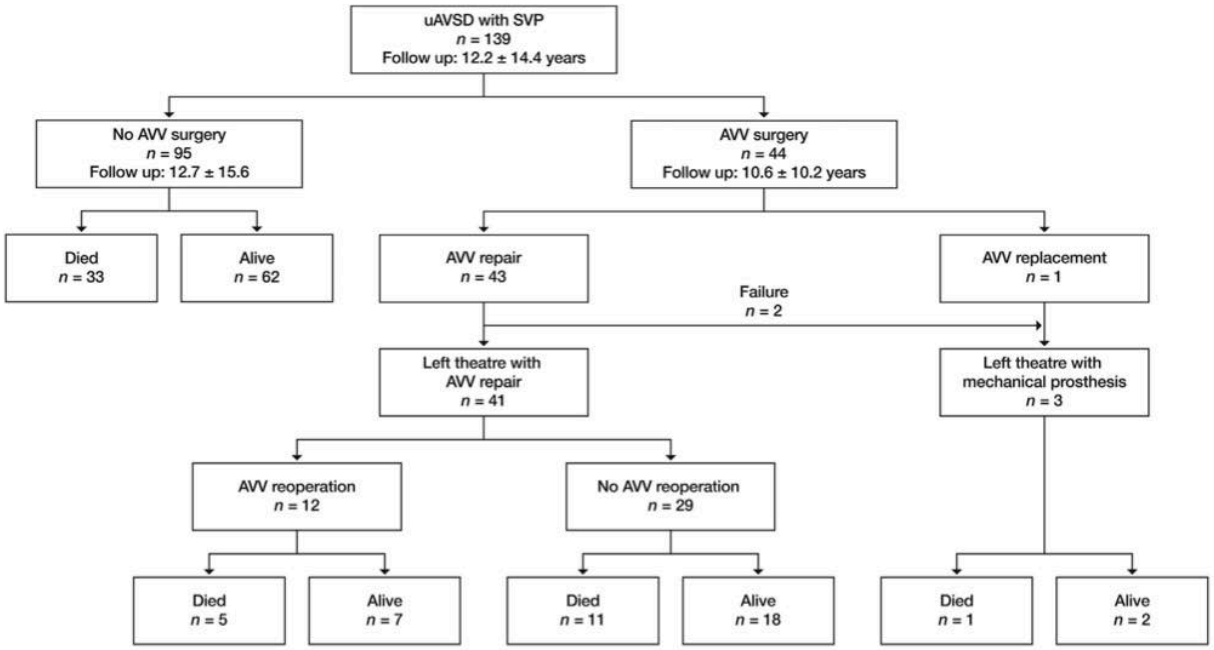

FIGURE 1. Consort diagram demonstrating outcomes after AVV repair in patients with uAVSD. *uAVSD*, Unbalanced atrioventricular septal defect; *SVP*, single-ventricle palliation; *AVV*, atrioventricular valve.

Preoperative echocardiographic AVVR grade was recorded in 86.4% of patients (38/44), of whom 84.2% (32/38) had moderate or greater AVVR.

Mechanism of Regurgitation

It was possible to determine the mechanism of AVV regurgitation for 79.5% of patients (35/44). The mechanisms of AVVR were central regurgitation with annular dilatation (42.9%, 15/35), central regurgitation with leaflet dysplasia (22.9%, 8/35), eccentric regurgitation due to prolapse of 1 or more leaflets (31.4%, 11/35), and eccentric regurgitation due to leaflet restriction (2.9%, 1/35).

Techniques of Repair

The techniques used for AVV repair are summarized in Table 2. Repair of the AVV was attempted in 97.7% (43/44) of patients. The most commonly used techniques were annuloplasty (31.8%, 14/44) and edge-to-edge repair (54.5%, 24/44), which included facilitation with an ePTFE bridge in 18.2% (8/44). In 2 patients (4.5%, 2/44) who initially underwent annuloplasty, repair was unsuccessful and conversion to mechanical AVV replacement was performed in the same procedure. Direct mechanical valve replacement was performed in 1 patient (2.3%, 1/44). Mean cross-clamp time was 78.6 ± 37.6 minutes, and mean cardiopulmonary bypass time was 159.0 ± 73.7 minutes.

Early Outcomes

Early mortality was 18.2% (8/44). A predischarge transthoracic echocardiogram was performed for 85.4% (35/41) of children who underwent AVV repair. Mild or less AVV regurgitation was recorded in 62.9% (22/35), and 37.1% (13/35) of patients had moderate regurgitation. The mean grade of AVVR in patients who had AVV repair decreased from 3.1 ± 0.4 preoperatively to 2.4 ± 0.9 at discharge ($P < .001$). Early permanent pacemaker implantation was required in 13.6% (6/44) of patients.

Late Outcomes

Mean follow-up time was 10.6 ± 10.2 years (median, 7.4 years; interquartile range, 2.2-15.4 years). Follow-up was complete for all patients.

The Kaplan–Meier survival function is shown in Figure 2, *A*, whereas the competing risk model of survival is shown in Figure 3, *A*. Freedom from death and transplantation at 10 years was 66.0% (95% confidence interval [CI], 49.1-78.5) and at 20 years was 53.3% (95% CI, 32.1-70.6).

Kaplan–Meier freedom from AVV reoperation is shown in Figure 2, *B*, whereas the competing risk model for freedom from reoperation is shown in Figure 3, *B*. Freedom from AVV reoperation at 10 years was 61.9% (95% CI, 41.9-76.8) and at 20 years was 56.3% (95% CI, 35.3-72.8).

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TABLE 1. Demographic data at initial atrioventricular valve repair

Total	44
Age (y)	3.0 (IQR, 0.7-4.4)
Sex, n (%)	
Male	28 (63.6)
Female	16 (36.4)
Ventricular dominance, n (%)	
Left	11 (25.0)
Right	28 (63.6)
2 balanced ventricles	5 (11.4)
Associated diagnoses, n (%)	
Heterotaxy	29 (65.9)
Double-outlet right ventricle	23 (52.3)
TGA	13 (29.5)
TAPVD	13 (29.5)
Aortic arch hypoplasia	5 (11.4)
Aortic atresia	2 (4.5)
Chromosomal anomalies, n (%)	
DiGeorge syndrome	1 (2.3)
Noonan syndrome	1 (2.3)
Other	1 (2.3)
Ventricular dysfunction	
Moderate or greater	5 (11.4)
Mild or less	28 (63.6)
Not recorded	11 (25.0)
Preoperative AVVR, n (%)	
Mild to moderate	6 (14)
Moderate	21 (48)
Moderate to severe	7 (16)
Severe	4 (9)
Unknown	6 (14)
Stage of palliation, n (%)	
Before stage I	1 (2.3)
At the time of stage I	1 (2.3)
Between stage I and II	5 (11.4)
At the time of stage II	16 (36.4)
Between stage II and Fontan	9 (20.4)
At the time of Fontan	10 (22.7)
After Fontan	2 (4.5)
Initial stage I palliation, n (%)	
RMBT	14 (31.8)
Central shunt	6 (13.6)
PA band	6 (13.6)
Norwood	3 (6.8)
Pulmonary valvuloplasty	1 (2.3)
Proceeded directly to stage II	10 (22.7)
Proceeded directly to Fontan	4 (9.1)

IQR, Interquartile range; *TGA*, transposition of great arteries; *TAPVD*, total anomalous pulmonary venous drainage; *AVVR*, atrioventricular valve repair; *RMBT*, right modified Blalock–Taussig shunt; *PA*, pulmonary artery.

A total of 3 patients underwent orthotopic cardiac transplantation, 2 of whom subsequently died at 22 days and 13.9 years after transplantation, respectively. The surviving patient was 1.2 years post-transplantation at the time of the most recent follow-up.

TABLE 2. Techniques of atrioventricular valve surgery

Techniques for first AVV operation, n (%)	
Annuloplasty	14 (31.8)
Isolated de Vega	9 (20.5)
de Vega with cleft closure	3 (6.8)
de Vega with neochords	1(2.3)
Commissuroplasty	2 (4.5)
Edge-to-edge	24 (54.5)
Suture	16 (26.4)
Isolated	8 (18.2)
With cleft closure	4 (9.1)
With annuloplasty	3 (6.8)
With neochord and commisuroplasty	1 (2.3)
ePTFE bridge	8 (18.2)
Isolated	1 (2.3)
With cleft closure	6 (13.6)
With chordal shortening	1 (2.3)
Chordal repair	3 (6.8)
Isolated neochords	1 (2.3)
With cleft closure	2 (4.5)
Closure of AVV component	2 (4.5)
Patch closure	2 (4.5)
Replacement	1 (2.3)
Techniques for second AVV operation, n (%)	
Repair	9 (64.3)
Edge-to-edge	4 (28.6)
Suture	3 (21.4)
ePTFE bridge	1 (7.1)
Leaflet patch augmentation	3 (21.4)
Annuloplasty	2 (14.3)
Replacement	5 (35.7)

AVV, Atrioventricular valve; *ePTFE*, expanded polytetrafluoroethylene.

Risk Factors for Death or Transplantation, and Reoperation

The risk factors for death or transplantation, and AVV reoperation are shown in Table 3. In univariable analysis, age less than 1 year (subhazard ratio [SHR], 10.6; $P < .001$), having a repair before stage II palliation (HR, 4.5, $P = .01$), and having moderate or greater AVVR at discharge (SHR, 2.7; $P = .001$) were predictors of death or transplantation. In multivariable analysis, moderate or greater predischarge AVVR (SHR, 6.4; $P = .002$), age less than 1 year (HR, 8.3; $P = .03$), and repair before stage II (SHR, 3.4; $P = .04$) were associated with a higher risk of death or transplantation. Significant AVVR at discharge was the only risk factor associated with an increased risk of AVV reoperation (SHR, 1.8; $P = .03$).

Kaplan–Meier curves for freedom from death and transplantation comparing infants with children aged more than 1 year are shown in Figure 4, *A*. Freedom from death and transplantation at 5 years was 86.1% (95% CI, 67.0-94.5) in those aged more than 1 year, compared with 19.4% (95% CI, 3.5-45.0) in infants ($P < .001$).

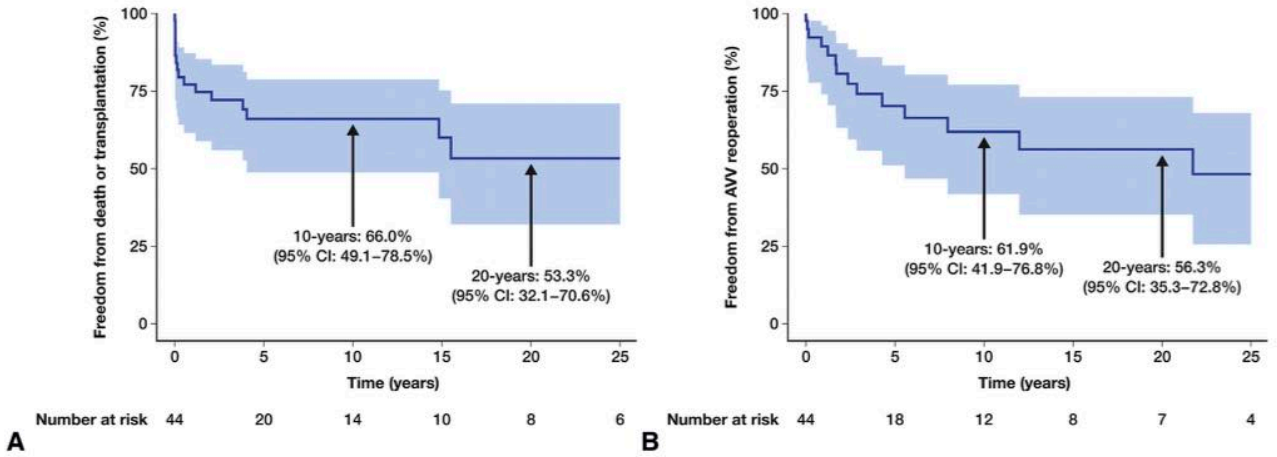

FIGURE 2. Kaplan–Meier curves for (A) freedom from death and transplantation and (B) freedom from reoperation on the AVV in patients with uAVSD. *CI,* Confidence interval; *AVV,* atrioventricular valve.

Kaplan–Meier curves for freedom from death and transplantation comparing patients with significant AVVR at discharge with patients who did not have significant AVVR are shown in Figure 4, *B*. The 5-year freedom from death and transplantation for the group without significant AVVR at discharge was 78.8% (95% CI, 52.3-91.6), compared with 33.0% (95% CI, 9.2-59.7) for the group with significant AVVR ($P < .001$). The 5-year freedom from reoperation was 84.4% (95% CI, 58.9-94.7) for the group without significant AVVR at discharge, whereas all patients with significant AVVR had undergone AVV reoperation ($P < .001$).

Freedom from death and transplantation of children aged more than 1 year comparing those with significant AVVR at discharge with children without significant AVVR is shown in Figure 4, *C*. The 5-year freedom from death and transplantation for the group without significant AVVR was 100.0% compared with 50.0% (95% CI, 11.1-80.4) for the group with significant AVVR ($P = .003$).

Freedom from death and transplantation of infants comparing those with significant AVVR at discharge with children without significant AVVR is shown in Figure 4, *D*. The 2-year freedom from death and transplantation for the group without significant AVVR was 71.4% (95% CI, 25.8-92.0), compared with 28.6% (95% CI, 4.1-61.2) for the group with significant AVVR ($P = .04$).

Outcomes of Atrioventricular Valve Replacement

A total of 8 patients underwent AVV replacement (3 as first AVV operation, 2 as second AVV operation, and 3 as third AVV operation). Kaplan–Meier freedom from death and transplantation is shown in Figure 5. Freedom from

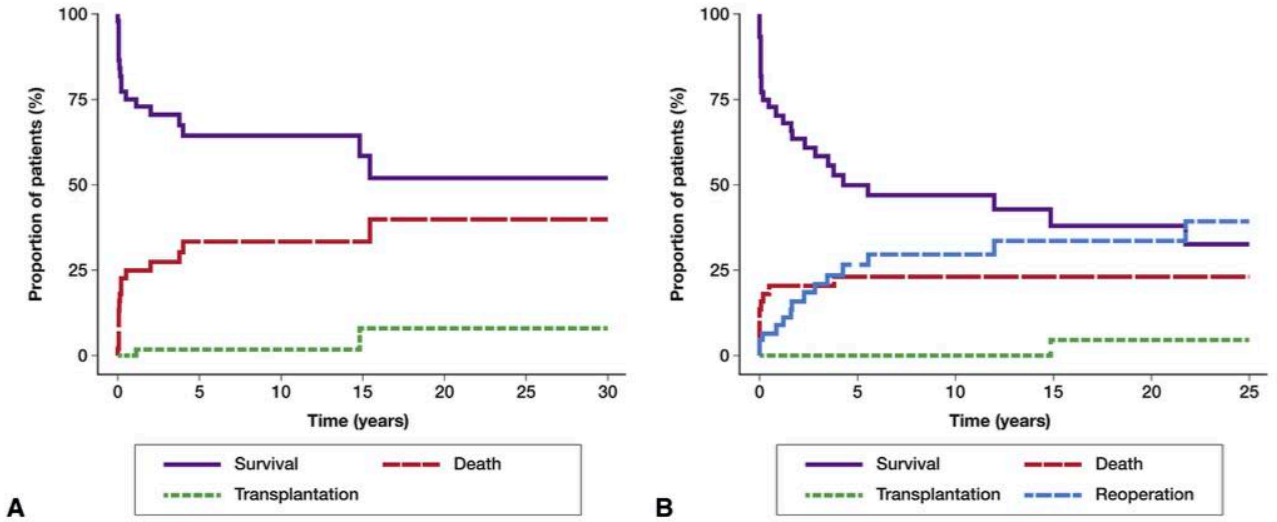

FIGURE 3. Competing risk models (A) for survival and (B) for reoperation on the AVV after AVV repair in patients with uAVSD.

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TABLE 3. Risk factors for death and reoperation

	Mortality		Reoperation	
Univariable predictor	**SHR (95% CI)**	***P* value**	**SHR (95% CI)**	***P* value**
Age <1 y	10.6 (2.7-41.6)	**.001**	1.0 (0.3-3.3)	.98
Dominant RV	1.2 (0.42-3.4)	.73	1.5 (0.48-4.8)	.47
Edge-to-edge repair	2.4 (0.79-7.4)	.12	1.7 (0.64-4.6)	.28
ePTFE bridge technique	0.74 (0.18-3.0)	.67	2.1 (0.57-7.9)	.26
Repair before stage II	4.5 (1.6-12.7)	**.004**	0.77 (0.10-6.0)	.81
Significant predischarge AVVR	2.7 (1.4-10.2)	**.01**	1.8 (1.1-3.1)	**.03**
Significant preoperative AVVR	2.0 (0.7-6.0)	.22	2.0 (0.40-10.0)	.40
TAPVD	0.77 (0.18-3.3)	.74	0.41 (0.06-3.1)	.39
Ventricular dysfunction	1.4 (0.2-8.3)	.69	*	*
Year of procedure	0.99 (0.94-1.0)	.61	1.03 (0.97-1.1)	.32

Multivariable predictor	**HR (95% CI)**	***P* value**
Significant predischarge AVVR	6.4 (1.9-20.9)	**.002**
Age <1 y	8.3 (1.1-49.8)	**.01**
Repair before stage II	3.4 (1.1-10.7)	**.04**

Bold indicates statistical significance. *SHR*, Subhazard ratio; *CI*, confidence interval; *RV*, right ventricle; *ePTFE*, expanded polytetrafluoroethylene; *AVVR*, atrioventricular valve regurgitation; *TAPVD*, total anomalous pulmonary venous drainage; *HR*, hazard ratio. *Insufficient number of events precludes analysis.

death and transplantation was 75.0% (95% CI, 31.5-93.1) at 10 years. Only 1 of these children was an infant at the time of AVV replacement and died 15 years after replacement.

Re-replacement was required in 3 patients; in 2 cases this was due to functional stenosis resulting from patient growth (6 and 12 years after replacement, respectively). In 1 patient, re-replacement was required due to thrombosis causing immobility of 1 leaflet, 4 years after implantation.

Reoperations

A total of 14 patients (14/44, 31.8%) underwent an AVV reoperation. The mean time from initial AVV operation to reoperation was 4.1 ± 6.0 years (median, 2.0 years; interquartile range, 0.9-4.3 years).

Of the 14 patients requiring reoperation, 85.7% (12/14) had undergone initial AVV repair, whereas 14.3% patients (2/14) had undergone replacement. The mechanism of AVVR for the patients who underwent initial AVV repair could be determined for 91.7% (11/12) of patients. The mechanism of AVVR was central regurgitation due to annular dilatation (63.6%, 7/11), eccentric regurgitation due to leaflet prolapse (18.2%, 2/11), central regurgitation due to leaflet dysplasia (9.1%, 1/11), and dehiscence of a previous repair (9.1%, 1/11).

The techniques used to perform reoperation are summarized in Table 2. Repair was performed in 64.3% (9/14) of patients, and replacement was performed in 35.7% (5/14) of patients. The most commonly used techniques for re-repair were edge-to-edge repair (21.4%, 3/14) and patch augmentation of a leaflet (21.4%, 3/14).

Early mortality after reoperation on the AVV was 7.1% (1/14). Freedom from death and transplantation after AVV reoperation was 76.2% (95% CI, 42.7-91.7) at 1 year and 55.5% (95% CI, 22.8-79.1) at 5 and 10 years. Freedom from reoperation after AVV reoperation was 78.6% (95% CI, 47.3-92.5) at 1 year and 68.8% (95% CI, 35.7-87.3) at 5 and 10 years.

Status at Last Follow-up

There were 26 transplant-free survivors (26/44, 59.1%) at most recent follow-up. Fontan completion had been achieved in 84.6% (22/26), whereas 15.4% (4/26) were awaiting Fontan completion. A transthoracic echocardiogram was performed at last follow-up for 96.1% (25/26) of transplant-free survivors, of whom the grade of AVVR was less than moderate in 60.0% (15/25), moderate in 32.0% (8/25), and severe in 8.0% (2/25). The New York Heart Association functional status was available for all patients who achieved Fontan completion, of whom 81.8% (18/22) were in class I and 13.6% (3/22) were in class II. One patient (1/22, 4.5%) was in class III with severe AVVR and awaiting AVV replacement.

DISCUSSION

Children with uAVSD who require SVP are challenging to manage, with substantial early mortality and less than 60% survival at 20 years.[2,3] One of the risk factors for mortality in children with uAVSD is significant AVVR.[2,3]

Owens and colleagues[14] described 44 patients with uAVSD who presented between 1998 and 2003, of whom 79.5% (35/44) underwent SVP. Of these patients, 27.3% (12/44) required AVV surgery. The need for AVV surgery was associated with a significantly higher risk of mortality.

Likewise, our group recently published the outcomes of SVP for uAVSD in 139 patients who underwent surgery between 1976 and 2016.[3] In this group, AVVR was associated with a significantly greater risk of death or transplantation.

Furthermore, it has been shown that AVVR is associated with increased risk of mortality in the overall population of patients undergoing SVP.[4,15] A previous report from our group, which included 499 patients who underwent SVP between 1990 and 2008, identified AVVR as a risk factor for death.[4] Likewise, Pundi and colleagues,[15] in a cohort of 1052 patients who underwent a Fontan procedure between 1973 and 2012 demonstrated that AVV replacement was associated with an increased risk of death.

Achieving a successful repair of the AVV in patients with single-ventricle physiology is challenging, and residual AVVR is known to increase the risk of mortality.[16,17] However, there are few reports of AVV repair techniques applied in the setting of uAVSD.

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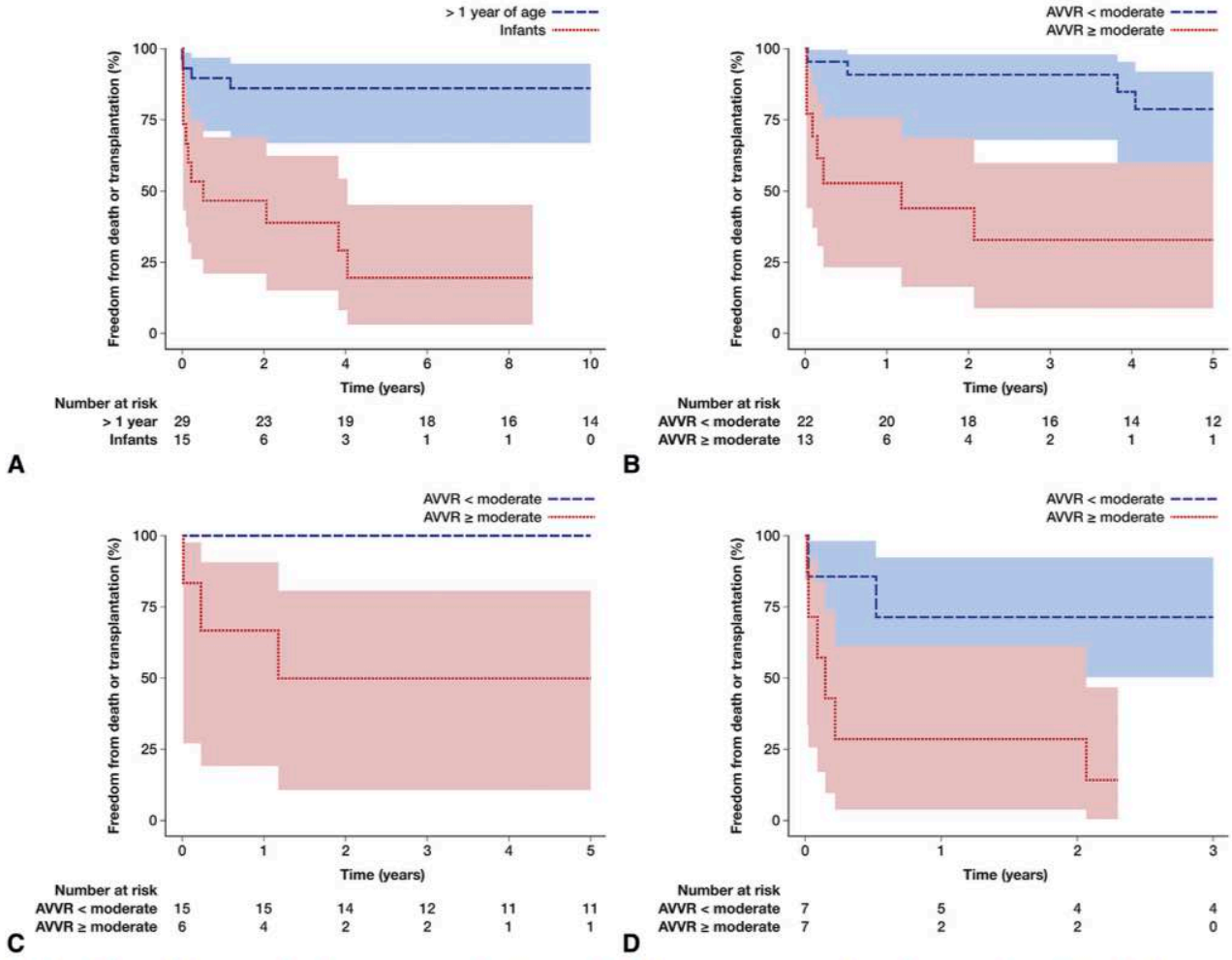

FIGURE 4. Kaplan–Meier curves for freedom from death or transplantation (A) comparing infants and those aged more than 1 year, (B) by degree of AVVR at the time of discharge from hospital, (C) for children aged more than 1 year by degree of AVVR at the time of discharge from hospital, and (D) for infants by degree of AVVR at the time of discharge. *AVVR*, Atrioventricular valve repair.

Misumi and colleagues[11] reported on 38 patients with common AVV and SVP (25 with uAVSD), who required AVV surgery between 1995 and 2012. They demonstrated a 15-year survival of 58.2% and 15-year freedom from reoperation of 45.3%, using an edge-to-edge repair facilitated with an ePTFE bridge. In their cohort, AVV surgery before bidirectional cavopulmonary shunt and the presence of total anomalous pulmonary venous drainage were risk factors for mortality.

Vijarnsorn and colleagues[18] recently reported a cohort of 9 patients with uAVSD and univentricular physiology who underwent AVV repair from 2003 to 2012. In this small study, 66.7% (6/9) of patients had residual moderate or greater AVVR postoperatively. Of the 6 patients with residual moderate AVVR, 50% (3/6) had died at 18 months follow-up.

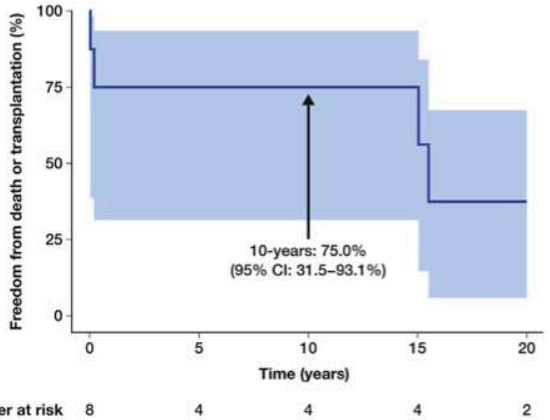

FIGURE 5. Freedom from death and transplantation following AVV replacement in patients with uAVSD. *CI*, Confidence interval.

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Imai and colleagues[19] reported 28 patients with uAVSD and univentricular physiology who underwent concomitant AVV repair and Fontan procedure between 1985 and 1998. The techniques used in this series were circular suture annuloplasty and cleft closure, and they reported a decrease in the mean grade of AVVR from 1.8 to 0.6 after repair. This study did not describe early mortality or long-term survival of patients who underwent repair of their common AVV. Most importantly, it seems that Imai and colleagues[19] described a subgroup of patients with a more favorable AVV anatomy that permitted survival to Fontan completion. We have previously observed that patients with uAVSD who survive to Fontan completion have favorable outcomes.[3]

Kotani and colleagues[16] reported 66 patients with SVP who underwent AVV repair from 1998 to 2011, of whom 10 patients had uAVSD. The mean grade of AVVR decreased from 2.1 to 1.3 after repair. At 5 years follow up, freedom from reoperation was 75%, whereas survival was 76%. Significant residual AVVR on intraoperative echocardiography was associated with increased risk of reoperation.

We have previously described 76 patients who underwent SVP and AVV repair between 1988 and 2010 at The Royal Children's Hospital. Of these patients, 14 had uAVSD.[5] In this group, the AVVR grade decreased from 3.3 to 2.3. Survival at 10 years was 61%, and freedom from reoperation was 56%. AVV surgery between initial palliation and stage II was associated with increased risk of mortality.

Compared with these results, our subgroup of patients with uAVSD had a mean preoperative AVVR grade of 3.1, whereas the mean postoperative degree of AVVR was 2.4. Although we demonstrated a significant improvement in AVVR after repair in patients with uAVSD, the residual degree of AVVR was greater than in the groups described. This is particularly important considering that moderate or greater AVVR at discharge was associated with a significantly higher risk of mortality and reoperation in our patients. Survival at 5 years was 79% in those without significant AVVR at discharge, compared with 33% in those with moderate or greater AVVR. In addition, although 84% of patients with less than moderate AVVR at discharge were free of reoperation at 5 years, all surviving patients with moderate or greater AVVR had required a reoperation over the same period. This suggests that AVV competency is more difficult to achieve in uAVSD compared with other forms of SVP. Furthermore, failure to achieve a satisfactory repair was associated with poor outcomes. Likewise, others have shown that significant postoperative AVVR in patients with SVP was associated with poorer survival and higher rates of reoperation.[16,17]

The risk of leaving residual AVVR must be balanced against the risks associated with AVV replacement. In our unit, there has been a strong preference to repair the AVV because of the perceived risks of AVV replacement in children. However, Jang and colleagues,[12] in a cohort of 33 patients with SVP undergoing AVV surgery, demonstrated that AVV replacement was associated with a significantly lower rate of reoperation when compared with patients undergoing repair. Furthermore, the actuarial survival was 20% greater in the replacement group at 7 years follow-up, although this did not reach significance. Mahle and colleagues[20] in a cohort of 17 children with SVP, who underwent AVV replacement at a mean age of 3 years, demonstrated 5-year survival of 75% in the recent era. In our cohort, the 10-year freedom from death and transplantation after AVV replacement was 75%, which is slightly better than the overall cohort, although direct comparison cannot be made as some of these AVV replacements were performed as a reoperation. Furthermore, it should be noted that only 1 of these patients was an infant. Thus, it may be better to replace the AVV when less than moderate AVVR cannot be achieved with repair, especially because a relatively large prosthesis can be implanted in children with uAVSD due to the common AVV. In the past, we tended to accept moderate AVVR, with close clinical follow-up. However, our data, presented in the current article, indicate that if infants are left with moderate or greater AVVR at the time of discharge from the hospital, they do poorly. Thus, it would be reasonable to replace AVV in these infants.

In addition to significant AVVR at discharge, AVV repair in infancy was associated with a higher risk of mortality in multivariable analysis. Moreover, there was increased mortality when AVV repair was performed before stage II palliation. This would suggest that in patients with uAVSD, earlier surgery is associated with higher risk. Indeed, a similar trend was observed in the overall population with SVP.[5] It is likely that children who required AVV repair earlier had more severe dysplasia of AVV, and this contributed to their poorer outcomes.

Despite the high rate of reoperations for AVVR and the fact that 40% of patients had moderate or greater AVVR, 96% of surviving patients who achieved Fontan completion were in New York Heart Association functional class I or II at most recent follow-up. This is consistent with results previously reported for the general population with univentricular physiology.[3,21]

Given the challenge associated with AVV repair in patients with uAVSD, several techniques have been used. In the early part of the series, de Vega annuloplasty was used for the majority of repairs. However, our group has previously shown that this technique was associated with poor results.[5] The edge-to-edge repair was used in many patients, but likewise has been shown to be an unreliable technique.[8,9] In more recent years, we used an ePTFE bridge to support edge-to-edge repairs, with the aim of providing apposition of the bridging leaflets and annular

stabilization.[8-10] Because the mechanism of AVVR is most frequently central regurgitation, related to annular dilatation or failure of the bridging leaflets to coapt properly, the PTFE bridge has been developed in an attempt to stabilize the annulus and support the bridging leaflets, while still allowing annular growth. Further follow-up will demonstrate if it is able to achieve this goal.

Study Limitations

This study is limited by its small sample size and retrospective nature. Particularly, the subgroup analysis of survival based on age and degree of AVV regurgitation at discharge were limited by small numbers of patients, and this must be kept in mind when interpreting the results. Furthermore, this study includes operations performed over a 40-year period, during which surgical techniques have changed. Also, ventricular function could not be assessed in all patients because echocardiography was not available in the early part of the study. Nevertheless, this represents the largest series of AVV repairs in patients who have undergone SVP for uAVSD published to date.

CONCLUSIONS

AVV repair in patients with uAVSD who have undergone SVP is associated with a substantial risk of reoperation and mortality. Achieving a competent valve is difficult, but important, because those with significant residual AVVR are at a greater risk of death and reoperation. Infants with residual AVVR represent a particularly high-risk group. When a satisfactory repair cannot be achieved, AVV replacement may be the better strategy.

Conflict of Interest Statement

C.P.B. serves on the advisory board of Admedus. Y.d'U. is a consultant for Actelion and MSD. All other authors have nothing to disclose with regard ro commercial support.

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Key Words: atrioventricular valve, Fontan, single-ventricle palliation, unbalanced atrioventricular septal defect

CONG

Chapter 7: Long-term outcome after pulmonary artery banding in children with atrioventricular septal defects.

7.1 Introduction

Most children with cAVSD undergo complete repair in infancy with excellent results. However, there is a subset of patients who present with heart failure prior to 3 months of age, or who have complex anatomy, which makes them unsuitable for early biventricular repair. In this groups of patients, the use of a PAB may allow growth while protecting the pulmonary circulation, thus allowing delayed complete repair (61 – 63). However, it is unknown whether these children progress to biventricular repair, and what impact PAB might have on the LAVV. In patients with uAVSD, PAB may be used as part of their three-stage palliation. However, these children may also have subsequent AVV dysfunction.

This study reviewed all patients with a diagnosis of AVSD who underwent PAB at the RCH between 1975 and 2016. During the study period, 68 patients had PAB, of whom 40 had cAVSD and 28 had uAVSD. Early results after PAB demonstrated a low early mortality and no significant increase in AVV regurgitation.

In patients with cAVSD we demonstrated that the majority of patients progressed to complete repair, but there was a somewhat higher rate of mortality and reoperation than observed in the overall cAVSD population.

In patients with uAVSD, survival and freedom from reoperation was similar to that observed in patients without PAB.

Overall, this study suggests that PAB can be used safely in the management of patients with AVSD without an acute increase in AVV regurgitation.

7.2 Buratto E, et al. Ann Thorac Surg. 2018 (*in press*).

Long-Term Outcome After Pulmonary Artery Banding in Children With Atrioventricular Septal Defects

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Background. Patients with atrioventricular septal defect (AVSD) may require pulmonary artery banding (PAB), either as a part of a staged univentricular palliation or to allow delayed biventricular repair in patients presenting with early heart failure. The long-term outcomes of PAB in children with AVSD have not been previously reported.

Methods. All children with AVSD who underwent PAB at a single institution were included in the study. Data were obtained from medical records and correspondence with general practitioners and cardiologists.

Results. A total of 68 patients with complete AVSD underwent PAB, of whom 58.8% of patients (40 of 68) had balanced AVSD (bAVSD) and underwent PAB with intent to subsequently perform biventricular repair. The remaining 41.2% of patients (28 of 68) had unbalanced AVSD (uAVSD) and underwent PAB as part of staged univentricular repair. PAB was not associated with a short-term increase in atrioventricular valve (AVV) regurgitation ($p = 0.24$). In patients with bAVSD, 83.8% (95% confidence interval [CI]: 67.4% to 92.4%) achieved biventricular repair. Survival was 73.4% (95% CI: 54.3% to 85.5%) and freedom from left AVV operation was 60.0% (95% CI: 36.1% to 77.4%) at 20 years of follow-up. In patients with uAVSD, 61.9% (95% CI: 40.5% to 77.5%) had achieved Fontan completion at 10 years of follow-up. Survival was 60.9% (95% CI: 36.2% to 78.5%) and freedom from AVV operation was 78.6% (95% CI: 55.5% to 90.6%) at 20 years.

Conclusions. PAB can be used in patients with AVSD without compromising AVV function. Most patients with bAVSD progress to biventricular repair, albeit with a high rate of AVV reoperation. Patients with uAVSD who undergo PAB have similar outcomes to the overall uAVSD population.

(Ann Thorac Surg 2018;■:■–■)

Atrioventricular septal defects (AVSDs) are a spectrum of congenital heart defects characterized by the presence of a common atrioventricular junction [1]. Patients with simple forms of partial AVSD (pAVSD) and complete AVSD (cAVSD) undergo biventricular repair in early childhood [2–8]. Patients with heart failure in the first 3 months of life, complex anatomy, or unbalanced ventricles (uAVSD) may not be suitable for immediate biventricular repair, and pulmonary artery banding (PAB) may be used to protect the pulmonary circulation, whereas the decision to perform complete repair or single ventricle palliation is deferred until the child grows [9–12]. It has previously been shown that across the spectrum of AVSD, atrioventricular valve regurgitation (AVVR) is a major cause of morbidity and mortality [13–19]. It is unclear what impact PAB has on survival, progression to complete repair or Fontan completion, and progression of AVVR. We performed a retrospective review of children with AVSD who underwent PAB.

Patients and Methods

Patients

All patients with a diagnosis of AVSD who underwent PAB before complete biventricular repair or a staged univentricular repair at the Royal Children's Hospital, Melbourne, between 1983 and 2016 were included in the study. Ethics approval was granted by the Royal Children's Hospital Human Research Ethics Committee (HREC 32047E).

The data were collected by retrospective review of medical records. Follow-up data were obtained by

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Abbreviations and Acronyms

AVSD = atrioventricular septal defect
AVV = atrioventricular valve
AVVR = atrioventricular valve regurgitation
bAVSD = balanced atrioventricular septal defect
BCPS = bidirectional cavopulmonary shunt
cAVSD = balanced atrioventricular septal defect
CoA = coarctation of the aorta
CI = confidence interval
DORV = double outlet right ventricle
ECMO = extracoroporeal membrane oxygenation
LAVV = left atrioventricular valve
LAVVR = left atrioventricular valve regurgitation
LVOT = left ventricular outflow tract
PAB = pulmonary artery banding
PAPVD = partial anomalous pulmonary venous drainage
pAVSD = partial atrioventricular septal defect
PDA = patent ductus arteriosus
TAPVD = total anomalous pulmonary venous drainage
TGA = transposition of the great arteries
uAVSD = unbalanced atrioventricular septal defect
VSD = ventricular septal defect

correspondence with the patients' general practitioners and cardiologists.

Early death was defined as death occurring within 30 days of operation or before discharge from the hospital.

The degree of AVVR was graded by echocardiography on an ordinal scale (0 = none, 1 = trivial, 2 = mild, 3 = moderate, 4 = severe). Grading was performed according to published guidelines [20]. Clinically significant AVVR was considered to be present when AVVR was moderate or greater.

Indications for PAB were signs of heart failure before 3 months of age in patients with balanced AVSD (bAVSD) or unbalanced ventricles. Patients were diagnosed with heart failure when they had failure to thrive (determined from age-matched growth curves) or were on antifailure therapy (at least one diuretic agent or angiotensin-converting enzyme inhibitor). A small number of patients (6 of 40, 15.0%) with bAVSD underwent PAB between 3 and 6 months of age for the following additional reasons: multiple muscular ventricular septal defects (3 of 40, 7.5%), failure to thrive younger than 6 months with refusal of blood products because of parental religion (2 of 40, 5.0%), and bronchiolitis and heart failure at 3 months of age (1 of 40, 2.5%).

uAVSD was defined as a cAVSD, which in the opinion of the treating team was not suitable for biventricular repair (ie, the ventricles could not be septated). The reasons for this were either one hypoplastic ventricle or a straddling atrioventricular valve (AVV).

The indication for AVV reoperation was moderate or greater AVVR in a symptomatic patient or severe AVVR in an asymptomatic patient.

Statistical Analysis

All data were analyzed with STATA version 13 (Stata Corp, College Station, TX). All continuous data are expressed as mean ± standard deviation unless otherwise specified. Continuous data were compared between groups by using the Mann-Whitney *U* test. Discrete variables were compared between groups by using the χ^2 test, unless group size was less than 10, in which case the Fisher exact test was used. The degree of preoperative and postoperative AVVR was compared with the paired two-tailed Student's *t* test. Time-dependent end points, specifically survival and freedom from AVV operation, were analyzed with the Kaplan-Meier method, with time commencing at the time of PAB. Univariable analysis of risk factors for mortality was performed with Cox proportional hazards test. Differences between groups were compared with the Mann-Whitney *U* test. Progression to complete repair of bAVSD and Fontan, respectively, was analyzed with a competing risk framework. The threshold for statistical significance was p value less than 0.05.

Results

Demographic Characteristics

A total of 68 patients with a diagnosis of AVSD underwent PAB during the study period. Baseline data, comparing patients with bAVSD and uAVSD, are included in Table 1. The majority of patients had bAVSD (58.8%, 40 of 68), whereas 41.2% (28 of 68) had uAVSD (Fig 1). Additional cardiovascular malformations were present in 70.0% (28 of 40) of children with bAVSD and 82.1% (23 of 28) of patients with uAVSD; this difference was not significant ($p = 0.39$). Details of the additional congenital heart defects are summarized in Table 1. Before 2000, there were 38 PAB procedures for AVSD (38 of 68, 55.9%), compared with 30 procedures (30 of 68, 44.1%) after 2000. Specifically regarding bAVSD, 24 procedures were performed before 2000 (24 of 40, 60%), compared with 16 procedures after 2000 (16 of 40, 40%).

A similar proportion of patients with bAVSD and uAVSD had failure to thrive at the time of PAB ($p = 0.40$). All patients with bAVSD had congestive heart failure at the time of PAB. Antifailure therapy included frusemide in 97.5% of patients (39 of 40), spironolactone in 55.0% of patients (22 of 40), captopril in 37.5% of patients (15 of 40), digoxin in 35.0% of patients (14 of 40). Other factors that may have contributed to the decision to perform PAB in patients with bAVSD included necrotizing enterocolitis in 12.5% of patients (5 of 40) patients, Hirschprung disease that required colectomy in 5.0% of patients (2 of 40), and severe bronchiolitis in 5.0% of patients (2 of 40).

Operative Data

Additional concomitant procedures were performed in 25.0% of patients with bAVSD (10 of 40), compared with

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Table 1. Demographic Data by Type of AVSD

Variable	bAVSD (n = 40)	uAVSD (n = 28)	*p* Value
Weight at PAB, mean ± SD, kg	3.2 ± 0.8	4.9 ± 0.3.0	0.17
Age at PAB, mean ± SD, days	54.7 ± 49.0	75.7 ± 111.3	0.66
Follow-up time, mean ± SD, years	8.9 ± 8.7	12.7 ± 10.9	0.06
Failure to thrive, n (%)	33 (82.5)	19 (67.9)	0.40
Sex, n (%)			0.27
Male	16 (40.0)	15 (53.6)	
Female	24 (60.0)	13 (46.4)	
Preoperative AVVR, n (%)			0.73
None/trivial	8 (20.0)	7 (25.0)	
Mild	20 (50)	9 (32.1)	
Mild–moderate	3 (7.5)	5 (17.8)	
Moderate	7 (17.5)	4 (14.3)	
Moderate–severe	1 (2.5)	2 (7.1)	
Severe	1 (2.5)	1 (3.6)	
Trisomy 21, n (%)	19 (47.5)	3 (10.7)	0.001
Additional CHD, n (%)			
CoA	6 (14.3)	4 (15.4)	
Cor triatriatum	0	1 (3.8)	
DORV	4 (10.0)	7 (25.0)	
Heterotaxy	5 (12.5)	10 (35.7)	
Hypoplastic aortic arch	5 (11.9)	4 (15.4)	
Interrupted arch	2 (4.8)	0	
LSVC	5 (11.9)	3 (11.5)	
Muscular VSDs	9 (21.4)	4 (15.4)	
PAPVD	1 (2.4)	1 (3.8)	
Subaortic stenosis	1 (2.4)	0	
TAPVD	3 (7.5)	3 (10.7)	
TGA	0	2 (7.7)	
Age at de-banding, mean ± SD, years	1.7 ± 1.7	3.8 ± 4.2	0.06

AVVR = atrioventricular valve regurgitation; AVSD = atrioventricular septal defect; bAVSD = balanced atrioventricular septal defect; CHD = congenital heart disease; CoA = coarctation; DORV = double outlet right ventricle; LSVC = left superior vena cava; PAB = pulmonary artery banding; PAPVD = partial anomalous pulmonary venous drainage; SD = standard deviation; TAPVD = total anomalous pulmonary venous drainage; TGA = transposition of the great arteries; uAVSD = unbalanced atrioventricular septal defect; VSD = ventricular septal defect.

57.1% with uAVSD (16 of 28), representing a significant difference ($p = 0.002$). The details of these procedures are included in Table 2.

Early mortality was 4.4% (3 of 68); all 3 patients had bAVSD. One child was 6 weeks old with bAVSD, double outlet right ventricle, right atrial isomerism, and pulmonary hypertension. The child had a pulmonary hypertensive crises after endotracheal suctioning 7 hours after PAB, arrested, and could not be resuscitated. The second child had bAVSD and coarctation of the aorta and underwent concomitant PAB and coarctation repair. This child experienced thrombosis of the aortic anastomosis and required reoperation. The postoperative course was complicated by sepsis, hemodynamic instability, and cardiac arrest. The child was resuscitated, but cerebral imaging performed on maximal inotropic support demonstrated changes consistent with global hypoperfusion, and care was withdrawn. The third child had bAVSD and interrupted aortic arch and underwent concomitant arch repair and PAB. The postoperative course was complicated by inability to wean from the ventilator, and the patient was found to have a severe tracheal stenosis. Slide tracheoplasty was performed but was complicated by hypoxia and sepsis, necessitating extracoroporeal membrane oxygenation (ECMO) support. The upper lobe bronchus was found to be stenotic, and this was subsequently repaired; however, because of severe sepsis the child could not be supported despite the use of ECMO and died.

The mean grade of AVVR was 1.1 ± 0.76 preoperatively, compared with 1.0 ± 0.87 on predischarge echocardiography. This did not represent a significant change in severity of AVVR ($p = 0.24$). In patients with bAVSD for whom preoperative and predischarge echocardiography was performed, 43.8% (14 of 32) had a decrease in left AVVR (LAVVR), 28.1% (9 of 32) had no change in LAVVR, and 28.1% (9 of 32) had an increase in LAVVR. In patients with uAVSD for whom preoperative and predischarge echocardiography was performed, 37.5% (9 of 24) had a decrease in AVVR, 45.8% (11 of 24) had no change in AVVR, and 16.7% (4 of 24) had an increase in AVVR.

Long-Term Outcomes for PAB in bAVSD

Mean follow-up for patients with bAVSD was 8.9 ± 8.7 years.

The Kaplan-Meier curve for survival for patients with PAB and bAVSD is shown in Figure 2A. Survival was 77.5% (95% confidence interval [CI]: 59.5% to 88.2%) at 5 years and 73.4% (95% CI: 54.3% to 85.5%) at both 10 and 20 years. For the children who had PAB performed in the first 3 months of life for early heart failure (35 of 40, 85.0%), long-term survival at 10 and 20 years was 88.0% (95% CI: 59.4% to 96.9%). Univariable predictors of mortality are shown in Table 3. There was a trend toward increased risk of mortality in patients with heterotaxy syndromes (hazard ratio 3.9, $p = 0.05$).

The Kaplan-Meier curve for freedom from left AVV (LAVV) reoperation for patients with bAVSD is shown in Figure 2B. Freedom from reoperation on the LAVV was 81.3% (95% CI: 60.2% to 91.9%) at 5 years, 66.0% (95% CI: 42.5% to 81.7%) at 10 years, and 60.0% (95% CI: 36.1% to 77.4%) at 20 years. Of the 6 patients (6 of 40, 15.0%) who underwent LAVV reoperation, the valve was repaired in all patients. One patient (1 of 40, 2.5%) underwent a second reoperation, and the valve was re-repaired. A single patient (1 of 40, 2.5%) underwent concomitant right AVV repair at the time of LAVV repair.

The competing risk model showing progression to complete biventricular repair for patients with a diagnosis of bAVSD is shown in Figure 2C. The cumulative incidence of complete repair was 40.1% (95% CI: 25.0% to 56.1%) at 1 year, 78.1% (95% CI: 60.8% to 88.4%) at 5 years, and 83.8% (95% CI: 67.4% to 92.4%) at 8 years. There were

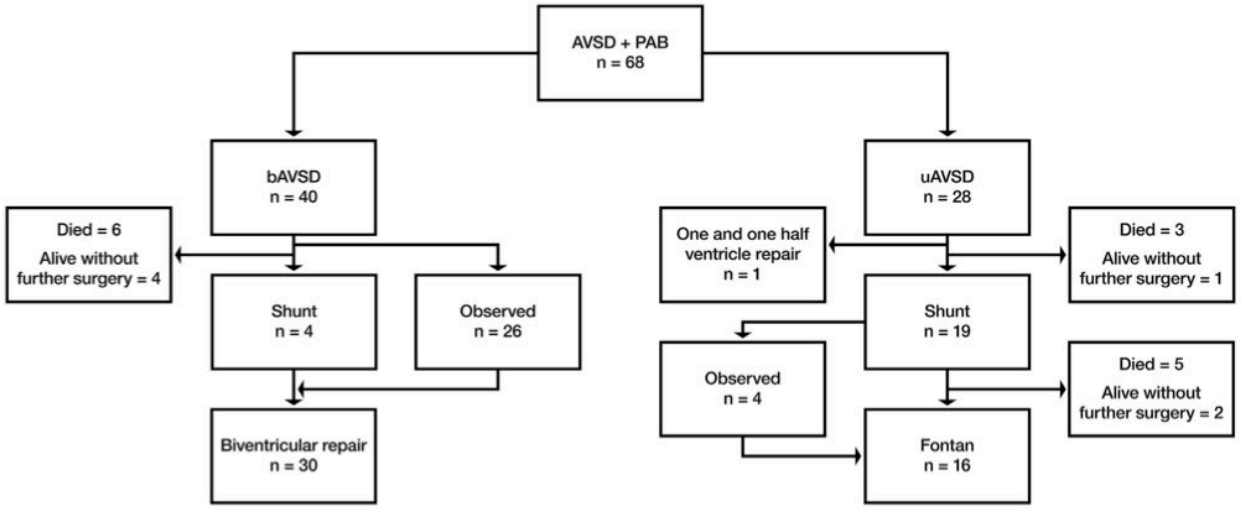

Fig 1. Procedure and outcomes for patients with atrioventricular septal defect (AVSD) undergoing pulmonary artery banding (PAB). (bAVSD = balanced atrioventricular septal defect; uAVSD = unbalanced atrioventricular septal defect.)

4 patients (4 of 40, 10.0%) who had a shunt before progressing to complete repair. All of these patients had the shunt taken down at the time of complete repair; no patients in the bAVSD group underwent one-and-one-half ventricle repair. Furthermore, there were 4 patients (4 of 40, 10.0%) who had not undergone complete repair by 4 years of age, and 3 of these patients (3 of 40, 7.5%) had a shunt before delayed complete repair as described above, whereas 1 patient (1 of 40, 2.5%) had multiple muscular VSDs and underwent complete repair just after 4 years of age.

In patients who achieved biventricular repair, before PAB the mean grade of LAVVR was 1.1 ± 0.8, compared with 1.2 ± 1.0 immediately before biventricular repair. This did not represent a significant progression in the degree of LAVVR ($p = 0.73$).

Long-Term Outcomes of PAB in uAVSD

Mean follow-up time for patients with uAVSD was 12.7 ± 10.9 years.

Table 2. Procedures Performed Concomitantly With Pulmonary Artery Banding by Type of AVSD

Procedure[a]	bAVSD, n (%)	uAVSD, n (%)
Arch repair	5 (11.9)	2 (7.7)
PDA ligation	3 (7.1)	8 (30.8)
BCPS	0	4 (15.4)
CoA repair	4 (9.5)	4 (15.4)
TAPVD	1 (2.4)	2 (7.7)
LVOT myomectomy	1 (2.4)	0

[a] Some patients underwent more than one concomitant procedure.

AVSD = atrioventricular septal defect; bAVSD = balanced atrioventricular septal defect; BCPS = bidirectional cavopulmonary shunt; CoA = coarctation; LVOT = left ventricular outflow tract; PDA = patent ductus arteriosus; TAPVD = total anomalous pulmonary venous drainage; uAVSD = unbalanced atrioventricular septal.

The Kaplan-Meier curve for survival is shown in Figure 3A. Survival was 74.4% (95% CI: 53.6% to 87.0%) at 5 and 10 years and 60.9% (95% CI: 36.2% to 78.5%) at 20 years of follow-up. This did not differ significantly from long-term survival for children with bAVSD ($p = 0.733$). Univariable predictors of mortality are shown in Table 3.

The Kaplan-Meier curve for freedom from AVV surgery is shown in Figure 3B. Freedom from AVV surgery was 83.5% (95% CI: 61.4% to 93.5%) at 5 years and 78.6% (95% CI: 55.5% to 90.6%) at 10 and 20 years. Of the 5 patients (5 of 28, 17.9%) who underwent AVV surgery, the valve was repaired in all patients.

The competing risk model for Fontan completion in patients with uAVSD is shown in Figure 3C. Cumulative incidence of Fontan completion was 24.4% (95% CI: 9.9% to 42.2%) at 5 years and 61.9% (95% CI: 40.5% to 77.5%) at 10 years. There were 3 patients who survived more than 10 years without Fontan completion. Two of these children (2 of 28, 7.1%) had elevated pulmonary pressures and were not considered Fontan candidates. One child (1 of 28, 3.6%) had a complex course after Kawashima procedure, including multiple strokes, and was eventually brought forward for Fontan completion at 16 years of age.

A single patients in the uAVSD cohort underwent one-and-one-half ventricle repair. This patient was alive at last follow-up, 2 years after repair.

Comment

There is a broad spectrum of disease severity in children with AVSDs. The more simple defects, pAVSD and cAVSD with balanced ventricles, have been well studied, and biventricular repair performed in early childhood has achieved good results [2–8]. More challenging forms of AVSD include those with bAVSD with early heart failure or additional malformations that render early repair difficult, as well as patients with uAVSD, in whom complete repair may not be feasible at all.

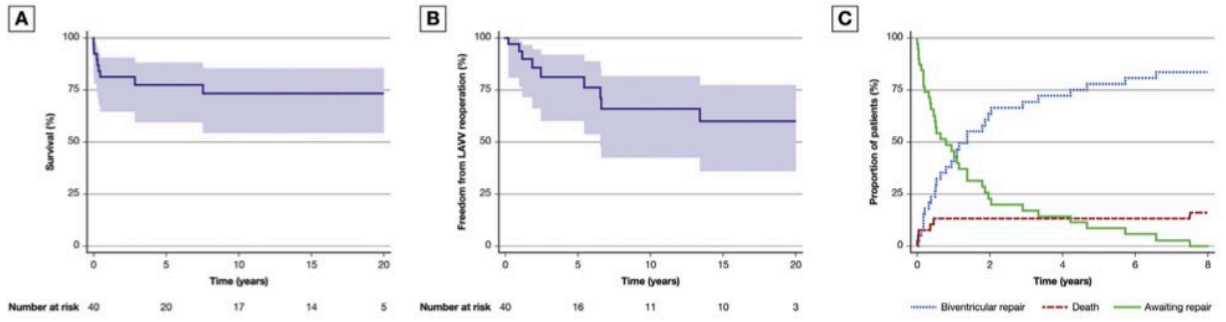

Fig 2. (A) Survival, (B) freedom from left atrioventricular valve (LAVV) surgery, and (C) competing risk model of complete atrioventricular septal defect repair for patients with balanced atrioventricular septal defect.

In patients with bAVSD, the use of PAB may allow for the patient to grow with a protected pulmonary circulation, permitting later biventricular repair [9–12]. However, it has previously been unclear how successful this strategy would be, and there has been concern that PAB may contribute to progressive LAVVR [12], which is a major contributor to morbidity in patients with AVSD [13–19].

Previous reports, with small numbers of patients, have demonstrated substantial early mortality for infants with AVSD undergoing PAB. Dhannapuneni and colleagues [12] in a group of 20 patients with AVSD who underwent PAB between 2000 and 2009 reported a 50% rate of in-hospital mortality. In their study, the use of an adjustable PAB significantly improved survival [12]. Historic series demonstrated hospital mortality of approximately 30% for PAB in young children with AVSD [21, 22]. Conversely, we have shown that PAB is associated with a relatively low early mortality in patients with AVSD, even when including the high-risk cohort with unbalanced ventricles. Furthermore, we have demonstrated that PAB was not associated with a short-term increase in the degree of AVVR, in either patients with bAVSD or uAVSD.

In children with bAVSD, the majority (78%) had progressed to complete repair within the first 5 years of PAB, and by 8 years more than 80% of patients had undergone complete repair. Furthermore, PAB did not seem to contribute to progressive LAVVR in patients awaiting delayed biventricular repair of cAVSD, because the mean grade of LAVVR did not increase before complete repair. However, in this cohort, the rate of reoperation for AVVR is somewhat higher than would be expected in patients with more simple forms of AVSD. In this study we have observed a 10-year freedom from AVV surgery of only 66%. We have previously reported that the overall cohort of patients with cAVSD and balanced ventricles at our institution has an 85% freedom from reoperation at 8 years [2]. Other groups have reported 80% to 90% freedom from reoperation at 10 years in patients undergoing cAVSD repair [5–8]. The higher rate of AVV surgery may be due to the more severe nature of disease in patients presenting with heart failure early in life, compared with patients undergoing elective repair at older ages. Indeed, we have previously demonstrated that patients presenting for complete repair younger than 3 months also have an increased risk of LAVVR [2]. However, it is also possible that the long-term presence of a PA band in these patients contributed to the rate of AVV surgery.

Table 3. Univariable Predictors of Mortality

	bAVSD		uAVSD	
Univariable Risk Factor	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Age at time of PAB	0.98 (0.96–1.0)	0.10	1.0 (1.0–1.0)	0.67
Additional CHD	0.73 (0.1–5.9)	0.77	0.40 (0.10–2.0)	0.26
Arch obstruction	3.4 (0.43–27.1)	0.25	2.9 (0.78–10.7)	0.12
Heterotaxy	3.9 (0.98–15.7)	0.05	1.4 (0.37–5.2)	0.63
Preoperative AVVR	1.1 (0.45–2.5)	0.90	0.82 (0.40–1.7)	0.60

AVVR = atrioventricular valve regurgitation; bAVSD = balanced atrioventricular septal defect; CHD = congenital heart disease; CI = confidence interval; HR = hazard ratio; PAB = pulmonary artery band; uAVSD = unbalanced atrioventricular septal defect.

The long-term survival in patients with bAVSD was 77% at 10 years. In our previous report on all patients undergoing bAVSD repair we demonstrated a 10-year survival of 92% at 8 years [2]. Other contemporary reports have found 10-year survival to be in the range of 85% to 90% for patients undergoing biventricular repair of bAVSD [5–8]. The poorer survival may be related because these children had presented in the first 3 months of life with heart failure. The previous study from our institution included 57 patients younger than 3 months who were not in heart failure and underwent primary biventricular repair. Although complete repair younger than 3 months was not associated with an increase in mortality, these younger children did have a higher degree of LAVVR as noted above, and the optimal age for elective repair was found to be 3 to 6 months [2]. However, although this is a selected group of higher risk patients, who were not considered suitable for immediate biventricular repair, it is not possible to rule out PAB as a contributor to the worse survival.

In the cohort with PAB and uAVSD the long-term survival was similar to what we have previously

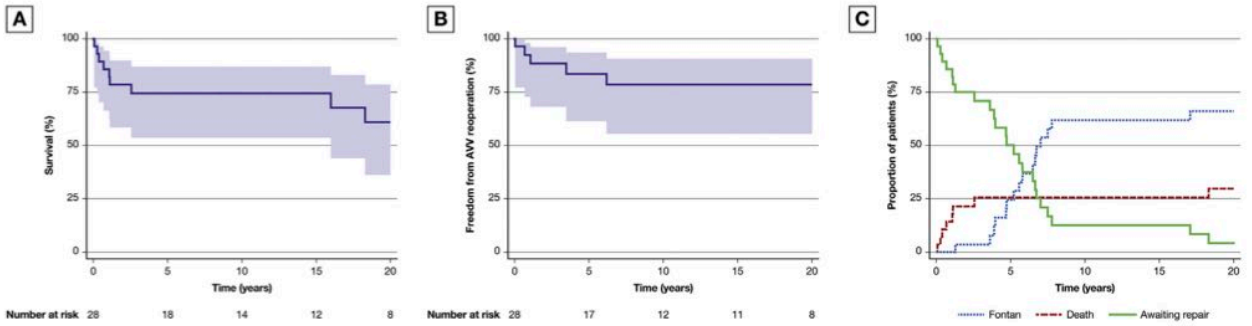

Fig 3. (A) Survival, (B) freedom from atrioventricular valve (AVV) surgery, and (C) competing risk model of Fontan completion for patients with unbalanced atrioventricular septal defect.

observed for the overall cohort of patients with uAVSD [14]. At 10 years more than 60% of patients had progressed to Fontan completion, whereas the 20-year freedom from AVV reoperation was 78.6%. In our previous report of 139 patients who underwent univentricular repair for uAVSD, 57.6% (80 of 139) achieved Fontan completion [14]. In that same group we demonstrated a freedom from AVV surgery of 63% at 15 years [14]. Other groups have demonstrated rates of AVV reoperation of approximately 30% in patients with uAVSD [18, 19]. Thus, PAB does not seem to affect the rate of progression to Fontan completion or the rate of AVV surgery in patients with uAVSD.

Limitations

This study is limited by its relatively small sample size and retrospective nature. Furthermore, the long period over which surgical procedures was performed meant that echocardiography performed on most patients was not detailed enough to allow for quantitative assessment of the degree of ventricular imbalance.

Conclusion

PAB can be used in patients with AVSD without acutely compromising AVV function and early survival. Most patients with bAVSD who undergo banding progress to biventricular repair, albeit with a relatively high rate of AVV reoperation. Patients with uAVSD who undergo PAB have similar outcomes to the overall uAVSD population.

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Chapter 8: Conclusions

8.1 Overview

In order to improve the lives of children with the spectrum of AVSDs, it is vital to understand the outcomes of our current management strategies. This thesis has focused on the two less well-studied ends of the spectrum of AVSD, namely, pAVSD and uAVSD. In the case of pAVSD, the severity of the lesion is often overlooked due to the excellent survival reported in modern series (25 – 27). However, this view oversimplifies the condition and the associated risk of reoperation observed in these patients. In the case of uAVSD, the severe and complex nature of the lesion, the very poor historical results, and enthusiasm for experimental BVR in these patients, have likely contributed to a lack of reporting on the outcomes of SVP in this group.

8.2 Findings

It has been well established that survival following pAVSD repair is excellent (25 – 27). However, the risk of LAVV dysfunction has been under-appreciated, and there has remained doubt about the necessity to routinely close the LAVV cleft and the optimal timing of elective repair (40, 86). Chapters 2 to 4 focused on patients with pAVSD.

In Chapter 2 we confirmed very low early mortality and excellent long-term survival in children with pAVSD. Importantly, we demonstrated that closure of the cleft in the LAVV was associated with improved survival, even in patients with mild or less regurgitation through the LAVV. This finding is important, as the notion that routine cleft closure should be performed in children with pAVSD and minimal LAVV regurgitation has been challenged recently (40). We also observed a high rate of reoperation, up to 25% at 30-years follow-up, suggesting that pAVSD is not as benign as was previously thought. Furthermore, the rate of cardiology follow-up in adults was low, with less than 50% of patients reviewed by a cardiologist in the 2-years leading up to the study, a particularly important consideration, given the high rate of reoperation. These findings suggested that routine closure of the LAVV cleft should be the standard of care, and improvements in cardiology follow-up into adulthood need to be made.

Given the high rate of reoperation following pAVSD repair we observed in Chapter 2, Chapter 3 focuses on the causes and outcomes of reoperation following pAVSD repair. The majority of reoperations were performed for LAVV regurgitation. The most common mechanism of regurgitation was through the cleft, either due to rupture of previous cleft closure or failure to adequately close the cleft at the original operation. We also demonstrated that the rate of successful repair significantly increased to above 90% with the introduction of a new repair technique involving patch augmentation of the LAVV cleft, a technique developed at the RCH. These results emphasized the importance of the cleft as a substrate for LAVV failure and the need to securely close the cleft at the time of primary repair.

An ongoing area of controversy in the management of pAVSD has been the optimal timing of elective repair. Traditionally, repair is performed in the preschool years, a strategy followed at RCH. Some units have begun to perform repair under 18 months of age, with the hope of reducing the rate of late reoperation for LAVV regurgitation (36, 86). In Chapter 4, we reviewed outcomes of pAVSD repair in infancy. In order to be able to compare infants and older children undergoing pAVSD repair, we performed propensity score matching to generate two groups which were well-matched for risk factors for pAVSD repair: heart failure, failure to thrive, LAVV regurgitation and the presence of additional congenital heart disease. Despite matching, we demonstrated that long-term survival was significantly worse when surgery was performed in infancy, with no improvement in the rate of reoperation. These findings suggest that repair of pAVSD should be deferred until children are older than 1 year, when possible.

In Chapters 5 and 6, we shifted our focus to uAVSD. Chapter 5 reviews the long-term outcomes of a strategy of SVP in patients with uAVSD. This study demonstrated a significant attrition rate, with less than 60% of patients surviving to 25-years follow-up. However, patients who achieved Fontan completion had better outcomes than was previously thought possible, with survival similar to the general population of patients undergoing Fontan completion. However, a high rate of AVV regurgitation necessitating surgery was observed, with nearly one third of patients requiring at least one operation on the AVV.

The high rate of AVV surgery observed in patients with uAVSD in Chapter 5, led us to investigate the mechanism of AVV regurgitation and the outcomes of AVV surgery in patients with uAVSD in Chapter 6. We observed that although most patients received repair rather than replacement of their AVV, at 20-years survival and freedom from AVV reoperation were both disappointing, at just over 50%. Patients with residual moderate or greater AVV regurgitation had particularly poor outcomes, and this was especially true in

patients under 1 year of age. This study suggests that patients with residual moderate or greater AVV regurgitation should have re-repair or replacement either during the same procedure or prior to discharge. Previously, valve replacement in these children has been considered a complication in its own right, however, our results suggest a paradigm shift is required, as the survival of children with mechanical prosthesis appears to be much better than those who underwent repair but were left with significant residual AVV regurgitation.

Chapter 7 investigated the effect of pulmonary artery banding on children with AVSD. Although not commonly required in children with AVSD, PAB can be used in patients with cAVSD and early heart failure, or in patients with uAVSD as part of their three-stage SVP. There have been concerns that PAB may increase the rate of LAVV regurgitation, and it has been unclear how many children with cAVSD would eventually progress to complete repair (64). Our results demonstrated that PAB is not associated with an acute increase in AVV regurgitation in either group. Most patients with cAVSD and PAB progress to complete repair, albeit with slightly lower survival and higher rates of reoperation than children, typically older than 3 months, who progress directly to complete repair. Children with uAVSD who underwent PAB had similar results to the overall population of children with uAVSD. These results suggest that the use of PAB is a safe and useful adjunct in the management of complicated patients with AVSD.

8.3 Future directions

Across the spectrum of AVSDs an important topic of future investigation is the long-term function of the AVV. Reoperation for the AVV is the single biggest cause of morbidity following pAVSD repair, and one of the major contributors to death in patients with uAVSD. Two relatively new techniques of AVV repair have been described in the studies included in this thesis: the patch augmentation for repair of the LAVV in pAVSD, and the ePTFE bridge technique for repair of the AVV in uAVSD. Long-term follow-up is not yet available for either technique, and as such both of these techniques need to be followed into the future to determine if they provide long-term freedom from regurgitation and reduce the risk of reoperation. For patients with uAVSD, research will also focus on understanding the limits of biventricular repair, and which, if any, patients with uAVSD may benefit from a biventricular repair strategy.

8.4 Conclusions

Repair of pAVSD is associated with excellent long-term survival, but a high rate of reoperation, which is not improved by performing repair in infancy. Improved results may be achieved by delaying repair to after 1 year of age, routinely closing the cleft and ensuring patients are closely followed into adulthood.

Single ventricle palliation for uAVSD is associated with substantial mortality. However, those who achieve Fontan completion have promising results. Atrioventricular valve regurgitation is a major cause of morbidity and mortality, when there is significant early regurgitation following repair, early reoperation should be performed either to re-repair or replace the valve.

Across the spectrum of AVSDs, achieving long-term competence of the atrioventricular valve is the key to improving survival and quality of life.

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Appendix A: Additional manuscripts authored during candidature

A.1 Buratto E, et al. J Thorac Cardiovasc Surg. 2016;151:1709-10.

EDITORIAL COMMENTARY

An intima affair adds to the dominion of the internal thoracic artery in coronary artery bypass grafting

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Central Message

The GEA has increased intimal thickness compared with bilateral ITAs, particularly in diabetic patients.

See Article page 1704.

An important study on the histomorphologic differences between the internal thoracic artery (ITA) and the gastroepiploic artery (GEA) by Nakajima and colleagues[1] is published in this issue of the *Journal*. By putting this study into perspective, it should be noted that it was initially observed in the very first studies[2] that atherosclerosis could develop early in childhood, often after acute infection. The earliest signs of atherosclerosis and fatty streaks appear in the areas of sheer stress and increased intimal thickness. However, not all arteries are affected to the same degree. Of note, the ITA appears to be least affected. Historically, the ITA was the first graft to be used in coronary revascularization[3] and became the graft of choice because of its superior patency rate. A recent study from Melbourne provided strong evidence that the use of the right ITA as the second conduit provides a significant survival advantage.[4] In this simple and convincing study, Nakajima and colleagues[1] clearly demonstrated that there was no histomorphologic difference between left and right ITAs. Despite the evidence of the superiority of using bilateral ITAs, the technique remains underused, with bilateral ITAs used in only 4% of patients included in the Society of Thoracic Surgery database.[5] The perceived and real drawbacks of bilateral ITA harvesting are the increased operative time and an increased risk of sternal wound infections, particularly in diabetic patients.[4] It also became clear that the patency of the graft will depend on the target coronary artery. Any graft placed onto the left anterior descending coronary artery is expected to last longer than its equivalent grafted to the right coronary artery system. For these reasons, determination of the proper arterial graft for the right coronary artery system is of particular importance.[6]

The radial artery (RA) is a reliable conduit with good long-term patency.[7] Because the RA is not always available, the GEA is an option. Suma and colleagues[8] evaluated 625 patients who underwent GEA grafting and demonstrated long-term patency rates of 80.2% at 5 years and 62.5% at 10 years, substantially lower than what has been reported for ITA and RA grafts.

In addition to its preferential use for the left anterior descending system, specific properties of the ITA may contribute to its superior patency. Greater release of nitric oxide and prostacyclin from the *intima* and better-developed internal elastic lamina, which may protect the *media* from noxious stimuli and prevent the migration of muscle cells into the *intima,* are thought to protect the ITA from atherosclerotic processes. It is fascinating that not all species of warm-blooded animals even have an intima. In humans, the intima develops only after birth and forms completely by 6 months of age.[9] As humans progress into adulthood, intimal hyperplasia could be a forerunner of developing atherosclerotic plaques.

Intuitively, it can be presumed that increased intimal thickness would make the arterial graft more prone to atherosclerosis. However, there is no evidence in the literature to confirm or refute the opinion that intimal thickness is related to arterial graft failure. Most important, Nakajima and colleagues[1] demonstrated correlation of intimal thickness with diabetes in GEA, but not in either ITA. GEAs from patients with poorly controlled diabetes had increased intimal thickness. Furthermore, atherosclerotic plaques were observed in the GEAs, but not in the ITAs.[1]

The study of Nakajima and colleagues[1] adds further biological evidence to the clinical finding that the ITA is the best conduit, particularly in diabetic patients. However, a practical challenge is to apply bilateral ITA grafting in diabetic patients without increased risk of sternal wound complication. The skeletonization approach to the ITA harvesting may decrease the risk of sternal wound infection.[10]

Bilateral ITA grafting with complete revascularization maximizes long-term survival and is recommended for patients with diabetes.[10]

In conjunction with the extensive and increasing clinical evidence of the superiority of bilateral ITAs over other conduits, this study provides further important evidence to encourage the use of bilateral ITAs more often.

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A.2 Buratto E, et al. J Thorac Dis. 2016;8:2994-2996

Editorial

Simple congenital heart disease: a complex challenge for public health

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Congenital heart disease (CHD) represents a broad spectrum of conditions, from simple defects with an excellent prognosis, to the complex and severe, which require multiple procedures and have uncertain long-term outcomes. As outcomes in cardiac surgery have improved, research has tended to focus on more complex cardiac lesions, rather than mild defects where results were already excellent (1). Simple defects have been defined as ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary stenosis (PS), patent ductus arteriosus (PDA), aortic stenosis (AS) and aortic coarctation in older children (2). In the case of many simple forms of CHD, survival has been said to be normal (3) and guidelines do not even recommend cardiology follow-up (4,5). Have these recommendations been made on sound evidence? Or has it simply become a truism that these patients have the same life expectancy as the general population?

Several reports have demonstrated that patients with simple CHD have equivalent survival to the general population (6,7). This is a view echoed in guidelines and major cardiology and cardiac surgery textbooks (3,8,9). However, although these studies have excellent longitudinal follow-up and include large cohorts of patients, the number of patients with each individual diagnosis is small (6,7). As a result, they are prone to having large confidence intervals (7), and may simply not show a difference in survival compared to the general population due to the small number of patients. More recently, large studies have begun to cast doubt on the assertion that patients with mild CHD will have a normal life expectancy (1,10,11). A large systematic review by Verheugt and colleagues (1) found that survival was decreased, in all forms of CHD. They specifically noted that patients with mild CHD were underrepresented in the literature, and had poorer survival than the general population (1).

In this context, we read with interest a recent paper by Videbæk and colleagues (12), which provides long-term, population-based outcomes of patients with simple CHD. Simple CHDs were defined as isolated and uncomplicated ASD, VSD, PDA and mild PS. Children with comorbidities, such as pulmonary artery hypertension, were excluded. This study is unique as it is a population-wide cross-section of patients that were all assessed by a single cardiologist, between 1963 and 1973. Furthermore, follow-up is complete thanks to Denmark's national registry of patients. The study included 1,241 patients with 58,422 patient years of follow-up.

At a median age of 47 years, they demonstrated that the risk of death in those with simple CHD was doubled the risk of the general population. Furthermore, the risk of sudden unexpected death was increased approximately 4-fold, and the risk of cardiac death was increased 6-fold. Furthermore, there was nearly a 6-fold increase in rates of morbidity, and in particular increased rates of cardiac surgery, heart failure, endocarditis, pulmonary hypertension, ventricular tachycardia and stroke. While these figures seem somewhat alarming, it must be remembered that they represent quite small absolute risks: the overall mortality rate in the simple CHD cohort was 2.2 per 1,000 patient years. Interestingly, the risk of mortality was remarkably consistent among the groups of patients, with each of the individual cardiac diagnoses (ASD, VSD, PS and PDA) having an individual

mortality rate in the range of 2.1–2.2 per 1,000 patient years.

There are several limitations of the study, which must be borne in mind when interpreting these data. Firstly, the patients included were diagnosed over 40 years ago, and patterns of treatment and diagnosis have changed over time. However, this will invariably be the case in studies with such a long follow-up. Furthermore, the patients were all diagnosed by a single cardiologist, which ensures consistency of diagnosis, but raises questions of generalizability, especially since these patients were recruited in a time when echocardiography was not yet available.

Nevertheless, this is an important study as it challenges the view that patients with simple CHD are cured. This information contributes to a growing body of evidence that defects perceived as simple and cured, may not be as benign as surgeons and cardiologists believe. In our own experience, children with partial atrioventricular septal defect, often grouped with mild CHD, have excellent survival, but a reoperation rate of approximately 25% at 20 years follow-up (13,14). Furthermore, only 43% of adult patients were under the care of a cardiologist (13).

This information is of particular importance due to the shifting demographic of patients with CHD. More than half of patients with CHD are now adults (15) and it is estimated that the total population of adults with CHD in the United States is in the range of 1.3–1.4 million patients (1,16). Of these patients, it is estimated that 750,000 have simple congenital defects (16). Previously this group had been considered cured, and would not have been required to attend specialist long-term follow-up. Clearly, the findings of Videbæk (12) are potentially very important at a population level. If all of these patients were to require specialist follow-up it would have substantial implications for the cost of health care, as well as creating additional workforce strain on the relatively small community of adult congenital cardiologists. In order to carefully inform recommendations regarding follow-up there would ideally be a way to stratify patients with simple CHD, so that follow-up could be focused on those at greater risk. For example, Kuijpers *et al.* (10) demonstrated that males, but not females, had decreased survival following closure of simple ASD. Furthermore it is known that older age at the time of ASD closure is an important risk factor for death (6). More work is required in this area to delineate, which patients are at higher risk and hence require closer follow-up.

Furthermore, these findings have important implications at the level of the individual patient-clinician interaction. It is no longer appropriate for clinicians to tell patients that they are cured of their disease by surgery in the case of simple CHD. While there is good reason to be optimistic about their long-term outcomes, a word of caution regarding the slightly higher risk of arrhythmias and death, as well as the need for reoperation is appropriate. This allows patients to be more vigilant about their health, with the potential that they may seek review earlier in the course of any late complications, hopefully mitigating some of the increased risk.

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Footnote

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A.3 Buratto E, et al. J Thorac Cardiovasc Surg. 2016;152:696-7.

EDITORIAL COMMENTARY

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

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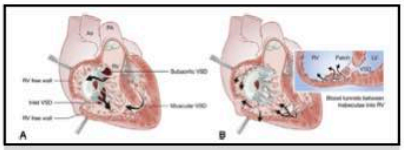

Intramural ventricular septal defects occur when blood flows underneath the trabeculations.

Central Message

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

See Article page 688.

Patel et al[1] 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 contruncal 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 al[1] 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

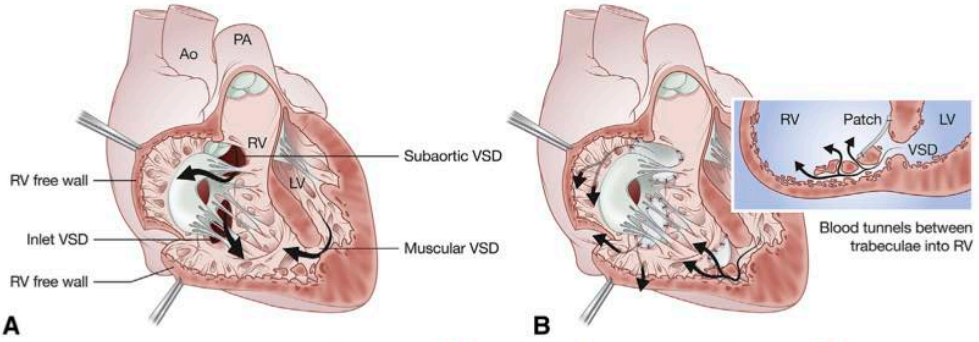

FIGURE 1. A, Intramural ventricular septal defect (*VSD*) may occur when the edge of the VSD is partially covered by trabeculations. It was originally described in subaortic area, but may occur in inlet or anteroapical septum, if the patch is sutured to right ventricular (*RV*) trabeculations rather 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 overemphasized. 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 together[8] 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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EDITORIAL COMMENTARY

Mitral repair in children with connective tissue disorders: On the edge, over the edge, or edge-to-edge?

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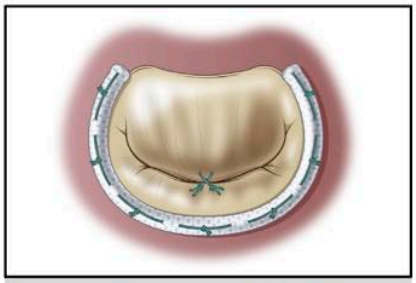

The edge-to-edge technique of mitral repair.

Central Message

The simplified edge-to-edge technique is a promising method for mitral repair in the challenging group of children with connective tissue disorders.

See Article page 399.

Mitral valve repair in patients with connective tissue disorders (CTDs) is challenging. The earlier in life that a repair has to be performed, the more difficult it is, because CTD that manifests in childhood represents the most severe end of the disease spectrum.[1] Whereas in adults with CTD mitral valve repair can be achieved with similar outcomes to those with myxomatous mitral valve disease,[2] the outcomes of mitral valve repair in children with CTD remain uncertain.[1] The literature on the topic is sparse, with only a few small series, which report high rates of valve replacement.[3,4]

Children with CTD tend to have complex mitral valve pathology with progressive annular dilatation, thickening and nodularity of the leaflets, elongation, and rupture of multiple chordae, which results in bileaflet prolapse with characteristic leaflet redundancy.[3] The complex repair is often on the edge of surgical ability and, if it fails, may push these fragile children over the edge, resulting in irretrievable deterioration. Although mitral replacement is an option in the face of such a challenging repair, survival after mitral replacement in young children is much poorer than survival after successful repair.[5,6] Thus, a durable and simple technique for mitral repair in patients with CTD is of paramount importance. An ideal repair must achieve both stabilization of the mitral annulus and secure coaptation of the leaflets. Stabilization of the leaflet edges is particularly difficult, because of the unpredictable and progressive elongation and rupture of the chordae that may occur in any, or all, segments. Because of the unpredictable nature of chordal elongation and rupture, one would have to perform a complex total chordal augmentation[7] or a simpler edge-to-edge approximation—the Alfieri stitch.[8]

The edge-to-edge technique was developed as a simplified method for the treatment of complex anterior and bileaflet mitral valve disease.[8] Substantial experience from the group of Alfieri and colleagues[8] has demonstrated that it is effective and provides durable long-term results in adults. An important article by Vricella and colleagues[9] published in the current issue of the *Journal* describes excellent mid-term results of mitral valve repair using the edge-to-edge approximation technique in children with CTD. In a series of 18 patients with CTDs, the authors performed mitral repair using the edge-to-edge technique combined with annuloplasty using an adult-size ring. At a median follow up of 1.7 years, 94% of patients had mild mitral regurgitation or less, and there had been no reoperations on the mitral valve. Furthermore, there was significant regression of left ventricular end diastolic diameter observed during the study period. This simplified repair technique resulted in a short mean cross-clamp time, which is important considering many patients also will require concomitant aortic root surgery. Although the mid-term results are excellent, it remains to be seen whether this technique will provide durable long-term repair, given the progressive nature of CTD.

A particular challenge in young children with mitral regurgitation is achieving stabilization of the mitral annulus while allowing for somatic growth. In most children, severe dilatation of the mitral annulus permits implantation of adult-size annuloplasty ring (Figure 1, *A*), as demonstrated by Vricella and colleagues.[9] In small children, when adult-size rings cannot be accommodated, annular stabilization can be achieved with a polytetrafluoroethylene band (Gore-Tex, Inc, Flagstaff, Ariz) divided into 2 or more segments to permit subsequent growth (Figure 1, *B*). Arguably, interconnecting the segments of the strip with absorbable suture may provide additional reinforcement and yet allow subsequent growth.[6]

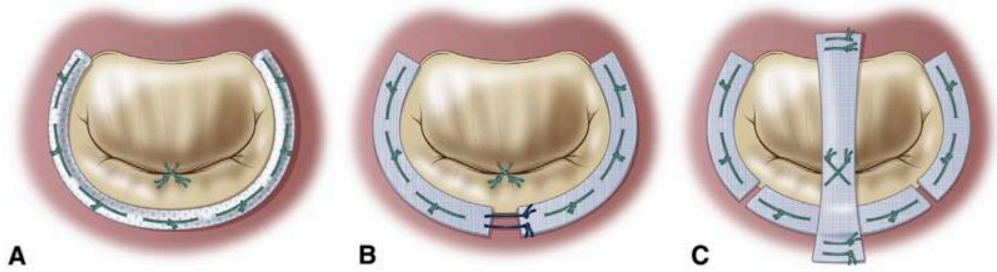

FIGURE 1. Edge-to-edge technique for mitral valve repair with (A) adult-size annuloplasty ring, (B) Gore-Tex strip annuloplasty and interconnecting absorbable suture, and (C) Gore-Tex bridge reinforcement.

Hopefully, the described technique will provide durable, long-term secure coaptation of the leaflets. This is yet to be seen. It is possible that further reinforcement of edge-to-edge approximation may be required to achieve long-term durability in these challenging patients. We recently have reinforced edge-to-edge repairs with Gore-Tex bridges in children with univentricular hearts.[10,11] This additional reinforcement (Figure 1, *C*) could be helpful in children with CTD. It is unclear which of these techniques will provide the best balance of annular stabilization and growth potential. Time will tell whether such additional stabilization will be required or not.

At the present time, we can say with certainty that edge-to-edge repair is here to stay. The technique described by Vricella and colleagues[9] is an important and brave step forward and must be in the armamentarium of every congenital heart surgeon.

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A.5 Buratto E, et al. J Thorac Cardiovasc Surg. 2017 ;153:547-548.

EDITORIAL COMMENTARY

The matrix reloaded: Which pill to take to attenuate thoracic aortic aneurysm development?

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Dr Buratto choosing between pills in a theatrical scene.

Central Message

Inhibition of matrix degradation may attenuate thoracic aortic aneurysm development.

See Article page 537.

The matrix of the aortic wall has been a topic of feverish research activity for decades. Medial degeneration of the aortic wall is a key feature of the development of thoracic aortic aneurysms (TAAs), and matrix metalloproteinases (MMPs) are major molecular mediators of TAA formation.[1,2] MMPs would therefore seem an obvious target for therapeutic intervention to prevent progression of TAAs. So far, only nonspecific MMP inhibitors, tetracyclines and statins, have been studied clinically in an attempt to reduce progression of the aortic aneurysms.[3,4] Selective therapeutic modification of MMP activity has remained elusive.

A novel study by Ikonomidis and colleagues[5] published in this issue of the *Journal* has revisited matrix remodeling as a target for new therapies, and it suggests that targeted inhibition of membrane type 1 (MT1) MMP (Figure 1) may attenuate TAA development. Ikonomidis and colleagues[5] demonstrated that phosphorylation of MT1-MMP caused its internalization and thus prevented MMP-2 activation. Activation of protein kinase C–δ by phorbol 12-myristate 13-acetate caused this internalization of MT1-MMP from the cellular membrane to endosomes. This change was associated with a decrease in MMP-2 activity. Yet in a somewhat surprising and subtle way it also resulted in increased phosphorylation of Smad2, a component of the transforming growth factor (TGF) β pathway. It has previously been shown that TGF-β may activate Smad family proteins and increase production of MMP-9, which in turn causes matrix degradation.[6] Furthermore, they demonstrated that a protein kinase C–δ inhibitor, Röttlerin, could prevent endosomal translocation of MT1-MMP and thus prevent its downstream effects. Normal aortic fibroblasts treated with phorbol 12-myristate 13-acetate displayed reduced MMP-2 activation and increased phosphorylation of Smad2. Both these effects were inhibited by pretreatment with Röttlerin. The activities of TGF-β and MMP-9, however, were not assessed. It is therefore not clear whether the effect of Smad2 phosphorylation on the downstream pathway is significant. Smad2, Smad3, and Smad4 proteins would still have to form a complex that would translocate into the nucleus to stimulate gene expression of MMP-9. Will MMP-9 production be lost in translation? It remains unclear how "deep the rabbit hole goes" and whether the observed isolated increase in Smad2 phosphorylation will have any impact on TGF-β signaling. One cannot help wondering where this pathway would lead. This insightful attempt to unveil the mystery of matrix degradation, as often happens in clinical surgery, gives somewhat contradictory results and raises more questions than it answers. How will these pathways balance themselves to affect matrix degradation? Is inhibition of MT1-MMP phosphorylation protective or harmful? Although it appears from the novel finding of the study of Ikonomidis and colleagues[5] that targeting MT1-MMP activity may indeed constitute a therapeutic strategy, whether this activity should be inhibited or activated is yet to be seen. So, to activate or to inhibit? One is left in suspense by this unanswered question. Yet it seems that Ikonomidis and colleagues[5] have come very close in their pioneering effort to providing the answer. The answer appears to be very close. It would require evaluation of TGF-β pathway and its effect on the matrix after MT1-MMP phosphorylation. In the words of a movie character, "The answer is out there and it is looking for you, and it will find you, if you want it to."

Nonetheless, the unique and strong findings of this study have demonstrated that MT1-MMP is elevated in clinical TAA specimens and that phosphorylation of MT1-MMP causes its intracellular localization and decrease in MMP-2 activation. This is an important step forward in

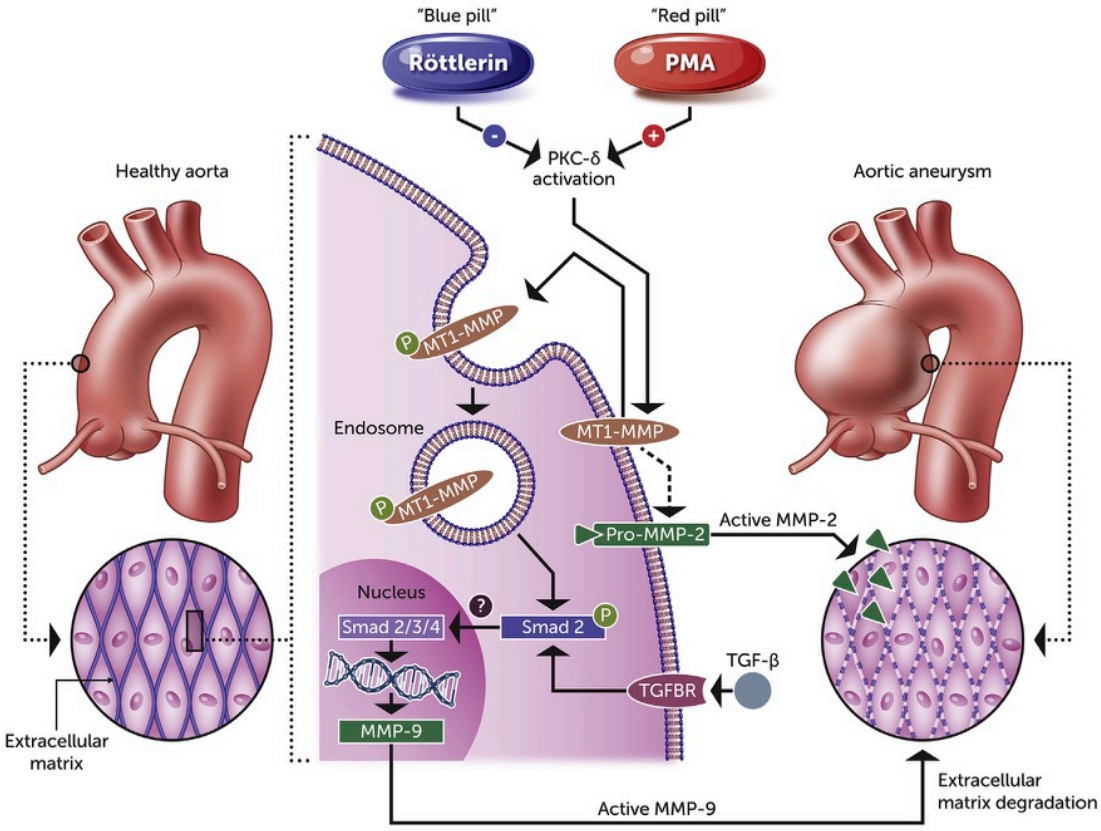

FIGURE 1. Membrane type 1 (*MT1*) matrix metalloproteinase (*MMP*) internalization and its effects on the aortic extracellular matrix. *PMA*, Phorbol 12-myristate 13-acetate; *PKC*, protein kinase C; *P*, phosphorylation; *TGF*, transforming growth factor; *TGFBR*, transforming growth factor β receptor.

our understanding of molecular mechanisms of the TAA development.

Although the feasibility of medical intervention to prevent matrix degradation remains unclear, this type of basic surgical research may help to discover "how deep the rabbit hole goes" and lead to important therapeutic applications. The alternative is to "remain in the current reality," steadily convinced that no medical intervention is possible to attenuate the development of this life-threatening surgical disease. The latter is not what the inquisitive mind of an academic surgeon does!

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A.6 Buratto E, et al J Thorac Cardiovasc Surg. 2017;154:1054-1055.

So near, yet so far: Is isolated cerebral near-infrared spectroscopy in neonates nearly as useful as it is noninvasive?

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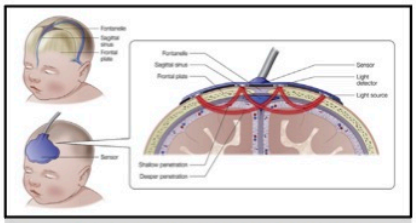

Application of near-infrared spectroscopy probe for cerebral oxygen monitoring in neonate.

Central Message

Isolated cerebral near-infrared spectroscopy in neonates correlated poorly with cerebral venous oxygen saturation.

See Article page 1056.

Near-infrared spectrometry (NIRS) provides noninvasive and continuous monitoring of cerebral and somatic tissue regional oxygen saturation (rSo_2). NIRS sensors for cerebral assessment of the rSo_2 are placed on the forehead. It is generally recommended to place the probe on the right or left side of the forehead and away from superior sagittal sinus. Such placement, however, is not always feasible, especially, in low–birth weight neonates. Some interference from the superior sagittal sinus thus may still occur, increasing the variability of measurements. Furthermore, some neonates tend to retain fluid after extensive cardiac surgical procedures, particularly procedures that require circulatory arrest with or without isolated cerebral perfusion. Such fluid retention in subdural and subarachnoid spaces may further affect cerebral rSo_2 measurements (Figure 1). Finally, cerebral rSo_2 is significantly lower in cyanotic neonates, particularly those with systemic-to-pulmonary circulatory shunting, than neonates with normal cardiac physiology, and usually ranges between 40% and 60%. Perioperative management of neonates with hypoplastic left heart syndrome (HLHS) undergoing stage 1 palliation is a perfect example of a clinical setting in which *reliable* cerebral oxygen monitoring would be utterly important yet often not feasible. To complicate the matter further, NIRS monitors are available from at least 10 manufacturers. None of them is identical.

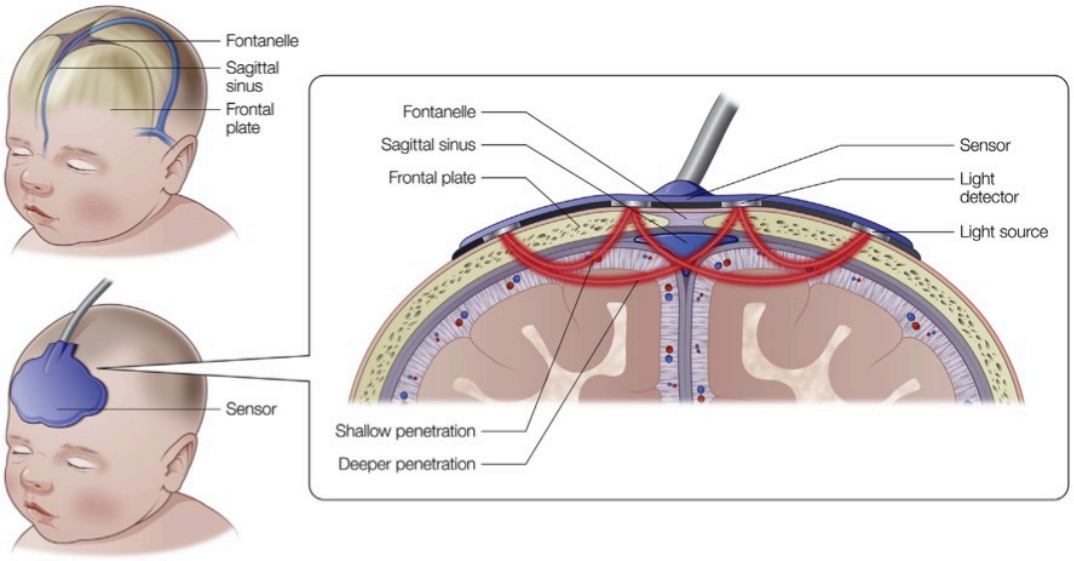

FIGURE 1. Application of a near-infrared spectroscopy probe for cerebral oxygen monitoring in a neonate.

In the recent decades, there has been substantial interest in perioperative continuous monitoring of cerebral oxygen saturation in neonates with HLHS undergoing stage 1 palliation.[1-3] The use of postoperative cerebral venous oxygen saturation ($Scvo_2$) monitoring through an internal jugular vein catheter allows better monitoring of circulation, which in turn may result in improved early outcomes.[4] Such invasive monitoring, however, is challenging. NIRS is therefore now gaining traction as a noninvasive method of monitoring adequacy of cerebral oxygen delivery in the perioperative period.[5] Inasmuch as the concept of NIRS oxygen monitoring seems attractive, clinical interpretation of NIRS data in neonates with HLHS after stage 1 palliation, in terms of both absolute values and trends, is difficult regardless of whether isolated cerebral or additional splanchnic monitoring is used.[6]

In an insightful and well-designed study published in this issue of the *Journal*, Rescoe and colleagues[7] have analyzed correlation of NIRS-derived data with $Scvo_2$ measured by co-oximetry from the internal jugular vein in 73 neonates after stage 1 palliation for HLHS. They demonstrated that cerebral rSo_2 correlated poorly with low $Scvo_2$, and they suggest that cerebral rSo_2 not be used in isolation. This problem was somewhat ameliorated by correction of the signal for arterial contamination.

Where do we go from here? NIRS appears to be too valuable a tool to be simply discarded. A perioperative risk assessment that would include multisite NIRS and hemodynamic monitoring might still allow early determination of low-cardiac output. Two numbers are better than one. Whether the NIRS technology will add any useful information to a simple bedside assessment by an astute clinician is yet to be seen.

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EDITORIAL COMMENTARY

The Pearls and Perils of Settling Scores in Public

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Settling scores in public is arduous. It is never perfect and someone always gets hurt. Fortunately, this is now a virtually forgotten legacy of the Wild West. However, setting risk scores using public databases could be somewhat similar. Furthermore, the expectations for the all-encompassing risk score, applicable to every patient, are so high that the pearls of wisdom are easily lost in the vast and confronting ocean of perils.

A valiant attempt by Chowdhury et al[1] to set a risk score for early mortality following the Norwood procedure, using a public database, is published in this issue of *Seminars*. The study has made use of the publically available Pediatric Heart Network Single Ventricle Reconstruction (SVR) trial database and incorporated risk factors into a simple 20-point risk score to predict hospital mortality.

The SVR trial was a multicentre randomized study to evaluate the effect of shunt type (right ventricle to pulmonary artery vs modified Blalock-Taussig shunt) on early outcomes following the Norwood operation.[2] Data from this trial have previously been used to investigate risk factors for death and transplantation following the Norwood procedure.[3,4] Tweddell et al[3] identified obstructed pulmonary venous drainage, anatomy other than hypoplastic left heart syndrome (HLHS), lower gestational age, lower socioeconomic status, smaller ascending aorta, and confirmed genetic syndrome or failure to perform genetic testing, as risk factors for intermediate term mortality. They also provided a series of parametric survival curves to allow prediction of mortality based on combinations of the earlier factors. Tabbutt et al,[4] identified lower birth weight, genetic abnormality or unknown status of genetic abnormality, duration of deep hypothermic circulatory arrest, requirement for extracorporeal membrane oxygenation at the time of surgery, and nonclosure of the sternum as risk factors for early mortality. In as much as this information is of crucial importance, it is rather difficult to practically apply it to individual patients.

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Thus, the work of Chowdhury et al[1] is very important, as it aims to overcome this drawback by condensing the data from this public database into a simplified prediction score, which can be applied to each individual patient. The risk factors in their model were birth weight, genetic syndrome, surgeon volume, anatomical subtype (HLHS vs other), ascending aorta size, and obstructed pulmonary venous return. To further simplify the application, they categorized patients as low, medium, or high risk based on their scores, and the predictive value of this was good in both the derivation and validation subsets. Although most of the risk factors assessed are strong and self-explanatory, any risk assessment system has to stand on its own, where *each* risk factor is meaningful and valid. Unfortunately, such an ambitious challenge is virtually insurmountable using public databases. The chain is no stronger than its weakest link.

Professor Igor E. Konstantinov, MD, PhD, FRACS

Central Message

The proposed risk score for the Norwood procedure is an important step forward, but limited by unknowns in the database used to create it.

See related article on pages 425-433.

As it stands now, the ideal risk score system for the Norwood procedure still remains elusive. For public databases to be useful in risk score setting, the data entered in the database must be known and well recorded. It is the unknowns from this public database that weaken the proposed risk scoring system. For example, HLHS is compared with "other single right ventricle anomalies," where those "other" subtypes were sometimes not recorded in the database and, thus, unknown. This likely reflects a shortcoming of the SVR database, where diagnoses associated with higher risk, such as unbalanced atrioventricular septal defect and heterotaxy,[6] are recorded simply as "other." Yet, it is not known exactly what the HLHS is compared with. Although it

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became clear recently that right ventricular dominance is the most important risk factor for death after stage I univentricular palliation,[7] the category "other single right ventricle anomalies" includes a broad spectrum of conditions. Similarly, if a child has a documented genetic syndrome, whereas the other has unknown genetic status, the unknown status gives higher predicted risk in the proposed scoring system. This does not appear correct. Yet, what is written or declared in public often goes to eternity. The United States Secretary of Defence Donald Rumsfeld stated once in public, it is the "unknown unknowns … that tend to be the difficult ones."[8] Indeed, the unknowns in public databases may derail even the best scoring system. Nevertheless, despite the unknowns, the work of Chowdhury et al[1] is a brave and important step forward. Once the perils of the unknown are sorted out, this scoring system may become a powerful tool for risk prediction for children undergoing Norwood operation. It is yet to come!

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REVIEW

Ventricular assist devices for the failing univentricular circulation

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ABSTRACT

Introduction: Improved survival following single ventricle palliation has led to a large population of patients with a univentricular circulation, many of whom develop heart failure. Increasing experience with ventricular assist devices (VAD) in children has paved the way for VAD support in those with failing univentricular circulation.

Areas covered: The use of VADs to support the failing univentricular circulation is a relatively new concept. Most studies have focused on supporting patients with the failing systemic ventricle. There are limited reports of VAD support of the pulmonary circulation in patients with Fontan failure despite preserved ventricular function. None of the current VADs have been designed to support the pulmonary circulation. Novel low-pressure, high-flow pumps, specifically designed to support the pulmonary circulation, are under development.

Expert commentary: The failing univentricular circulation is one of the great challenges in the field of congenital heart disease. While current VADs are designed to support the systemic circulation, many patients require support of the pulmonary circulation. A fully implantable VAD for support of the pulmonary circulation as destination therapy would be beneficial for patients with preserved systolic function, but must have low energy requirements, negligible risk of stroke and low risk of device thrombosis and failure.

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KEYWORDS
Univentricular circulation; Fontan failure; ventricular assist devices; Fontan circulation; single ventricle palliation

1. Introduction

1.1. The univentricular circulation

The current standard of treatment for patients with a functional single ventricle is multistage palliation, resulting in a Fontan circulation [1,2]. The absence of a subpulmonary ventricle results in elevated central venous pressure (CVP) that, in turn, contributes to failure of the univentricular circulation and, in particular, Fontan failure, despite preserved ventricular function [1–3]. While improvements in surgical technique and postoperative care have meant that early survival has improved in recent years [4–8], it appears inevitable that many univentricular circulations will eventually fail [1–3]. Heart transplantation in patients with a Fontan circulation is technically challenging [9,10], but recent reports have demonstrated improving results, comparable to other forms of congenital heart disease [11–13]. Nevertheless, there is limited donor supply and substantial mortality while awaiting transplantation [14]. Thus, ventricular assist devices (VADs) are an emerging option for the management of the failing univentricular circulation (Figure 1), both to reduce waiting list mortality [14–16] and, potentially, as a destination therapy [2]. We review the current status of VAD therapy in patients with univentricular circulation and discuss the principles guiding the application VAD technology in these patients.

1.2. Ventricular dysfunction in the univentricular circulation

Systemic ventricular dysfunction may cause failure of the univentricular circulation at any stage of palliation. Ventricular failure in these patients tends to be multifactorial [17]. Firstly, the single ventricle palliated with a systemic to pulmonary artery shunt is subjected to excessive volume work and dilatation, increasing stress on the growing ventricle [18]. The presence of relatively poor cardiac output and low blood pressure contributes to vasoconstriction, increased peripheral resistance and hence increased afterload [18]. Secondly, multiple operations with prolonged cross-clamp times cause ischemia–reperfusion injury to the myocardium, contributing to long-term ventricular dysfunction [17]. In fact, prolonged cross-clamp time during the Fontan procedure has been associated with risk of Fontan failure [19]. Thirdly, the systemic ventricle may be of right ventricular morphology and hence not developmentally suited to withstand systemic ventricular pressures [3,20]. Finally, in association with the patient's structural heart disease, there may be genetic mutations affecting the myocardium itself [17]. Hence, ventricular dysfunction in patients with univentricular circulation is multifactorial and challenging to manage. The use of VADs to support the failing systemic ventricle has emerged as a new treatment option for these patients.

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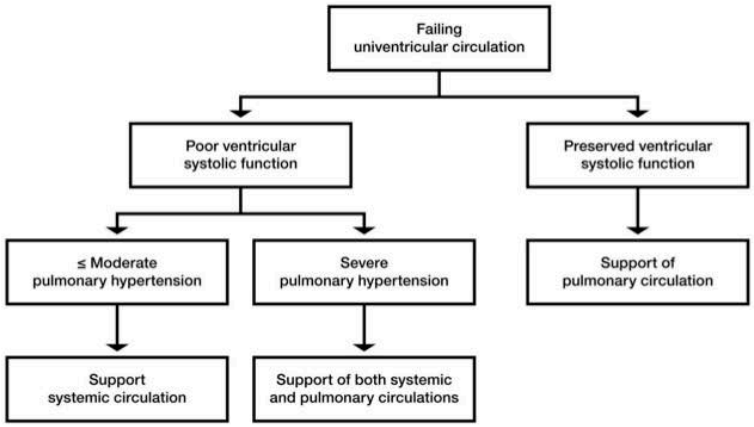

Figure 1. Algorithm for selection of the appropriate configuration of ventricular assist devices in the univentricular circulation.

2. VADs in the univentricular circulation

2.1. Current status of VADs

In adults, VADs have an established role in the treatment of end-stage heart failure as a bridge-to-transplantation, destination therapy, or rarely, recovery [21]. Over an 8-year period, the INTERMACS registry has documented the implantation of over 15,000 VADs in North America, of which 60.9% were implanted as bridge-to-transplantation and 38.2% as destination therapy [21]. Over this short period, there has been an expansion of indications, refinement in technology and implantation strategies, improvement in survival and reduction in complications [21–24]. One of the most important advances has been the development of continuous flow VADs, which are associated with lower rates of complications and improved survival [21,25]. Recent experience from the INTERMACS registry has demonstrated a 1-year survival of 80% for left ventricular assist devices (LVAD) and 50% for biventricular assist devices (biVAD) [21].

In contrast, in the pediatric population, VAD therapy is more challenging due to patient size as well as the complex anatomy associated with congenital heart disease [26]. Nevertheless, there is evidence that the advent of VAD technology has reduced the risk of waiting list mortality in children listed for heart transplantation [14–16] and improved survival compared to extracorporeal membrane oxygenation (ECMO) [26]. The only available VAD developed specifically for children is the Berlin Heart EXCOR (BHE), a pulsatile paracorporeal device, which is suitable for supporting children with a body weight as low as 2.5 kg [26,27]. Due to the improved outcomes associated with the use of continuous flow devices in adults, they have been increasingly used in children [28]. So far the smallest child supported with a continuous flow VAD (HeartWare) was 3.7 years of age, with a body surface area (BSA) of 0.6 m^2, weighing 13.5 kg [29]. The relationship between patient size and selection of VAD technology is demonstrated in Figure 2.

The first report of the PediMACS registry, a multicenter database including pediatric VAD implantations performed at 66 North American centers, included 200 durable VADs, of which just over half (109/200, 54.5%) were continuous flow devices [31]. Almost all patients below 20 kg of weight were supported by the BHE, while more than 80% (105/130) of patients over 20 kg of weight were supported with continuous flow devices [31]. At 6-month follow-up, 58% of patients had been transplanted, 28% were alive on VAD support and 14% had died. Survival of patients with continuous flow devices was significantly better than those with pulsatile flow devices; however, these patients were significantly older and had higher BSA [31]. Nevertheless, the PediMACS registry demonstrated that the rate of device malfunction was much higher with the pulsatile flow devices [32], and as such continuous flow VADs appear to be the device of choice for children large enough to accommodate them.

Historically, Matusuda et al. [33] described the first attempts at supporting children with univentricular circulation with VADs in 1988. However, these initial attempts were unsuccessful. The modern era of VAD support of the failing univentricular circulation began in 2005, with Frazier et al. [34] implanting a HeartMate VAD in a patient with Fontan failure. To date, the total reported experience with VAD in patients with univentricular circulation is 53 patients, which is summarized in Table 1.

2.2. VAD support following stage I palliation

The experience of VAD support of patients following stage I palliation is limited. The largest report is from Weinstein et al. [50], who supported nine patients following stage I palliation, of whom only one survived to transplantation. Specifically, they had no survivors when VAD was implanted for failure to wean from bypass in the operating theater or for failure to wean from ECMO. The only survivor was 17-months post stage I palliation at the time of VAD implantation. The authors suggested that ECMO should be the preferred strategy in this scenario due to the poor outcomes with VADs. Pearce et al. [43] reported a 15-month-old boy with double outlet right ventricle, d-transposition of the great arteries and mitral atresia with circulatory failure following pulmonary artery banding. The patient was treated with construction of a central shunt, ligation of the pulmonary trunk and implantation of BHE, with inlet cannula in the right atrium and outflow into

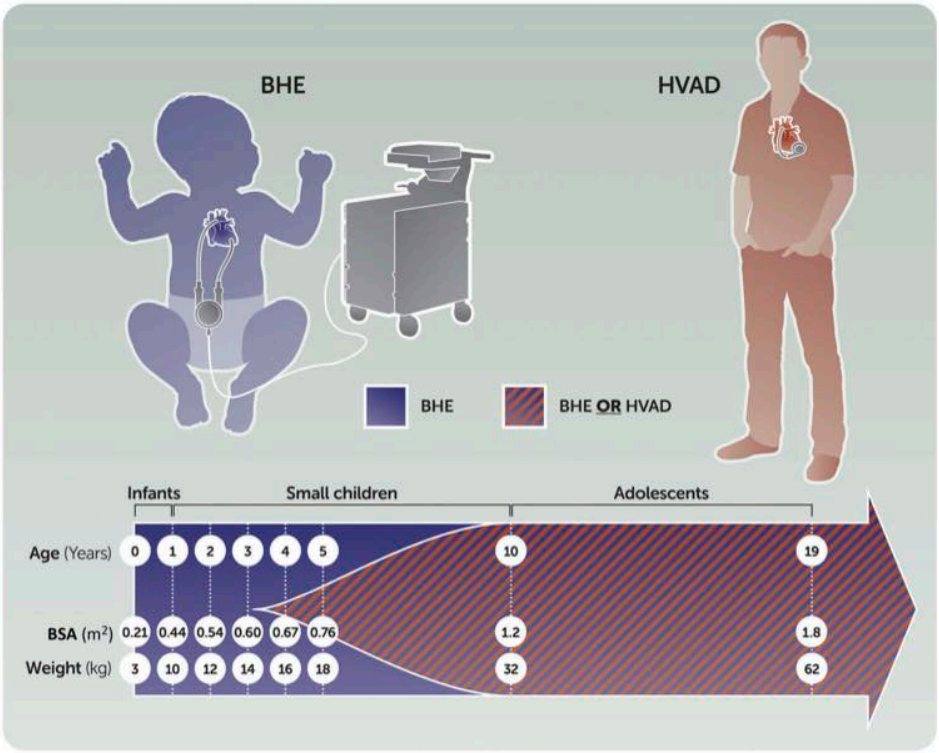

Figure 2. The relationship between choice of ventricular assist device, patient age and size. The use of continuous flow devices becomes increasingly prevalent as age increases. Reproduced from Rossano J, Villa C, Konstantinov I [30], with permission.

the ascending aorta. The patient was supported for 7 weeks and then transplanted.

Support of children following stage I palliation has most commonly been performed for postoperative ventricular dysfunction. There are numerous factors which may contribute to the poor outcomes in this group, including the physiology of the shunt-dependent circulation, patient age and size, and the fact that support was generally used as salvage, due to inability to wean from bypass. Given the poor results reported thus far, VADs do not seem to provide an advantage over ECMO in this setting.

2.3. VAD support following bidirectional cavopulmonary shunt (BCPS)

There have been several reports of VAD support in patients following BCPS, which are summarized in Table 1. The largest experience is from Weinstein et al. [50], who reported 12 patients supported with BHE VADs following BCPS, of whom 58.3% (7/12) survived to transplantation. Niebler et al. [52] described four patients treated with BHE following BCPS, of whom 75% (3/4) survived to transplantation. They found that despite achieving high cardiac output, patients continued to have an elevated CVP, which they attributed to abnormal aortopulmonary and venovenous connections. To overcome this challenge, they advocated selecting a larger chamber size than would normally be used for the same sized patient with biventricular physiology [52]. Brancaccio et al. [47] reported two cases of VAD support following BCPS, of whom 50% (1/2) survived to transplantation. Of a further four individual cases described in the literature, 25% (1/4) survived to transplantation. While the overall experience with VADs in the setting of BCPS is limited, it appears to be a feasible strategy with just over half of patients surviving to transplantation.

2.4. Strategies of VAD support for the failing Fontan

Patients with Fontan failure fall into one of two categories: those with impaired ventricular function and those with preserved ventricular function [2]. The choice of VAD strategy needs to be tailored to the nature of the patient's physiology. In initial reports of VAD therapy in the Fontan circulation, the devices were used much like a conventional LVAD, with the inflow cannula in the dominant ventricle or atrium, and the outflow cannula in the ascending aorta. This is the strategy of choice for patients with ventricular dysfunction as the cause of Fontan failure. It has been suggested that this strategy may also work for patients with predominantly right-sided failure in order to 'pull' blood flow across the pulmonary vascular bed [2]. However, it may be ineffective in the setting of high venous pressures due to increased pulmonary resistance, and so 'biventricular' support has been described for patients with both ventricular dysfunction and elevated venous and pulmonary pressures [35,49,51]. Furthermore, there is a group of Fontan patients who primarily have high venous pressure and pulmonary resistance as the cause of their failure, despite preserved ventricular function. In this group, the use of

Table 1. Reported experience of ventricular assist devices used to support failing univentricular circulation.

Author	Year	*N*	Device	Age (years)	Stage	Preserved systolic function	Duration of support (days)	Outcome
Frazier [34]	2005	1	Heartmate IP LVAS	14	Fontan	No	45	Transplantation
Nathan [35]	2006	1	BiVAD: Berlin Heart	4	Fontan	Not reported	28	Transplantation
Newcomb [36]	2006	1	Thoratec	25	Fontan	No	152	Transplantation
Calvaruso [37]	2007	1	Berlin Heart	10	Fontan	No	7	Transplantation
Chu [38]	2007	1	Berlin Heart	4	BCPS	No	10	Death
Pretre [39]	2008	1	RVAD Berlin Heart	27	Fontan	Yes	395	Transplantation
Russo [40]	2008	1	Centrifugal pump	14	Fontan	No	>6	Transplantation
Cardarelli [41]	2009	1	Berlin Heart	1.5	Fontan	No	183	Recovery
Irving [42]	2009	1	Berlin Heart	3	BCPS	No	7	Transplantation
Pearce [43]	2009	1	Berlin Heart	1.3	PAB	No	49	Transplantation
Meira [44]	2011	1	HeartWare	12	Fontan	No	1	Transplantation
VanderPluym [45]	2011	1	Berlin Heart	3	Fontan	Yes	174	Transplantation
Mackling [46]	2012	2	Berlin Heart	4	Fontan	No	309	Death
				4	BCPS	No	270	Death
Brancaccio [47]	2013	2	Berlin Heart	2	BCPS	No	2	Transplantation
			Berlin Heart	4	BCPS	No	166	Death
Sanders [48]	2014	1	Berlin Heart	16	Fontan	No	2	Transplantation
Valeske [49]	2014	1	Berlin Heart BiVAD	19	Fontan	No	23	Transplantation
Weinstein [50]	2014	26	Berlin Heart		Stage 1 = 9	Not reported	Median:	Stage 1: transplantation in 1/9
			LVAD = 24		Stage 2 = 12		52	Stage 2: transplantation in 7/12
			BiVAD = 2		Stage 3 = 5			Stage 3: transplantation in 3/5
Arnaoutakis [51]	2016	5	Heartware	18	Fontan	Not reported	Median: 60 (for survivors)	Transplantation
			TAH	14	Fontan	Not reported		Transplantation
			Berlin heart	3	BCPS	Not reported		Death
			Berlin Heart	5	Fontan	Not reported		Transplantation
			Thoratec	23	Fontan	Not reported		Death
Niebler [52]	2016	4	Berlin Heart	0.6 – 2.3	BCPS	Not reported	9 – 312	3 transplantations, 1 death
Total Experience		**53**			**Stage 1 = 10**			**Stage 1: 2/10 (20%) transplanted**
					BCPS = 22			**BCPS: 12/22 (55%) transplanted**
					Fontan = 21			**Fontan: 16/21 (76%) transplanted**

BCPS: bidirectional cavopulmonary shunt; LVAD: left ventricular assist device; BiVAD: biventricular assist device; PAB: pulmonary artery banding; RVAD: right ventricular assist device; TAH: total artificial heart.

VADs to support the pulmonary circulation, so-called 'cavo-pulmonary support', has been described [39]. These strategies are demonstrated in Figures 3 and 4.

2.5. VADs to support the systemic ventricle

In the majority of reported cases, VADs have been used to support the systemic ventricle in patients with univentricular physiology [45–48,50–52], similarly to how an LVAD is used in the biventricular circulation (Figures 3(a) and 4(a)). In the majority of these cases, BHE has been used (see Table 1), although there have also been reports of Thoratec [36,51], HeartMate [34], and HeartWare [44]. The technique of VAD implantation to support the systemic ventricle is similar to standard LVAD insertion; however, some specific technical considerations have been described, particularly regarding the positioning of the inlet cannula. Challenges include adhesions due to previous surgery, coronary artery abnormalities, presence of a prominent nondominant ventricle obscuring access to the dominant ventricle, and cannula obstruction from ventricular trabeculations and the subvalvular apparatus, especially when the right ventricle is dominant [36,47,50,52]. Nevertheless, in most reported cases, the inflow cannula has been placed in the apex of the dominant left ventricle [36,37,41,42,48,50–52] or in the diaphragmatic surface of the dominant right ventricle [38,44,47]. Additional strategies have been described to deal with inlet cannula obstruction, such as resection of muscular bands and resection of the atrioventricular valves and their subvalvular apparatus [34,52]. Placement of the inflow cannula in the pulmonary venous atrium has been described as another strategy to avoid inlet cannula obstruction [33,40,51].

Outcomes of VAD support of the systemic ventricle have been reported in two small case series and a number of case reports

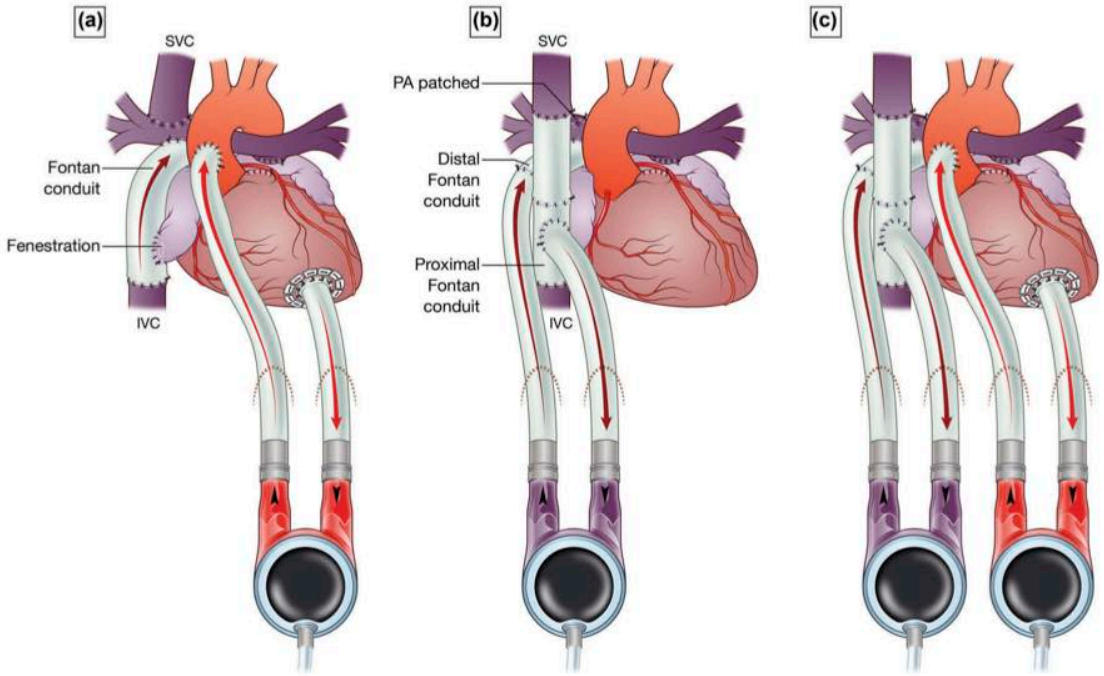

Figure 3. Configurations of Berlin Heart Excor VAD in the Fontan circulation. (a) supporting the systemic ventricle, (b) supporting the pulmonary circulation and (c) supporting both.

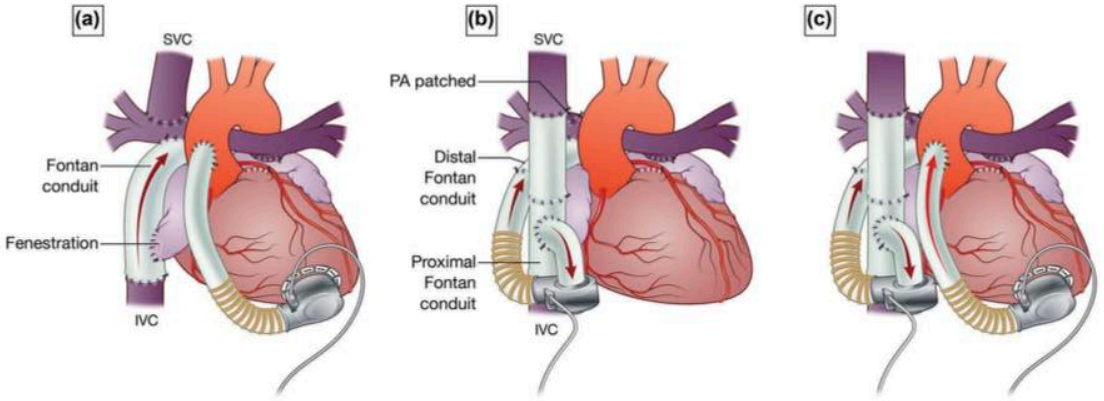

Figure 4. Configurations of continuous flow VAD in the Fontan circulation. (a) supporting the systemic ventricle, (b) supporting the pulmonary circulation and (c) supporting both.

(Table 1). The largest report, from Weinstein et al. [50], includes five patients with a Fontan circulation, of whom 60% (3/5) survived to transplantation. By comparison, 72% of children with biventricular physiology from the same database survived to transplantation. Arnatoukakis et al. [51] reported four patients with Fontan circulation who underwent VAD implantation, three of whom (75%) survived to transplantation. Taken together, the remaining case reports included 14 patients, of whom 78.6% (11/14) survived to transplantation, 7.1% (1/14) were successfully weaned and 14.3% died (2/14) [34,36,37,40,41,44–46,48]. These results are similar to those reported for the overall population of children supported with VAD in the PediMACS registry, which demonstrated that at 6-month follow-up, 61% of patients had been transplanted, 31% remained on VAD support, and 8% had died prior to transplant [32]. These results are encouraging and seem to be similar to the overall results reported for VAD support in the pediatric population. However, it must be recognized that data from case reports are particularly prone to publication bias toward good results, and that none of these reports contains significant long-term follow-up.

The complications observed during VAD support were similar to those seen with VAD in children with biventricular circulations, dominated by bleeding, neurological events, and infection [32]. Weinstein et al. [50] reported an overall adverse event rate of 73.1%, with respiratory failure (42.3%), bleeding (38.5%), infection (23.1%), and neurologic dysfunction (15.4%) being the most common complications. Furthermore, pump change due to thrombus was required in 26.9% of patients. For comparison, in the PediMACS database, the commonest adverse events were device malfunction (39.5%), infection (39.0%), bleeding (34.0%), and neurological dysfunction (26%) [32].

Despite the technical challenge of implanting VADs in patients with a univentricular circulation, survival to transplantation is in the range of 60–80% across the small number of published cases. Furthermore, the complication profile appears to be similar to that reported for VADs in the general population of children requiring ventricular support. The use of VAD therapy as a bridge to transplantation for patients with a failing univentricular circulation is emerging as a viable option.

2.6. 'Biventricular' support in the univentricular circulation

In patients with both ventricular dysfunction and raised venous pressure and pulmonary resistance, supporting the systemic ventricle may not be sufficient to achieve stable hemodynamics. In these patients, it may be better to convert to 'biventricular support,' with one pump supporting the systemic ventricle, and another supporting the cavopulmonary circulation, much like a conventional right ventricular assist device (RVAD) (Figures 3(c) and 4(c)). There are few reports of biventricular support in the setting of univentricular circulation, comprising three patients with BiVADs and one patient with a total artificial heart (TAH).

Nathan et al. [35] reported BiVAD implantation in a 4-year-old girl with a failing Fontan circulation. The child had plastic bronchitis, pleural effusions, and a pulmonary vascular resistance of 3.8 Wood units. Initially, a 30 mL BHE VAD was implanted from the systemic ventricular apex to the ascending aorta. However, as there was significant venous hypertension, it was decided to place a 25 mL BHE as an RVAD. The cavopulmonary anastomosis was taken down, the inflow cannula was inserted into the lateral tunnel, and the outflow cannula was inserted into the pulmonary arteries. This child underwent transplantation after 28 days of support.

Valeske et al. [49] reported a 19-year-old male who had undergone Fontan with a total cavopulmonary connection (TCPC) and presented in New York Heart Association (NYHA) class IV heart failure with a severely dilated systemic ventricle. They implanted two Berlin Heart pumps as a BiVAD. The RVAD drained both vena cavae via the extracardiac conduit, with the outflow placed in the pulmonary artery. The LVAD was placed between the left atrium and the ascending aorta. The patient underwent successful orthotopic heart transplantation after 23 days of support.

Arnaoutakis [51] reported a single case of TAH implantation in a 14-year-old child with a failing Fontan circulation complicated by renal failure and plastic bronchitis. They reported recovery of end-organ function on TAH support and survival to heart transplantation.

Although there is limited data on the use of BiVAD in univentricular patients, there are promising results and this strategy offers the potential to support patient with both a failing systemic ventricle and high venous pressures, in whom support of the systemic ventricle alone may not be sufficient.

2.7. Failure of Fontan circulation with preserved ventricular function

Due to the lack of a sub-pulmonary ventricle, patients with a Fontan circulation generally have a CVP of 10–15 mmHg, three times greater than the normal physiological level [1] (Figure 5). Hence, these patients are prone to complications of elevated venous pressures, including hepatic congestion and cirrhosis, ascites, peripheral edema, and protein-losing enteropathy [18]. Due to the low flow across the pulmonary vasculature, there is chronic under-filling of the systemic ventricle, which in combination with ventricular hypertrophy, contributes to diastolic dysfunction [3,18]. Additionally, the systemic ventricle may also fail due to the factors described earlier: dilatation and overloading prior to BPCS, increased afterload, repeated cardiac procedures, genetic mutations, and right ventricular morphology. All of these factors may contribute to Fontan failure, which although lacking a standardized definition, is generally said to be any of death, transplantation, takedown, Fontan conversion, NYHA class III/IV symptoms, protein-losing enteropathy, or plastic bronchitis [53]. Based on the mechanism of Fontan failure, patients may be classified into two groups: those with ventricular dysfunction and those with preserved ventricular function [3]. Importantly, more than half of patients with Fontan failure have preserved ejection fraction [20]. The importance of understanding the mode of Fontan failure is highlighted by the fact that those with preserved ejection fraction have poorer survival after transplantation [54], demonstrating that patients will respond differently to interventions depending on their underlying mechanism of Fontan failure.

2.8. Isolated support of pulmonary circulation

As has been previously described, more than half of patients with a failing Fontan have preserved function of their

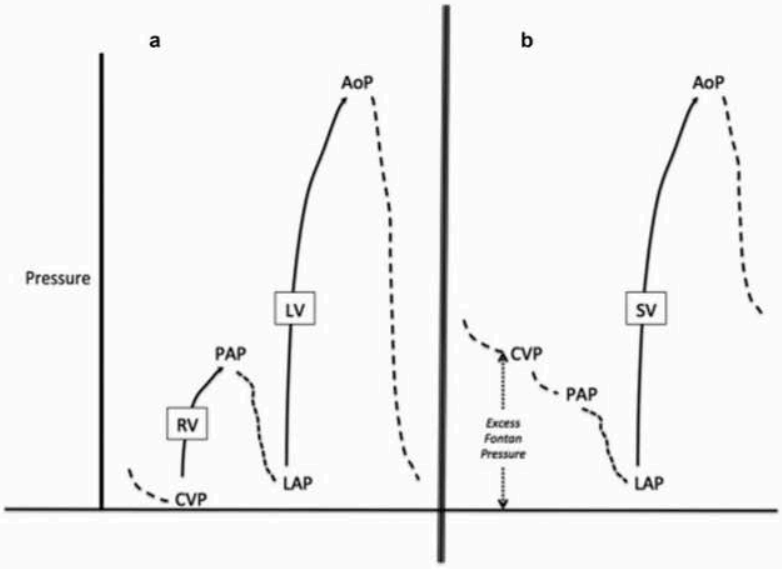

Figure 5. Diagrammatic representation of the haemodynamics of (a) the normal biventricular compared to (b) the Fontan circulation compared to. Note the elevated central venous pressure due to the lack of a subpulmonary ventricle to drive pulmonary blood flow. Reprinted from Jaquiss and Aziz [2] with permission from Elsevier.

dominant ventricle, and thus effectively have 'right-sided' failure [53]. These patients could be supported by a VAD placed between the extracardiac conduit and the pulmonary arteries (Figures 3(b) and 4(b)). There is only a single case report of cavopulmonary support using a VAD in a patient with a univentricular circulation. Prêtre et al. [39] presented a 27-year-old man who underwent Fontan conversion from an atriopulmonary connection to extracardiac conduit and developed severe cardiac failure 16 weeks later. The patient had normal ventricular function but an elevated CVP of 33 mmHg. The cavopulmonary anastomoses were taken down and the pulmonary arteries repaired. The extracardiac conduit was replaced with a larger graft and the superior vena cava (SVC) and inferior vena cava (IVC) both anastomosed to it. The inflow cannula of a 60 mL Berlin Heart was inserted into the extracardiac conduit, while the outflow cannula was inserted into the reconstructed pulmonary arteries. The patient's clinical condition improved substantially and he underwent cardiac transplantation after 13 months of support. Given the large proportion of Fontan patients with failure despite preserved ventricular function, this is a very promising strategy and represents a 'proof of concept' for the possibility of cavopulmonary support for the treatment of Fontan failure. However, the VADs currently available are designed for support of the systemic ventricle rather than the low-pressure pulmonary circulation, and hence this strategy is currently limited by the lack of appropriate pump technology.

3. Emerging technologies

While there have been encouraging results using VADs to support the univentricular circulation, none of the devices currently available has been designed for this application. Given that more than half of patients with Fontan failure effectively have 'right-sided' failure [53], with elevated venous pressures and pulmonary resistance, much of the current research focuses on the development of a 'cavopulmonary assist device'. As previously discussed, the major hemodynamic limitations of the Fontan circulation are systemic venous hypertension, decreased pulmonary blood flow, and under-filling of the systemic ventricle [55]. Based on the hemodynamic complications observed with the Fontan circulation, it has been postulated that the ideal hemodynamic effect of the pump for cavopulmonary support is a small decrease in venous pressure, with a small increase in pulmonary pressure and flow, each of approximately 5 mmHg [55–57]. As such, the ideal pump for cavopulmonary support differs markedly from currently available VAD technology. Current VADs are designed to generate a high-pressure gradient at partial flow rates, and as a result have significant energy requirements and generate significant negative pressures at their inflow cannula [2,55]. A device for cavopulmonary support, which is a low-pressure, high-volume pump providing a pressure step up of only 5 mmHg, is likely to be sufficient for supporting the Fontan circulation [55–57]. This should allow for greater pump efficiency and improved battery life, potentially allowing for a completely implantable design with a long-life battery similar to pacemaker, or even transcutaneous charging [2]. Finally, the ideal assist device would not obstruct the cavopulmonary blood flow in the case of mechanical failure. Such developments would make destination therapy a viable option for patients with Fontan failure.

Initial experimental research on cavopulmonary support of the failing Fontan has utilized existing VAD technology in animal models immediately after construction of the single-stage TPCP. Several groups have shown that short-term support of the TCPC in an animal model is feasible, providing adequate cardiac output and an increase in pulmonary arterial (PA) pressures with stable or decreased venous pressures compared to the biventricular circulation at baseline [55,57–62]. However, venous collapse and hence circulatory obstruction, as well as entrainment of air through the Goretex graft,

have been observed due to the high negative pressures generated by these devices [58,59]. Furthermore, when placed in the large caliber vessels of the TCPC, micro-axial pumps are associated with recirculation of almost half of the pump flow, as well as retrograde SVC flow, requiring higher pump speeds, decreasing efficiency, and increasing the risk of hemolysis [55,57,60].

To overcome the shortcomings of current generation VADs, several groups are working on the development of novel pumps specifically designed for cavopulmonary support. Rodefeld's group [63,64] have developed a design based on the Von Kàrmàn impellar pump, which is implantable at the junction of the TCPC, augmenting flow in all four directions, directing outflow down both pulmonary arteries. Importantly this is a low-power design, which provides a small step up in pressure, replicating the role of the right ventricle. Furthermore, even when stationary it improves efficiency of the Fontan circulation by reducing turbulence, rather than causing circulatory obstruction. This means that even in the case of device failure it would still be of hemodynamic benefit, which is an ideal situation. So far, however, only results of computation modeling and *in vitro* experimentation have been published.

Lacour-Gayet et al. [65] described the application of a novel micro-axial flow pump in a modified *in vitro* mock-up of the Fontan circulation. The extracardiac conduit in their model had a Y-shaped configuration, with SVC and IVC inflow and an outflow arm anastomosed to the pulmonary trunk. The micro-axial pump was implanted in the outflow arm. Using this strategy, recirculation and retrograde flow into the SVC were minimized. In their model, CVP was reduced, PA pressures were modestly increased, and cardiac output was increased by up to 2L/min. However, they did observe collapse of the vena cavae at pump speeds above 3000 rpm. This design, however, has yet to be tested *in vivo*.

Throckmorton et al. [66] also described a novel, low-pressure axial pump tested *in vitro* in a mock TCPC. The pump demonstrated a pressure step up of 2–16 mmHg, without evidence of cavitation. A further evolution of this pump is designed to be percutaneously inserted in the IVC while providing the same hemodynamic benefits, and it has also been tested *in vitro* [67]. Most recently, this group has published work on refinements of axial flow pump design in order to maximize efficiency for the specific application as cavopulmonary support [68,69]. None of these designs has been tested *in vivo* as of yet.

In vitro tests of existing VAD technology have provided proof of concept for cavopulmonary support of the Fontan circulation. However, these pumps have several limitations as they are designed to support the systemic circulation. Novel pumps designed specifically to address the requirement of cavopulmonary support have shown promising results *in vitro*, but have yet to be tested *in vivo*.

4. Conclusions

The failing Fontan circulation is one of the major challenges in the field of congenital heart disease. There is a growing number of patients with a Fontan circulation and many, if not all, will eventually experience failure of their Fontan circulation. Results of VADs applied to failing univentricular circulation are encouraging, and currently VAD support of the failing Fontan as a bridge to transplantation is a viable strategy. However, none of these devices have been designed to address the majority of patients who have a Fontan circulation with predominantly 'right-sided' failure. Novel devices designed to support the low pressure, high flow cavopulmonary circulation are under development, but have not yet been tested *in vivo*. These devices offer hope of a fully implantable pump for cavopulmonary support of the failing Fontan as destination therapy.

5. Expert commentary

As the population of patients with a Fontan circulation surviving into adulthood continues to increase, clinicians will face the clinical challenge represented by Fontan failure ever more frequently. The current mainstay of therapy is heart transplantation, but waiting times are long, donor supply is limited, waiting list mortality is high, and we are often replacing the heart in patients who have preserved systolic function. Furthermore, heart transplantation substitutes one terminal disease for another and does not offer these patients a chance at normal life expectancy. The results of VAD use in patients with a univentricular circulation are indeed encouraging, suggesting that they are suitable for supporting patients with Fontan failure who are deteriorating while awaiting transplantation. However, the currently available technology is not well suited to this application, being designed for support of the systemic circulation, while more than half of all patients with Fontan failure actually have preserved ventricular function. Although the use of these devices to support the pulmonary circulation has been reported, as they are designed for high pressure environment, they are not optimized for this situation, unnecessarily increasing the risk of complications such as pulmonary hypertension, venous collapse, obstruction of flows and hemolysis.

We believe that a fully implantable low-pressure, high-volume pump inserted into the Fontan pathway as cavopulmonary support for use as destination therapy represents the future of managing the failing Fontan. The low power requirements of this type of pump means that a long-life battery, similar to that of a permanent pacemaker, should be feasible, allowing intermittent replacement of a subcutaneous power supply. Alternatively, the advent of transcutaneous charging may eliminate the need for battery replacement entirely. Allowing the device to become fully implantable is a key to reducing the risk of infections. The new pump designs are encouraging, especially that of Rodefeld's group [63,64], which promotes a complex flow pattern from the IVC and SVC into both pulmonary arteries. Most impressively, the pump improves Fontan efficiency even when stationary, minimizing the risk posed by device failure, and providing a unique opportunity to more easily conduct weaning trials. This is a key feature for the totally implantable device to be successful as destination therapy – device failure must not result in circulatory obstruction. The final major challenge which needs to be addressed is the

risk of thrombogenicity, as the Fontan circulation is already prone to thrombosis. However, devices such as Rodefeld's design, which improves blood streaming and reduces turbulence at the TPCP, may go some way to mitigating this risk.

As exciting as these technologies are, they remain a long way from clinical practice, as none has yet been tested even in animal models. Nevertheless, the growing population of children and adults with a failing Fontan circulation creates an urgent need for such devices, which will no doubt expedite their development. A generation of children is relying on the community of cardiac surgeons to provide them with a more certain future; a fully implantable pump for cavopulmonary support appears to be the way forward.

6. Five-year view

Given the promising results reported so far, in the next 5 years we are likely to see increased use of current generation VADs to support the failing Fontan circulation. It can be expected that in the majority of cases these devices will be used as a bridge to transplantation, as none of the devices are suitable for destination therapy. Hence, heart transplantation will remain the mainstay therapy for management of the failing univentricular circulation, with VAD increasingly playing a supporting role.

Testing of new-generation devices can be expected to progress from the current *in vitro* experiments to animal testing. It is possible, however, that toward the end of the next 5 years period we may see the first human trials of these novel cardiopulmonary assist devices. While these developments are exciting, the goal of a totally implantable cavopulmonary support device as destination therapy appears to be more than 5 years away from realization.

Key issues

- As the population of Fontan patients increases, Fontan failure will be an increasingly common problem.
- Current VADs are designed to support the systemic ventricle. They are high-pressure pumps.
- VADs have promising results for the support of the failing Fontan circulation as a bridge to transplantation.
- Most patients have 'right sided failure' with preserved systolic function. These patients would benefit from a low powered pump for cavopulmonary support.
- While novel low-pressure pumps for cavopulmonary support are under development, currently they remain at the stage of *in vitro* testing.
- The goal is a totally implantable pump for cavopulmonary support with prolonged battery life which can be used as destination therapy.

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EDITORIAL COMMENTARY

Scorpions, snakes, and Fontan failure: The dawn of a new ERA?

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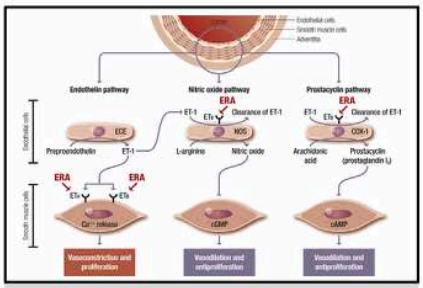

Vascular actions of endothelin-1.

Central Message

Endothelin receptor antagonists may be helpful in decreasing pulmonary resistance and improving functional capacity in patients with failing Fontan circulation.

See Article page 1468.

It never ceases to amaze us how often the most fascinating mysteries of evolution intertwine with our routine surgical practice in subtle and unexpected ways. Relentless work of evolution over millions of years has resulted in venom peptides that rapidly incapacitate both prey and predators. The most dangerous scorpions and snakes have evolved to produce highly potent venom that induces severe coronary vasoconstriction and almost immediate ventricular fibrillation. It is remarkable that the most toxic component of this venom, sarafotoxin, is structurally very similar to another 21-residue peptide—endothelin (ET)—a natural compound of the human vascular system.[1]

The family of ETs consists of 4 peptides that are converted from a common precursor, preproendothelin, by ET-converting enzyme in endothelial cells (Figure 1). The major isoform in the human vascular system is ET-1. ET-1 causes vasoconstriction and cell proliferation via activation of ET_A and ET_B receptors on vascular smooth muscle cells.[2] Stimulation of endothelial ET_B receptors causes vasodilatation via nitric oxide and prostacyclin pathways.[3] Furthermore, ET_B receptors in the pulmonary endothelium are a major route for the clearance of ET-1.[4] In patients with congestive heart failure, increased ET-1 level correlates with adverse outcomes. The main source of ET-1 in congestive heart failure appears to be the pulmonary vascular bed and it contributes significantly to increased pulmonary vascular resistance.[5] Negating ET-1–induced pulmonary vasoconstriction would be of utmost importance in patients with failing Fontan circulation, particularly, because the majority of these patients have preserved systolic ventricular function, yet elevated pulmonary vascular resistance and impaired ventricular relaxation.[6] Elevated pulmonary vascular resistance in patients with failing Fontan circulation is, at least in part, due to decreased nitric oxide production and elevated plasma ET levels.[7,8] Current medical management of patients with Fontan failure is extremely limited and, at its very best, may somewhat delay a steady decline in functional capacity of patients with a failing Fontan circulation. The current mainstay of treatment for patients with Fontan failure is cardiac transplantation, yet transplantation is challenging in these patients and, due to its complexity, limited donor supply, and substantial waiting list mortality, may not be readily available to most patients.[9] Thus far, only a few small studies have examined the effects of pulmonary vasodilators on patients with a Fontan circulation. Two small, randomized trials have shown that that sildenafil could improve cardiac index, pulmonary blood flow, oxygen consumption, and ventilatory efficiency in patients with a Fontan circulation who underwent cardiopulmonary exercise testing.[10,11] Results for endothelin receptor antagonists (ERAs) have been equivocal, with 2 small randomized trials showing improvement exercise capacity, oxygen consumption, and functional class,[11,12] whereas a third trial showed no benefit.[13]

A very interesting article by Agnoletti and colleagues[14] describes the effects of ERAs in patients with raised pulmonary vascular resistance and a Fontan circulation. In this small, nonrandomized trial they treated 24 patients with 2 different types of ERAs (bosentan for children, including adolescents, and macitentan for adults). They demonstrated that over a 6-month period, the use of ERAs was associated with a decrease in pulmonary resistance, improvement in cardiac output, and spirometric parameters. Furthermore, cardiopulmonary exercise testing

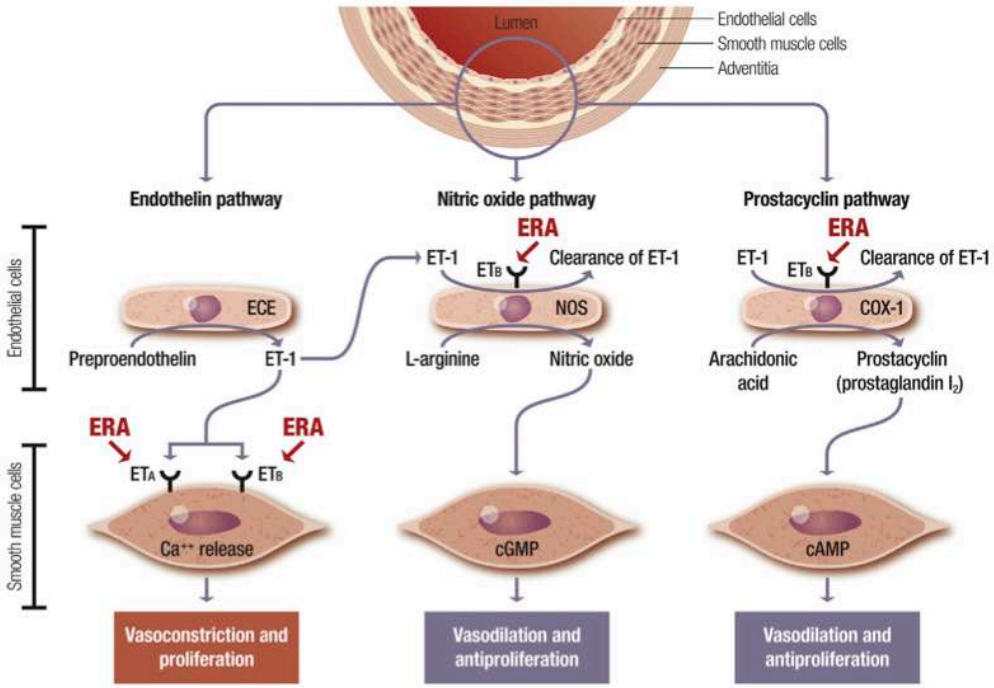

FIGURE 1. Vascular actions of endothelin-1. *ECE*, Endothelin converting enzyme; *ERA*, endothelin receptor antagonist; *ET*, endothelin; *NOS*, nitric oxide synthetase; *COX*, cyclo-oxygenase; *cGMP*, cyclic guanylyl triphosphate; *cAMP*, cyclic adenylyl monophosphate.

showed improvement in both younger children and adolescents, but not in adults.

There are several key findings in this study. This is the first demonstration that ERAs do not only decrease pulmonary vascular resistance, but also improve hemodynamic and respiratory parameters in patients with a Fontan circulation. Furthermore, they observed that functional improvement was essentially limited to children and adolescents, although significant decrease in pulmonary vascular resistance occurred in all patients. This could be because of a more advanced and often multifactorial circulatory failure in adult patients with long-standing failure of Fontan circulation. This may also explain why some trials, which enrolled older patients, have shown no benefits of ERAs in patients with Fontan failure. Alternatively, because adults received macitentan, whereas minors received bosentan, this may reflect the differential efficacy of drugs within the ERA class. It should be remembered that although both are dual ERAs, macitentan has a 50-fold increased selectivity for the ET_A subtype compared with the ET_B subtype.[15] Because there are higher numbers of ET_A receptors than ET_B receptors in smooth muscle cells of the pulmonary arteries, blocking the ET_A receptors would appear more important in the treatment of pulmonary hypertension.[16] Furthermore, macitentan has a high receptor occupancy half-life (17 minutes) compared with that of bosentan (70 seconds), and this essentially makes macitentan act as a noncompetitive antagonist of ET receptors, whereas bosentan remains a completive antagonist.[16] At least in theory, macitentan would block the vasoconstriction effect of ET_A receptors and yet preserve, to some extent, vasodilation and clearance effects of ET_B receptors. Why then was macitentan not effective in improving functional capacity in adults? Provided that there were no issues with sample size, the more advanced multifactorial failure of Fontan circulation would be a logical explanation. It should also be said that although ET_B receptors mediate vasodilatation in healthy individuals, ET_B receptors may cause vasoconstriction in patients with heart failure.[17]

Although the true influence of ERA on management in patients with failing Fontan circulation remains unclear, the study by Agnolletti and colleagues[14] is an important step forward because it is the first study to clearly demonstrate beneficial effects of ERA in Fontan patients with increased pulmonary resistance. One can only hope that such profound effects on pulmonary resistance will be confirmed in randomized controlled trials and will result in long-term benefits. The path of least resistance may truly prove to be the path of the winner!

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LETTER TO THE EDITOR

Does biventricular conversion bring survival benefits to patients with an unbalanced atrioventricular septal defect?

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Keywords: Unbalanced atrioventricular septal defect • Single ventricle palliation • Fontan

We read with great interest the recent paper by Nathan *et al.* [1] published in this journal. The authors presented a cohort of 212 patients with unbalanced atrioventricular septal defects (uAVSDs), comparing the results of 3 different surgical strategies: single-ventricle palliation (SVP; 82 patients), biventricular repair (67 patients) and biventricular conversion or recruitment (BiVC/BiVR; 63 patients). They reported significantly better survival with both biventricular repair and BiVC/BiVR strategies compared with SVP.

However, their comparison was biased in favour of the BiVC/BiVR group in several ways. Their time series analysis began at the time of first stage palliation for SVP patients, while it began at the time of complete repair for BiVR/BiVC patients, introducing a substantial survivorship bias. All patients who died prior to conversion were counted in the SVP group, leaving a selected group of survivors to undergo BiVC/BiVR. Furthermore, patients who underwent SVP had higher rates of RV dominance (86.6% vs 61.9%), which had previously been shown as a risk factor for death in SVP [2]. The SVP group also had a much greater proportion of neonates (68.3% vs 3.2%), pulmonary vein disease (31.7% vs 22.2%) and associated cardiac anomalies (43.9% vs 27.0%), all of which have been associated with mortality. It is likely that the highly selected group undergoing BiVC/BiVR would have had similarly good results with the Fontan circulation.

In Melbourne, SVP is performed for patients with uAVSD who are not candidates for initial biventricular repair. We have recently published the long-term outcomes of 139 uAVSD patients who underwent SVP [3]. We observed a similar attrition to Nathan *et al.* in the overall cohort, with a survival rate of 61.8% at 15 years. However, patients who achieved Fontan completion had much better results than previously thought, with 83.5% freedom from death and Fontan takedown at 15 years. This is similar to the results for BIVC/BiVR reported by Nathan *et al.* [1], and it is likely that this cohort includes a similar degree of survivorship bias.

Importantly, we observed that atrioventricular valve (AVV) regurgitation is a major contributor to morbidity and mortality observed in these patients [4, 5]. Patients with AVV regurgitation who achieved successful repair had much better outcomes than those with a significant residual regurgitation [4]. Our focus is on improving the outcomes of AVV repair in these patients, as we believe this will be the key to improved survival.

The work by Nathan *et al.* is important, and their results are encouraging. However, we emphasize that palliation with the Fontan circulation remains an important option for these patients. Advancements in techniques for repairing the AVV might further improve the outcomes for patients with uAVSD who undergo SVP.

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Improved Survival After the Ross Procedure Compared With Mechanical Aortic Valve Replacement

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ABSTRACT

BACKGROUND It is unclear whether the Ross procedure offers superior survival compared with mechanical aortic valve replacement (AVR).

OBJECTIVES This study evaluated experience and compared long-term survival between the Ross procedure and mechanical AVR.

METHODS Between 1992 and 2016, a total of 392 Ross procedures were performed. These were compared with 1,928 isolated mechanical AVRs performed during the same time period as identified using the University of Melbourne and Australia and New Zealand Society of Cardiac and Thoracic Surgeons' Cardiac Surgery Databases. Only patients between 18 and 65 years of age were included. Propensity-score matching was performed for risk adjustment.

RESULTS Ross procedure patients were younger, and had fewer cardiovascular risk factors. The Ross procedure was associated with longer cardiopulmonary bypass and aortic cross-clamp times. Thirty-day mortality was similar (Ross, 0.3%; mechanical, 0.8%; $p = 0.5$). Ross procedure patients experienced superior unadjusted long-term survival at 20 years (Ross, 95%; mechanical, 68%; $p < 0.001$). Multivariable analysis showed the Ross procedure to be associated with a reduced risk of late mortality (hazard ratio: 0.34; 95% confidence internal: 0.17 to 0.67; $p < 0.001$). Among 275 propensity-score matched pairs, Ross procedure patients had superior survival at 20 years (Ross, 94%; mechanical, 84%; $p = 0.018$).

CONCLUSIONS In this Australian, propensity-score matched study, the Ross procedure was associated with better long-term survival compared with mechanical AVR. In younger patients, with a long life expectancy, the Ross procedure should be considered in centers with sufficient expertise. (J Am Coll Cardiol 2018;71:1337-44) Crown Copyright © 2018 Published by Elsevier on behalf of the American College of Cardiology Foundation. All rights reserved.

Several large studies have demonstrated that young adult patients undergoing the Ross procedure exhibit similar survival to an age- and sex-matched population in the country of study (1-5). In contrast, survival after mechanical aortic valve replacement (AVR) falls well short of what would be expected in the general population (6,7).

Given the limited number of surgeons currently performing the Ross procedure and the long follow-up required to demonstrate a survival advantage, performing a randomized control trial comparing mechanical AVR and Ross procedure would pose a formidable challenge. There has been a single randomized trial comparing the Ross procedure with

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ABBREVIATIONS AND ACRONYMS

AVR = aortic valve replacement

homograft AVR, which did demonstrate improved survival and freedom from reoperation for the Ross procedure (3). Conversely, there have only been 3 nonrandomized, matched analyses comparing Ross procedure with mechanical AVR, which have failed to show a survival benefit for the Ross procedure (8-10). However, these studies have included relatively small numbers of patients, potentially rendering them underpowered, and relatively short duration of follow-up (8-10).

SEE PAGE 1345

Although the Ross procedure has clear advantages compared with a mechanical prosthesis, namely the avoidance of anticoagulation and the attendant hemorrhagic and thromboembolic complications, it has remained unclear whether the Ross procedure provides a survival advantage. Hence, in this study we performed a risk-adjusted analysis to compare the outcomes of the Ross procedure performed in younger patients, over a 25-year period, with a contemporaneous cohort of patients undergoing mechanical AVR.

METHODS

PATIENTS. All patients who underwent the Ross procedure between 1992 and 2016 were included in this study. The procedures were predominantly performed by the senior author (P.D.S.) at 3 hospitals within the University of Melbourne group. To generate a contemporaneous cohort of patients undergoing isolated AVR, we combined 2 Australian multi-institutional cardiac surgery databases, because no single database spanned the entire study period.

For the years 1992 to 2001, all patients undergoing isolated mechanical AVR were identified from the University of Melbourne cardiac surgery database, which included 7 cardiac surgery units, and has previously been described (11). In 2001 the University of Melbourne database was superseded by the Australian and New Zealand Society of Cardiac and Thoracic Surgeons database, a multi-institutional Australian database including 31 cardiac surgery centers, which has previously been described in detail (12). There are currently no New Zealand centers contributing to this database. As such, between 2001 and 2016, all patients undergoing isolated mechanical AVR were selected from the Australian and New Zealand Society of Cardiac and Thoracic Surgeons database. Only patients undergoing elective, isolated mechanical AVR were included in the comparison group. Patients who underwent urgent surgery, had other concomitant cardiovascular procedures, or a diagnosis of aortic dissection or endocarditis were excluded from the study. The enrolment periods for the 2 databases did not overlap, and as such no patient was included twice.

Baseline patient demographic and operative data were prospectively recorded for inclusion in the previously mentioned databases at the time of surgery. Survival data were obtained by matching with the Australian National Death Index, the date of censoring for mortality was December 1, 2016.

Ethics approval was obtained from the Royal Melbourne Hospital Human Research Ethics Committee (QA2013104), the Australian and New Zealand Society of Cardiac and Thoracic Surgeons database ethics committee, and the National Death Index (EO2016/2/260).

SURGICAL TECHNIQUE. The techniques used in the 392 patients who underwent the Ross procedure have been described elsewhere (13). Pulmonary autograft root replacement using a modified inclusion cylinder method with autologous support of the autograft within the patient's own aorta (root within root) was used in 92% (361 of 392). The pulmonary autograft was inserted inside a Valsalva Dacron graft in 5% (20 of 392) of patients (11 of 392). The remaining 3% had a mixture of techniques including unsupported root replacement and subcoronary implant technique. The pulmonary valve was replaced using a cryopreserved pulmonary homograft in all cases. Most mechanical aortic valve prostheses in the matched cohort were manufactured by St. Jude Medical (SJM) (St. Paul, Minnesota) (51.6%; 142 of 275). The individual valve models implanted in the matched patients included the American Thoracic Society standard in 16.7% (46 of 275), American Thoracic Society AP in 3.6% (11 of 275), Carbomedics in 8.0% (22 of 275), Carbomedics Reduced in 1.1% (3 of 275), Duromedics in 0.4% (1 of 275), Medtronic Advantage in 1.5% (4 of 275), Medtronic Hall in 1.8% (5 of 275), Medtronic Open Pivot Standard in 4.4% (12 of 275), On-X in 9.8% (27 of 275), SJM standard in 24.7% (68 of 275), SJM HP in 0.7% (2 of 275), SJM Masters in 9.8% (27 of 275), and SJM Regent in 16.4% (45 of 275). The prosthesis model was not recorded in 0.7% (2 of 275).

STATISTICAL ANALYSIS. Pre-operative demographic and investigative data and 20-year survival data were compared between patients receiving a Ross procedure and mechanical aortic valve prosthesis. Categorical variables were expressed as frequencies and compared using the Fisher exact and chi-square tests. Continuous variables were expressed as mean ± SD and compared using the unpaired Student's *t*-test.

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TABLE 1 Clinical Profile of Entire Study Cohort

	Mechanical AVR (n = 1,928)	Ross (n = 392)	p Value	Standardized Difference
Age, yrs	52 ± 11	39 ± 13	<0.001	−108.2
<40	307 (16)	212 (54)	–	87.3
41–50	406 (21)	89 (23)	–	4.0
51–60	783 (41)	78 (20)	–	−46.3
>61	432 (22)	13 (3)	<0.001	−59.5
Male	1,379 (72)	271 (69)	0.36	−5.2
Time period				
1992–1999	332 (17)	110 (28)	–	26.1
2000–2010	676 (35)	166 (42)	–	15.0
2011–2016	920 (48)	116 (30)	<0.001	−37.9
Hypertension	837 (43)	65 (17)	<0.001	−61.2
Diabetes	276 (14)	5 (1)	<0.001	−50.1
Cerebrovascular disease	120 (6)	14 (4)	0.043	−12.3
Peripheral vascular disease	43 (2)	0 (0)	0.001	−21.4
Dialysis pre-operative	139 (7)	0 (0)	<0.001	−39.4
COPD	276 (14)	16 (4)	<0.001	−36.0
NYHA functional class				
I	562 (29)	185 (47)	–	37.8
II	700 (36)	154 (39)	–	6.1
III	537 (28)	52 (13)	–	−36.7
IV	105 (5)	1 (0)	<0.001	−31.6
(missing)	24 (1)	0 (0)	–	−15.9
LVEF <45%	185 (10)	17 (4)	<0.001	−20.8
Aortic stenosis	1,301 (67)	249 (64)	0.14	−8.3
AR	900 (47)	201 (51)	0.11	9.2
Mixed aortic valve disease	391 (20)	83 (21)	0.68	2.2
Isolated AR	508 (26)	118 (30)	0.13	
Re-do surgery	252 (13)	35 (9)	0.023	−13.3
Previous MI	80 (4)	1 (0)	<0.001	−26.8
Congestive HF	565 (29)	11 (3)	<0.001	−77.4

Values are mean ± SD or n (%), unless otherwise indicated.
AR = aortic regurgitation; AVR = aortic valve replacement; COPD = chronic obstructive pulmonary disease; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association.

TABLE 2 Intraoperative Data and Early Mortality

	Mechanical AVR (n = 1,928)	Ross (n = 392)	p Value
Bypass time, min	89 ± 53	199 ± 23	<0.001
Cross-clamp time, min	75 ± 31	173 ± 21	<0.001
30-day mortality	15 (0.8)	1 (0.3)	0.50

Values are mean ± SD or n (%).
AVR = aortic valve replacement.

The Kaplan-Meier method was used to analyze unadjusted survival, which was compared using the log-rank test. Multivariable Cox regression was used to examine the association between Ross procedure and mortality. The variables used for multivariable analyses were age, sex, era of surgery, hypertension, diabetes mellitus, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, myocardial infarction, dialysis, New York Heart Association functional class, ejection fraction <45%, aortic stenosis, aortic regurgitation, mixed aortic valve disease, reoperation, congestive heart failure, and Ross procedure.

Propensity-score matching was performed to correct for the bias associated with receiving a Ross procedure. A propensity-score was generated for each patient by performing a logistic regression with the Ross procedure as the dependent variable. Baseline clinical and investigative variables, which are expected to influence cardiac surgery patient outcomes, were included (Table 1). The C-statistic was calculated for the propensity model. Once generated, patients were matched 1 to 1 on their propensity score without replacement using the "greedy" matching method with a fixed caliper width of 0.05.

Following matching, standardized differences were used to assess the degree of baseline variable balance in the manner described by Austin (14). A high degree of balance is reflected by a standardized difference of ≤10%. Among the matched pairs, the test proposed by Klein and Moeschberger was used to compare long-term survival to calculate the p value (14).

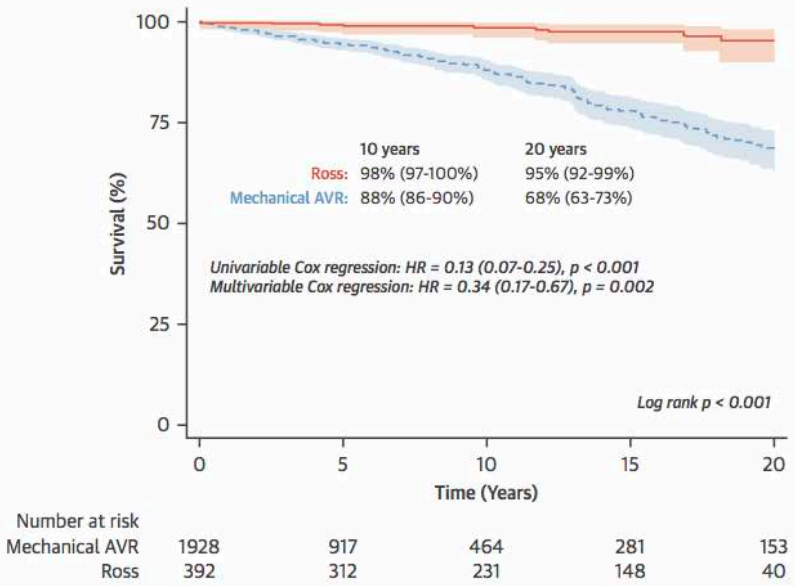
RESULTS

The pre-operative and investigative profile of the entire study population is presented in Table 1. Those receiving the Ross procedure tended to be younger with a lower proportion exhibiting major cardiovascular risk factors.

Intraoperative data and 30-day mortality are presented in Table 2. Those in the Ross procedure group experienced longer cardiopulmonary bypass and aortic cross-clamp times. The proportion of 30-day mortality was similar (Ross, 0.3%; mechanical AVR, 0.8%; p = 0.50). The Ross procedure was not associated with increased risk of 30-day mortality on multivariable analysis (hazard ratio: 0.65; 95% confidence interval: 0.07 to 5.96; p = 0.70).

Survival data from the National Death Index were available with a mean follow-up of 10 ± 7 years (range: 0 to 25 years). Figure 1 displays the Kaplan-Meier survival analysis for the entire study cohort. The Ross procedure was associated with superior unadjusted 20-year survival. Multivariable analysis showed the Ross procedure to be associated with a reduced risk of late mortality (hazard ratio: 0.34; 95% confidence interval: 0.17 to 0.67; p < 0.001). The full multivariable model is shown in Table 3.

FIGURE 1 Unadjusted Survival Comparing Those Receiving the Ross Procedure With Mechanical AVR



Kaplan-Meier survival curves with 95% confidence intervals demonstrating better crude survival following Ross procedure than mechanical AVR. AVR = aortic valve replacement; HR = hazard ratio.

The propensity-score model performed well with a C-statistic of 0.88. We matched 275 Ross procedure patients to 275 patients receiving mechanical AVR, representing a 70% matching rate. Baseline variables were well balanced as displayed in Table 4.

Among propensity-score matched pairs, those receiving the Ross procedure experienced longer cardiopulmonary bypass and aortic cross-clamp times as displayed in Table 5. There was comparable 30-day mortality between the 2 groups after matching (Ross, 0%; mechanical AVR, 0.4%; p > 0.99).

Analysis of long-term survival among the 275 matched patient pairs showed those receiving the Ross procedure to experience better survival compared with those receiving mechanical AVR as displayed in the Central Illustration.

DISCUSSION

There have now been several large studies showing that young adult patients undergoing a Ross procedure exhibit similar survival to an age- and sex-matched population in the country of study (1-5). Also, many studies have shown that survival after mechanical AVR falls well short of what would be expected of the general population (6,7). However, it is true that the Ross operation is generally not offered to high-risk patients, such as those with extensive coronary artery disease, multivalvular heart disease, and other major comorbidities. Also, this young adult group is expected to have excellent survival, regardless of prosthetic choice, purely because of their young age and a few comorbidities.

TABLE 3 Full Multivariable Cox Model for Mortality Following AVR

	HR (95% CI)	p Value
Age	1.1 (1.0-1.1)	<0.001
Aortic stenosis	0.47 (0.31-0.73)	0.001
Cerebrovascular disease	1.5 (0.85-2.6)	0.18
Congestive heart failure	1.5 (0.97-2.4)	0.07
COPD	0.89 (0.47-1.7)	0.71
Diabetes	1.5 (0.99-2.1)	0.06
Dialysis pre-operative	0.99 (0.47-2.1)	0.98
Time period		
1992-1999	0.64 (0.43-0.95)	0.03
2000-2010	0.01 (0.51-1.6)	0.91
LVEF >45%	1.5 (0.85-2.5)	0.17
Male	1.2 (0.89-1.6)	0.24
NYHA functional class		
I	0.64 (0.44-0.93)	0.02
II	0.82 (0.58-1.2)	0.26
III	1.0 (0.14-7.6)	0.99
IV	1.0 (0.14-7.6)	0.99
Peripheral vascular disease	0.92 (0.42-2.0)	0.82
Previous MI	1.8 (1.0-3.3)	0.04
Re-do surgery	1.3 (0.84-2.0)	0.24
Ross procedure	0.34 (0.17-0.67)	0.002

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

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TABLE 4 Clinical Profile of Propensity-Score Matched Patient Pairs

	Mechanical AVR (n = 275)	Ross (n = 275)	p Value	Standardized Difference
Age, yrs	44 ± 11	43 ± 11	0.37	5.4
<40	103 (37)	108 (39)	–	3.7
41-50	83 (30)	83 (30)	–	0.0
51-60	77 (28)	74 (27)	–	−2.4
>61	12 (4)	10 (4)	0.95	−3.7
Male	202 (73)	196 (71)	0.56	−4.9
Time period				
1992-1999	73 (27)	75 (27)	–	1.6
2000-2010	114 (41)	114 (41)	–	0.0
2011-2016	88 (32)	86 (31)	0.98	−1.6
Hypertension	59 (21)	58 (21)	>0.99	−0.9
Diabetes	1 (0)	5 (2)	0.1	14.0
Cerebrovascular disease	17 (6)	12 (4)	0.45	−8.1
Peripheral vascular disease	0 (0)	0 (0)	–	0.0
Dialysis pre-operative	0 (0)	0 (0)	–	0.0
COPD	14 (5)	12 (4)	0.84	−3.4
NYHA				
I	120 (44)	120 (44)	–	0.0
II	109 (40)	106 (39)	–	−2.2
III	45 (16)	48 (17)	–	2.9
IV	1 (0)	1 (0)	0.99	0.0
LVEF <45%	18 (7)	13 (5)	0.46	−7.9
Aortic stenosis	187 (68)	180 (65)	0.59	−5.4
AR	143 (52)	150 (55)	0.61	5.1
Mixed aortic valve disease	55 (20)	55 (20)	>0.99	0.0
Isolated AR	88 (32)	95 (35)	0.59	5.4
Re-do surgery	21 (8)	24 (9)	0.76	4.0
Previous MI	0 (0)	1 (0)	>0.99	8.5
Congestive HF	7 (0)	10 (0)	0.62	6.3

Values are mean ± SD or n (%), unless otherwise indicated.
Abbreviations as in Table 1.

Unfortunately, the challenges involved in conducting a randomized trial comparing the Ross operation with mechanical AVR are formidable. The treatment choices are quite different, with the necessity for life-long warfarin after mechanical AVR, whereas ongoing follow-up of both aortic and pulmonary valves is required after Ross procedure. Furthermore, with relatively few Ross procedures being performed and limited number of surgeons with experience in the procedure, the very long recruitment and follow-up periods are required before meaningful results are obtained. Impressively, El-Hamamsy et al. (3) have published a randomized control trial comparing Ross procedure with homograft AVR, demonstrating superior survival and freedom from reoperation in patients receiving the Ross procedure. However, there has never been a randomized control trial comparing the Ross procedure with mechanical AVR. Propensity-score matched studies, such as this, although less powerful, offer an alternative to determine a difference in survival between these 2 radically different prosthesis choices. Intuitively, one would expect worse survival after mechanical AVR, because of worse hemodynamic function, and the problem of thromboembolism, valve thrombosis, and bleeding, secondary to life-long anticoagulation. However, this has been difficult to demonstrate until now.

TABLE 5 Intraoperative Data and 30-Day Mortality Among Propensity-Score Matched Patient Pairs

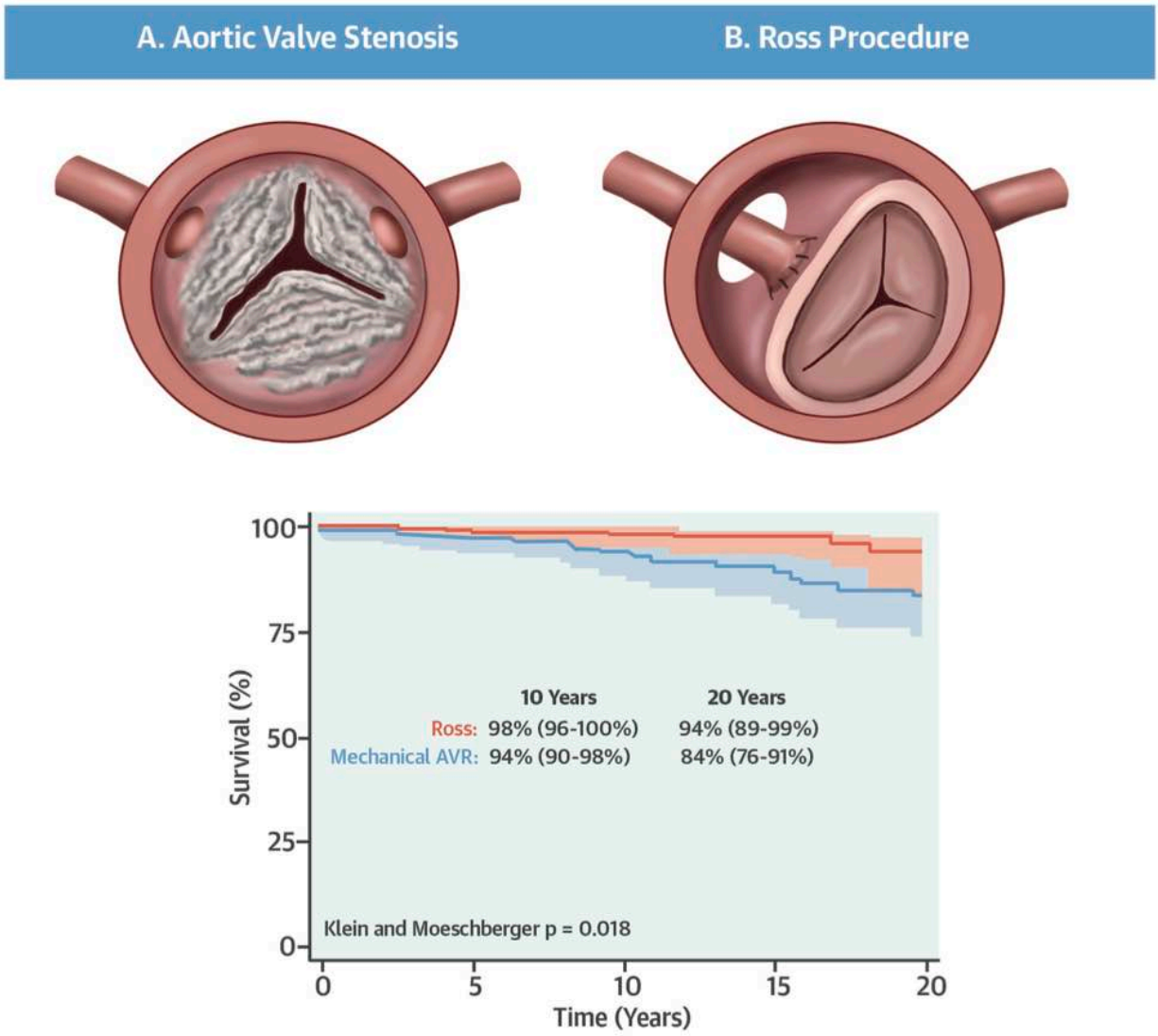
	Mechanical AVR (n = 275)	Ross (n = 275)	p Value
Bypass time, min	74 ± 62	199 ± 24	<0.001
Cross-clamp time, min	74 ± 27	173 ± 22	<0.001
30-day mortality	1 (0.4)	0 (0.0)	>0.99

Values are mean ± SD or n (%).
AVR = aortic valve replacement.

Thus far, 3 studies including matched analyses comparing Ross procedure with mechanical AVR have failed to demonstrate a significant difference in survival. Mokhles et al. (8) used propensity score matching to compare 236 Ross procedure patients with 252 patients undergoing mechanical AVR, and demonstrated equivalent survival. In this study the mean follow up was only 5.1 years, which was perhaps insufficient to demonstrate an advantage for Ross procedure. Furthermore, those receiving a mechanical prosthesis were drawn from a randomized control trial of state-of-the-art anticoagulation management, with patients being self-managed and telemonitored. The comparison in this study is thus biased, because those receiving mechanical valves likely experienced lower rates of bleeding and thromboembolism than would patients receiving standard monitoring of anticoagulation, which would potentially improve survival (15). Finally, the survival of the Ross cohort was somewhat lower than we have observed, and the patients were drawn from several different institutions, and in fact, from >1 country.

Mazine et al. (9) compared 208 propensity-matched pairs undergoing the Ross procedure with those undergoing mechanical AVR, demonstrating equivalent long-term survival. The smaller number of matched patients and the relative paucity of late deaths may have rendered the study underpowered to detect a significant difference in all-cause survival. However, there was a significant difference in late cardiac deaths at 20 years, favoring the Ross procedure.

CENTRAL ILLUSTRATION **Ross Procedure With Autologous Support: Survival With the Ross Versus Mechanical AVR**



Buratto, E. et al. J Am Coll Cardiol. 2018;71(12):1337-44.

(A) Stenotic aortic valve. **(B)** Ross procedure as performed in this study, with the pulmonary autograft implanted within the patient's native aortic root, which provides autologous support. Survival of the propensity-score matched cohort comparing those receiving the Ross procedure with mechanical AVR. Kaplan-Meier survival curves with 95% confidence intervals demonstrating better survival following Ross procedure than mechanical AVR in a propensity-score matched population. AVR = aortic valve replacement.

Most recently, Sharabiani et al. (10) published a large study derived from the UK national database, comparing Ross procedure with mechanical and bioprosthetic AVR in a matched cohort of children and young adults (<40 years old). In a subgroup analysis of 16- to 40-year-old patients, survival was significantly better for Ross procedure patients than those receiving bioprosthetic AVR, but there was only a trend to improved survival when compared with patients receiving mechanical AVR. However, this study included a much younger group of patients, with overall Ross procedure patients having a mean age of only 13.1 years. Furthermore, in the subgroup analysis, 224 young adults underwent Ross procedure, and it is

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not clear what proportion was included in the matched analysis. Given a cohort of only 224 patients from which to draw matched pairs, it is quite likely this study was underpowered to detect a difference between the groups.

Despite the proven advantages of the Ross procedure, including excellent hemodynamic function, lack of need for permanent anticoagulation, lack of valve ticking noise, and low reoperation rate, when the operation is performed in an experienced center, its use is still confined to a relatively small number or centers worldwide (16). Until recently, this could be explained by the wide variety of different techniques used by various surgical groups to implant the pulmonary autograft in the aortic root. However, there has more recently been identification of perhaps 3 or 4 successful techniques, mostly involving some degree of support of the autograft, to prevent late dilation of the aortic root, which have led to more consistent and reproducible results (3,5,17). Even so, this has not led to an increase in the number of Ross procedures performed, despite evidence that this procedure, notwithstanding its complexity, can be taught to junior surgeons, without a concomitant increase in early mortality during the so-called "learning curve" (18). If survival post-Ross procedure can be proven to be superior to that of mechanical AVR, in this younger adult population group, this could provide the incentive for revival of the Ross procedure, possibly dictated by patient and cardiologist preference.

The long-term clinical outcomes of the Ross procedure performed in our centers has been previously reported (13,17). We have previously demonstrated low rates of early mortality, reoperation, and recurrent valvular dysfunction. This study represents the largest in the literature comparing the Ross procedure with mechanical AVR. In this paper, the Ross procedure is shown to be associated with a 10% adjusted survival benefit over 20 years. Also, there is nearly 3 times the incidence of late death at 20 years after mechanical valve versus Ross procedure (16% vs. 6%). This is in addition to the benefits of being free from anticoagulation after Ross procedure, and free of the other disadvantages of mechanical prostheses (19).

The survival benefit may be multifactorial. It could be partially explained by the absence of anticoagulation and its complications. However, it may also reflect the more favorable valve hemodynamics associated with a Ross procedure, whereby the effective orifice area is much greater than that which can achieved with a prosthesis.

Unsurprisingly, Ross procedure cases experienced longer cardiopulmonary bypass and aortic cross-clamp times. This may have a negative impact on post-operative complications. We were unable to analyze these given that early post-operative outcomes were not uniformly collected across both databases over the relatively long study period. However, the low early mortality rates observed in both groups are reassuring. Nevertheless, the long-term survival advantage afforded by the Ross procedure seems to outweigh any possible early morbidity differences between the groups.

One important consideration is that most Ross procedures in this study were performed by a single surgeon. Although we believe the Ross procedure—with our local modification—can be reproduced with appropriate training, we accept that this may limit generalizability. However, this is a reflection of the fact that few surgeons are currently performing the Ross procedure worldwide. Furthermore, this cohort includes our entire experience with the Ross procedure, including the learning curve, which we believe increases generalizability. By demonstrating favorable outcomes with the Ross procedure compared with mechanical AVR we hope that more surgeons will seek appropriate training, and similar results will be achieved in other centers.

STUDY LIMITATIONS. Limitations of this study include its retrospective nature, whereby multivariable and propensity-score analyses are inherently subject to the presence of hidden and unquantifiable biases. In this study, we did not analyze the cause of death, or freedom from morbidity, such as thromboembolism, bleeding, reoperation, and prosthetic valve endocarditis, because these data were not uniformly available via the multicenter databases. Another limitation of using multicenter databases is that matching can only be performed on the data collected; some variables, such as left atrial size and left ventricular mass, would have ideally been included in the model, but are not in the database. It is possible that including some of these variables that could not be analyzed would have affected the significance of our findings. Multiple different mechanical prostheses were used throughout the study period, and although this may be considered a limitation, it reflects real-world practice in Australian institutions. We have not investigated the performance of bioprostheses compared with Ross procedure patients, and it is unclear how newer generation bioprostheses will perform. Other studies that have examined the survival after bioprosthetic AVR in young patients have shown it to be no better and in some studies, even worse than after mechanical AVR (20–22). A comparison of Ross procedure and bioprosthetic AVR will be the subject of a future report from our group.

CONCLUSIONS

In this long-term, propensity-score matched study, the Ross procedure is associated with better long-term survival in suitable patients compared with mechanical AVR. In younger patients, with a long life expectancy, the Ross procedure should be considered in centers with sufficient expertise.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In young adults with aortic valve disease, the Ross procedure improved survival compared with aortic valve replacement with a mechanical prosthesis.

TRANSLATIONAL OUTLOOK: Further studies are required to determine whether the survival advantage associated with the Ross procedure can be generalized to patients operated in other surgical centers where techniques may differ.

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KEY WORDS aortic valve replacement, mechanical valve, propensity score matching, Ross procedure

Appendix B: Additional manuscripts co-authored during candidature

B.1 King G, et al. Eur J Cardiothorac Surg. 2017;51:1037-1043.

European Journal of Cardio-Thoracic Surgery 0 (2017) 1–7
doi:10.1093/ejcts/ezx025

ORIGINAL ARTICLE

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CONGENITAL

Common atrioventricular valve failure during single ventricle palliation†

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Abstract

OBJECTIVES: To determine the risk of atrioventricular valve failure (valve intervention or moderate or greater regurgitation) during the lifetime of patients with single ventricle physiology and common atrioventricular valve.

METHODS: Patients' data were extracted from an existing bi-national, population based registry. A retrospective review of their medical records was undertaken to determine the incidence of atrioventricular valve repair/replacement or moderate or greater regurgitation.

RESULTS: From a registry of 1468 Fontan survivors, 136 patients with common atrioventricular valve were identified. Complete echocardiographic follow-up was available for 114 patients. Median length of follow-up was 10.2 years (interquartile range 5–15 years). Twenty-five year survival and freedom from Fontan failure were 94% [95% confidence interval (CI), 88–100%] and 74% (95% CI, 64–87%), respectively. Twenty-eight patients underwent 24 initial repairs and 4 replacements. The 24 patients undergoing repair subsequently needed 6 re-repairs, 2 replacements and 8 had moderate or greater regurgitation at last follow-up. Four-year freedom from atrioventricular valve repair failure was 50% (95% CI, 34–75%). An additional 30 patients developed moderate or greater atrioventricular valve regurgitation (6 New York Heart Association ≥3, 10 Fontan failures, 0 deaths). Cumulative incidence of the composite endpoint of atrioventricular valve failure at 28 years was 62% (95% CI, 49–74%).

CONCLUSIONS: Patients with single ventricle physiology and common atrioventricular valve experience a continuous decline in valve function. The majority of patients experience valve failure in the first 30 years of life.

Keywords: Common atrioventricular valve • Unbalanced atrioventricular septal defect • Single ventricle • Regurgitation • Valve repair • Fontan

INTRODUCTION

Patients with common atrioventricular valve are at increased risk of mortality and adverse outcomes during single ventricle palliation, likely because of the tendency of this valve to become regurgitant [1–4]. The common atrioventricular valve is prone to failure in biventricular repair, however the rate of failure during the lifetime of a patient with single ventricle physiology is unknown [5, 6]. The presence of regurgitation of common atrioventricular valve has been identified to significantly impact the outcomes of patients with single ventricle, but we still do not know what proportion of patients born with single ventricle and common atrioventricular valve will ultimately see a failure of their valve [2]. We decided to review the data of the Australian and New Zealand Fontan registry to determine the incidence of atrioventricular valve intervention or regurgitation during the lifetime of patients with common atrioventricular valve undergoing single ventricle palliation.

†Presented at the 30th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Barcelona, Spain, 1–5 October 2016.

METHODS

The Australian and New Zealand Fontan Registry, created in 2008, includes patients who had their Fontan procedure in either country, as well as patients who had their Fontan procedure overseas who are followed within the region. When the Registry was created, all Fontan procedures were audited retrospectively and this information was entered into the database. Prospective follow-up information has continued to be collected annually for patients who consented to participate in the Registry. The full design, structure and protocol of the Fontan Registry are described elsewhere [7]. A total of 1521 Fontan operations, excluding Bjork procedures, were recorded between January 1975 and April 2016. A total of 53 patients were excluded because they had early Fontan takedown (7) or died in hospital (46). Of the 1468 patients surviving to hospital discharge with a Fontan circulation, 136 patients with common atrioventricular valve were identified. Pre- and peri-operative variables were extracted from the Registry. Follow-up data were extracted from the Registry and were based on clinical summaries detailing echocardiography reports, outpatient appointments and hospital admissions. Data on the presence of atrial isomerism was extracted from clinical files. Patients who had atrioventricular valve procedures or developed moderate or greater atrioventricular valve regurgitation during their lifetime were identified. Twenty-two patients (22/136, 16%) had inadequate follow-up information available (11 patients had follow-up inferior to 2 years, 11 patients had no echocardiographic follow-up available beyond the first 2 years following Fontan). A sensitivity analysis, performed with the inclusion of the 22 patients excluded due to inadequate follow-up information, gave comparable estimates to the main analysis (results not shown). The remaining 114 patients constitute the cohort of this study.

Atrioventricular valve regurgitation

The degree of atrioventricular regurgitation was graded on an ordinal scale of 0 to 3 based on available echocardiography reports and clinical correspondence from initial and pre-Fontan presentation, and during follow-up (0 = none/trivial, 1 = mild, 2 = moderate, 3 = severe).

Definitions

Fontan failure was defined as death, heart transplantation, Fontan takedown, plastic bronchitis, protein-losing enteropathy (PLE) or New York Heart Association functional class III or IV at follow-up. Atrioventricular valve failure was defined as atrioventricular valve repair or replacement or development of moderate or greater atrioventricular valve regurgitation. Atrioventricular valve operation failure was defined as atrioventricular valve reintervention (re-repair or replacement) or the presence of recurrent moderate or greater atrioventricular valve regurgitation at follow-up. Patients were defined to have collaterals if their presence was mentioned in the pre-Fontan catheterization report.

Statistical analyses

Patient baseline characteristics were summarized using mean [standard deviation (SD)] for normally distributed variables, median [interquartile range (IQR)] for non-normally distributed variables and count (%) for categorical variables. Unless stated otherwise the calculation of proportions did not include the missing category. Cox proportional hazard models were used to test the association between potential predictors and time-to-event end-points in univariable analyses. Competing risks regression methods were used for outcomes where death was a competing risk. Multivariable models were not considered due to either small event size or lack of variables reaching statistical significance in univariable models. All statistical analyses were performed in R (Version 3.2.3, http://www.r-project.org/).

RESULTS

Patient characteristics of included and excluded patients are displayed in Table 1. Seventy-one patients had the following extracardiac anomalies: right atrial isomerism (41), left atrial isomerism (22), intestinal malrotation (1), short stature (1), tracheomalacia (1), Tourette syndrome (1), epilepsy (1), CHARGE syndrome (2), global developmental delay (2), trisomy 21 (1), DiGeorge syndrome (1), Noonan's syndrome (1) and undiagnosed syndrome (1).

Survival

The median length of follow-up of the 114 patients with a common atrioventricular valve was 10.2 years (IQR 5–15 years). Five deaths were observed. The causes of mortality included seizure (1), death following heart transplant rejection (1), PLE (1), intractable ascites and generalized oedema secondary to unknown

Table 1: Patient characteristics of included and excluded patients

Variable		Included patients (*N* = 114)	Excluded patients (*N* = 22)
Age at Fontan (years)	Mean (SD)	6.52 (4.47)	6.32 (3.67)
Sex	Female	53 (46%)	6 (27%)
	Male	61 (54%)	16 (73%)
Fontan type	AP	10 (9%)	3 (14%)
	LT	26 (23%)	2 (9%)
	ECC	78 (68%)	17 (77%)
Fontan fenestration	No	69 (61%)	16 (73%)
	Yes	45 (39%)	6 (27%)
Heterotaxia	Left	22 (19%)	4 (18%)
	None	51 (45%)	11 (50%)
	Right	41 (36%)	7 (32%)
Dextrocardia	No	91 (80%)	17 (77%)
	Yes	23 (20%)	5 (23%)
Dominant ventricle	Biventricular	15 (13%)	5 (23%)
	Indeterminate	3 (3%)	2 (9%)
	Left	27 (24%)	2 (9%)
	Right	69 (61%)	13 (59%)
Extracardiac anomaly	No	43 (38%)	11 (50%)
	Yes	71 (62%)	11 (50%)
Collaterals	No	64 (82%)	9 (82%)
	Yes	14 (18%)	2 (18%)
	Missing	36	11

AP: atriopulmonary; LT: lateral tunnel; ECC: extracardiac conduit.

cause (1) and unknown (1). Survival at 10 and 20 years post-Fontan was 96% (95% CI, 92–100%) and 94% (95% CI, 88–100%), respectively. Three patients ultimately required heart transplantation and one of them subsequently died. Freedom from death or transplantation at 10 and 20 years post-Fontan was 96% (95% CI, 92–100%) and 89% (95% CI, 81–98%) (Fig. 1A).

Fontan failure

Fontan failure occurred in 21 patients, consisting of 4 deaths, 2 transplants, 8 patients who developed PLE, 3 patients who developed plastic bronchitis and 4 patients who were classified as NYHA class 3 or greater during follow-up. One patient was known to have developed plastic bronchitis but the date was unknown. This patient was excluded from analysis, bringing the sample size to 113 and the number of Fontan failures to 20. The 10 and 20 year freedom from Fontan failure was 84% (95% CI, 76–92%) and 74% (95% CI, 64–87%), respectively (Fig. 1B). On univariable analysis, extracardiac conduit (ECC) Fontan type was the only predictor of Fontan failure ($P = 0.02$, Table 2).

Analysis of patients with incomplete data

There were 3 deaths among the 22 patients excluded from the principal analysis due to insufficient follow-up compared with 5 deaths among the 114 included patients. In the excluded group, the cause of death was cardiac failure in 2 patients (3 and 14 months post-Fontan) and unknown in 1 patient (3 months post-Fontan). Excluded patients had a higher proportion of men (73%) compared to the included patients (54% men). Age at Fontan was similar between both groups (median, 5.4 vs 5.5) as was the incidence of dextrocardia (23% vs 20%). The incidence of left [4 (18%) vs 22 (19%)] and right [7 (32%) vs 29 (34%)] heterotaxy was similar between both groups, respectively. Extracardiac anomalies were less prevalent among excluded patients (50%) compared to included patients (62%). Excluded patients had a lower rate of Fontan fenestration (27% vs 39%) and higher proportion of lateral tunnel (9% vs 23%) and extracardiac conduit (77% vs 68%) Fontan procedures.

Atrioventricular valve intervention

There were 28 patients who underwent at least 1 atrioventricular valve procedure. The timing of first atrioventricular valve intervention in relation to other single ventricle palliation procedures is displayed in Table 3. The median age at first atrioventricular valve procedure was 3.5 years (IQR 2–7 years). There were 24 repairs and 4 replacements. The 10 and 20 years cumulative incidence of atrioventricular valve procedure was 21% (95% CI, 14–29%) and 25% (95% CI, 17–33%), respectively (Fig. 2A). Univariable competing risks regression failed to identify any predictors of atrioventricular valve procedure.

Atrioventricular valve regurgitation

In addition to 28 patients undergoing atrioventricular valve procedure, a further 30 patients developed moderate or greater atrioventricular valve regurgitation during their lifetime. Of these patients, 6 were classified as NYHA class III or IV during follow-up and 10 experienced Fontan failures.

Atrioventricular valve failure

A total of 58 patients reached the composite endpoint of atrioventricular valve failure during their lifetime. The 10-, 20- and 28-year cumulative incidence of valve failure was 34% (95% CI, 25–43%), 48% (95% CI, 37–58%) and 62% (95% CI, 49–74%), respectively (Fig. 2B). Univariable analysis identified ECC Fontan type ($P = 0.01$), Fontan fenestration ($P = 0.02$) and the presence of collaterals ($P < 0.01$) as predictors of atrioventricular valve failure (Table 4). Among patients who experienced atrioventricular valve failure there were 2 deaths and 3 transplants and 1 Fontan takedown. One patient developed plastic bronchitis, 8 patients developed protein losing enteropathy and 8 patients experienced NYHA class III or IV during follow-up. A time-varying Cox-regression model was used to analyse the difference in the rate of Fontan failure between patients who experienced atrioventricular valve failure and those who did not. The date of Fontan failure or latest follow-up was the same as the date of atrioventricular valve

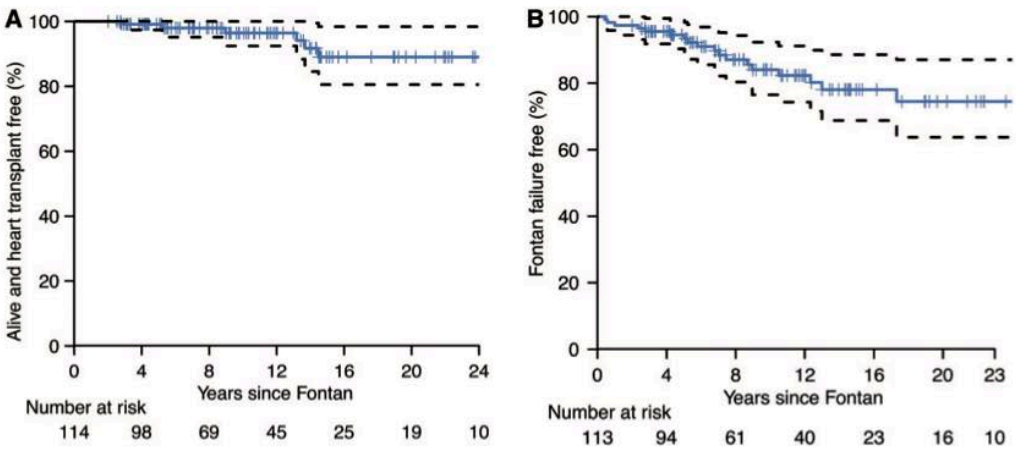

Figure 1: (**A**) Kaplan–Meier curve for estimated freedom from death in hospital survivors of Fontan operation with a common atrioventricular valve and (**B**) Kaplan–Meier curve for estimated freedom from Fontan failure in patients with a common atrioventricular valve. Dashed lines denote 95% confidence intervals. Tick marks denote censored observations.

Table 2: Univariable Cox regression models for freedom from Fontan failure

Variable		*N*	No. events	HR (95% CI)	*P*-value*
Age at Fontan (years)	Per year increase	113	20	1.05 (0.99–1.11)	0.2
Sex	Female (ref)	52	11	1	0.3
	Male	61	9	0.56 (0.22–1.45)	
Fontan type	LT (ref)	25	2	1	
	ECC	**78**	**14**	**6.53 (1.32–32.4)**	**0.02****
	AP	10	4	2.23 (0.31–15.87)	
Fontan fenestration	No (ref)	68	14	1	0.9
	Yes	45	6	0.92 (0.34–2.46)	
Heterotaxia	Left (ref)	21	2	1	0.2
	None	51	8	1.96 (0.41–9.37)	
	Right	41	10	3.50 (0.73–16.6)	
Dextrocardia	No (ref)	90	18	1	0.4
	Yes	23	2	0.55 (0.13–2.38)	
Dominant ventricle	Biventricular (ref)	15	2	1	0.2
	Indeterminate	3	0	Not estimable	
	Left	27	3	0.40 (0.05–2.94)	
	Right	68	15	1.51 (0.34–6.64)	
Extracardiac anomaly	No	43	7	1	0.7
	Yes	70	13	1.20 (0.48–3.01)	
Collaterals	No	64	11	1	0.5

Statistically significant *P*-values (i.e. *P*-value <0.05) are reported in bold.
LT: lateral tunnel; ECC: extracardiac conduit; AP: atriopulmonary.
*Likelihood ratio test.

Table 3: Timing of first atrioventricular valve intervention

	Number of patients		
	Repair	Replacement	Total
Palliative stage	(*N* = 24)	(*N* = 4)	(*N* = 28)
Initial palliation	1	0	1
Between palliation and BCPS	0	0	0
BCPS	7	1	8
Between BCPS and Fontan	8	2	10
At Fontan operation	6	1	7
After Fontan completion	2	0	2

BCPS: bidirectional cavopulmonary shunt.

failure for 3 patients and so they were included in the 'no atrioventricular valve failure' group. A further 3 patients experienced Fontan failure before the onset of atrioventricular valve failure and so they were included in the 'no atrioventricular valve failure' group. The rate of Fontan failure was higher among patients who experienced atrioventricular valve failure compared to those who did not (10/52 vs 10/62, HR = 2.6, 95% CI, 1.06–6.41, $P = 0.04$). For 58 patients with atrioventricular valve failure, freedom from Fontan failure at 5 and 10 years was 93% (95% CI, 86–100%) and 78% (95% CI, 65–93%), respectively. Of the 58 patients with atrioventricular valve failure, 36 were either not offered valve repair or replacement or had an unsuccessful valve intervention. For these 36 patients, Fontan failure occurred in 9 patients (25%), consisting of 1 takedown, 5 patients who developed PLE, 1 patient who developed plastic bronchitis and 2 patients who were classified as NYHA class 3 or greater during follow-up. There was 1 transplant and no deaths observed among this group of patients. Freedom from Fontan failure at 6.8 years was 65% (95% CI, 47–92%) (Fig. 3).

Durability of valve procedure

Out of the 24 patients undergoing repair as the first atrioventricular valve procedure, 16 patients (67%) experienced failure of the repair. There were 8 re-interventions (6 re-repairs and 2 re-placements) and 8 patients developed moderate or greater regurgitation during follow-up. The mean time to reoperation following initial valve repair was 2.9 ± 0.75 years. The 4-year freedom from atrioventricular valve failure post-repair was 50% (95% CI, 34–75%). Durability of atrioventricular valve repair is displayed in Fig. 4.

Atrioventricular valve replacement

A total of 8 valve replacements were performed on 6 patients. Of 4 patients undergoing replacement as the first atrioventricular valve procedure, 2 patients required re-replacement of the valve (12 and 6 years post-initial replacement, respectively). Of the 6 patients who received a valve replacement, there were 2 deaths and 2 transplants (1 patient had a transplant and subsequently died).

DISCUSSION

Common atrioventricular valve has repeatedly been identified to be a predictor of adverse outcomes along the single ventricle pathway because of the propensity of these valves to leak [1–4]. Patients with common atrioventricular valve have been identified to be less likely to reach Fontan completion and to be at increased risk of post-Fontan mortality and Fontan failure [1–4]. In biventricular circulation, common atrioventricular valve is prone to failure [5, 6]. Even in patients with partial atrioventricular septal defects (primum atrial septal defect), common

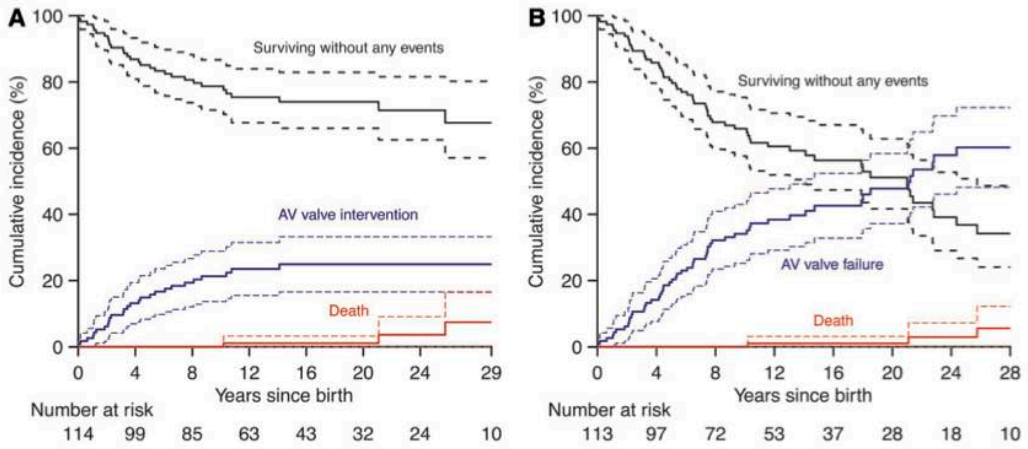

Figure 2: (**A**) Cumulative incidence curve for estimated incidence of atrioventricular valve intervention (repair or replacement) in patients with a common atrioventricular valve undergoing single ventricle palliation. (**B**) Cumulative incidence curve for estimated incidence of the composite endpoint of atrioventricular valve failure (atrioventricular valve operation or moderate or greater atrioventricular valve regurgitation) in patients with a common atrioventricular valve undergoing single ventricle palliation.

Table 4: Univariable competing risks regression models for freedom from composite endpoint of atrioventricular valve failure

Variable		*N*	No. events	HR (95% CI)	*P*-value*
Sex	Female (ref)	53	32	1	
	Male	61	26	0.75 (0.45–1.26)	0.3
Fontan type	LT (ref)	26	12	1	
	ECC	**78**	**41**	**2.53 (1.32–4.86)**	**0.01**
	AP	10	5	0.68 (0.26–1.77)	0.4
Fontan fenestration	No (ref)	69	33	1	
	Yes	**45**	**25**	**1.97 (1.14–3.4)**	**0.02**
Heterotaxia	None (ref)	51	26	1	
	Left	22	10	0.87 (0.41–1.84)	0.7
	Right	41	22	1.18 (0.68–2.04)	0.5
Dextrocardia	No (ref)	91	45	1	
	Yes	23	13	1.5 (0.84–2.68)	0.2
Dominant ventricle	Biventricular (ref)	15	5	1	
	Left	27	15	1.53 (0.55–4.27)	0.4
	Right	69	36	1.38 (0.52–3.7)	0.5
	Indeterminate	3	2	3.16 (0.64–15.58)	0.2
Extracardiac anomaly	No (ref)	43	20	1	
	Yes	71	38	1.33 (0.78–2.26)	0.3
Collaterals	No (ref)	64	29	1	
	Yes	**14**	**11**	**2.56 (1.41–4.65)**	**<0.01**

Statistically significant *P*-values (i.e. *P*-value <0.05) are reported in bold.
LT: lateral tunnel; ECC: extracardiac conduit; AP: atriopulmonary
*Wald tests.

atrioventricular valve has been found to become regurgitant and require reoperation in as many as 25% of patients [5, 6]. A similar incidence has been found in patients with complete atrioventricular septal defect [5, 6, 8]. Until now, the rate of failure of these valves during the lifetime of a patient undergoing single ventricle palliation had not previously been well elucidated. Our results demonstrated that patients with single ventricle physiology and common atrioventricular valve have continuous attrition of their valve function. Two thirds of patients will require valve operation or develop moderate or greater regurgitation during the first three decades of their life. However, this fact hides the real impact of this anatomical feature because our cohort consisted only of patients who had survived the Fontan procedure. The cumulative incidence of valve intervention and significant regurgitation in our group was steadily increasing. It is therefore likely that, with longer follow-up, the incidence of valve failure will continue to rise and one could suspect that all of those valves are ultimately doomed to fail. Interestingly, most of the interventions on these valves occurred before the Fontan stage, but these valves continued to fail well after Fontan completion [4]. These patients received a valve intervention to prepare them for Fontan or concomitantly to it, but not later. Patients

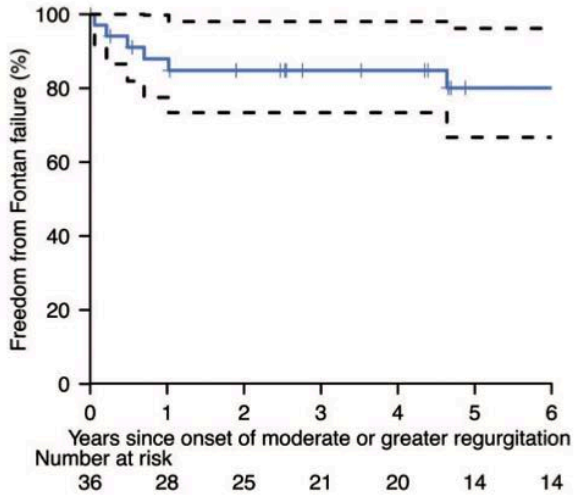

Figure 3: Kaplan–Meier curve for estimated freedom from Fontan failure after the onset of moderate or greater atrioventricular valve regurgitation in patients with a common atrioventricular valve who were not offered valve intervention or had a failed valve intervention. Dashed line denotes 95% confidence interval. Tick marks denote censored observations.

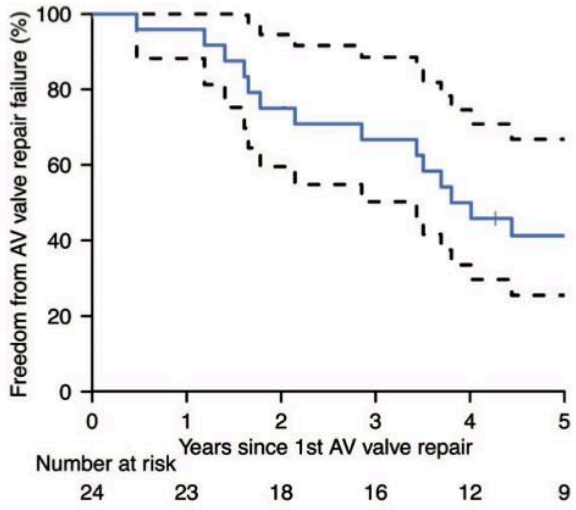

Figure 4: Kaplan–Meier curve for estimated freedom from atrioventricular valve repair failure (re-repair or replacement or the presence of recurrent moderate or greater regurgitation) after initial atrioventricular valve repair in patients with a common atrioventricular valve. Dashed line denotes 95% confidence interval. Tick marks denote censored observations.

with moderate valve regurgitation seemed to have a significant risk of failure of their circulation. Therefore, it is likely that a significant proportion of this population should be offered valve surgery after Fontan completion and that, in the current situation, these patients are not referred for surgery as often as they should be. Interestingly, patients identified to have systemico-pulmonary collaterals at the time of the Fontan were at increased risk of seeing their valve fail. It has been suggested to occlude these collaterals at the time of the Fontan and maybe this practice should be further recommended in patients with common atrioventricular valve [9].

Historically, repair of common atrioventricular valve has produced unreliable results [10]. Some teams have recently reported more encouraging outcomes [11–13]. We have reported a technique of stabilization of the annulus that we hope will improve outcomes after this challenging surgery [14]. Currently, all the publications presenting favourable outcomes have been limited by the small number of patients reported and short follow-up. The longest follow-up published in such a report was 7 years following 21 patients [15]. In our historical series, repair of common atrioventricular valves produced disappointing results. Half of these repairs failed within 4 years. One should realistically expect that a large proportion of these patients will ultimately require a valve replacement, especially if survival after Fontan continues to extend beyond 3 decades. Three of our patients receiving valve replacement died or required transplantation. This anecdotal experience does not allow us to reach any conclusion about the efficacy of valve replacement in these patients, especially as it is likely that our teams were keeping replacement as a last resort.

It appears that the fate of these valves is to eventually fail. If a technique of stabilization of these valves was proven to be efficient, one could wonder whether a preventative operation could be offered to these patients at the time of Fontan surgery. It could be imagined that stabilization of the central portion of the valve before the development of regurgitation and annular dilatation may be of benefit. We have not yet initiated this strategy but we are contemplating adopting this preventative operation in the near future.

Limitations and strengths

Patients with common atrioventricular valve and atrioventricular valve regurgitation are less likely to reach Fontan completion. The entry point in this study was survival from the Fontan procedure, and accordingly, the selection process may have decreased the incidence of the composite end point of atrioventricular valve failure. This population of 114 patients may seem limited in its ability to predict outcomes. This cohort however, is extracted from one the largest database of its kind and provides the longest follow-up ever on this population. The onset of outcomes were dated at the time the event was first referenced in clinical correspondence available in the Registry. This may impact time to event analyses. ECC Fontan type was found to be a predictor of Fontan failure and the composite endpoint of atrioventricular valve failure. We attributed that finding to the fact that more detailed follow-up information was available in this subgroup of patients, but we cannot eliminate that other parameters may have played a role. As an example, in the recent era, a larger proportion of patients with dysplastic valves may have survived the early stages of palliation and a larger proportion of patients undergoing this more recent technique of Fontan would have worse valve morphology.

CONCLUSION

Patients with single ventricle physiology and common atrioventricular valve have continuous attrition of their valve function. Two thirds of patients will require valve repair or replacement or develop moderate or greater regurgitation in the first three decades of their life.

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Conflict of interest: Yves d'Udekem is a consultant for MSD and Actelion.

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Repair of partial atrioventricular septal defects in infancy: a paradigm shift or a road block?

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Atrioventricular septal defects (AVSDs) are a spectrum of diseases affecting the atrioventricular septum and valves. Characteristic features are a common atrioventricular junction, deficient inlet ventricular septum, *ostium primum* atrial septal defect (ASD), abnormal left and right atrioventricular valves (AVV) and a 'gooseneck' deformity of the left ventricular outflow tract.[1] In the complete form of AVSD, there is free interatrial and interventricular communication, with free-floating AVV leaflets. Transitional AVSD (tAVSD) is defined as AVSD associated with free interatrial communication, but a restrictive VSD component. Partial AVSD (pAVSD) refers to forms of AVSD with no interventricular communication, as the AVV leaflets are attached to the crest of the interventricular septum. In the past, this disease was referred to as *ostium primum* ASD, but this belies the other complex anatomy including the trifoliate left AVV and deficient ventricular septum. In these patients, the left AVV, while homologous to the mitral valve, markedly differs to the normal anatomy due to the small mural leaflet, and two bridging leaflets separated by a 'cleft' or 'zone of apposition', and for this reason should not be referred to as a mitral valve. Repair involves approximating the bridging leaflets to create a bifoliate valve, and applying a patch, usually autologous pericardium, to the *ostium primum* ASD.

Partial AVSDs are usually repaired in early childhood with excellent early and late survival, with nearly 95% of children alive at 30 years.[2] However, it has become clear that these children have a high rate of reoperation, mostly due to left atrioventricular valve regurgitation (LAVVR), nearing 25% at 30 years.[2 3] Traditionally, repair of pAVSD is performed at 2–4 years of age, unless signs of heart failure develop earlier. Historical reports of pAVSD repair performed during infancy demonstrated poor survival, with early mortality of 9%–36%.[4 5] More recently, a paradigm shift has appeared to emerge in elective pAVSD repair in younger children, particularly in infants, on the presumption that an earlier repair may prevent progressive left ventricular dilatation and degeneration of the LAVV leaflets, thus improving long-term outcomes and freedom from reoperation.[6 7]

A multicentre study from the Paediatric Heart Network Database that involved seven North American institutions[6] included 87 children who underwent pAVSD repairs between 2004 and 2006 at a median age of 1.8 years. In hospital, mortality was 1.1% (1/87). It appeared that children who had pAVSD repair between 3 and 18 months had an earlier return to normal age-matched weight, while children who were >4 years of age at the time of repair had a higher degree of LAVVR at follow-up.

Devlin *et al*[7] reported a series of 86 children who underwent pAVSD repair between 1990 and 2014 at a median age of 1.5 years. They reported no early deaths and identified no difference in rates of reoperation when comparing children by quartiles of age. They concluded that repair of pAVSD under the age of 18 months was safe, and recommended that repair should be performed under 2 years of age.

An interesting article by Krupickova *et al*[8] is published in the current issue of *Heart* describing their experience with repair of partial and tAVSD in infants with heart failure. The study included 51 infants from three institutions who underwent surgery between 2000 and 2015. Early mortality was 5.9%, somewhat higher than expected for elective repair of pAVSD, which is typically 1%–2% in a group of children of all ages,[3 7 8] yet much lower to what has been previously described for infants.[3 4] Survival at 10 years was 87%, which is also lower than observed with elective repair, where 10-year survival is usually >95%.[2 6]

Our group has recently performed a propensity score-matched analysis comparing children who underwent pAVSD repair in infancy, with those who underwent repair after 1 year of age.[9] In a total of 75 infants, we observed an early mortality of 5.3% and long-term survival of 85% at 10 years, very similar to the results reported by Krupickova *et al*. We then generated 52 matched pairs of infants and children >1 year of age. Our study demonstrated that children who had surgery during infancy had poorer survival, but similar rates of reoperation when compared with older children. This suggested that elective repair should be deferred until after 1 year of age.

Interestingly, Krupickova *et al* specifically analysed the impact of unfavourable LAVV morphology on outcomes, demonstrating that patients with unfavourable anatomy were more likely to undergo LAVV reoperation. Unfortunately, no data are provided to determine whether unfavourable anatomy was associated with poorer long-term survival.

Unfavourable LAVV anatomy, particularly abnormalities of the subvalvular apparatus, has been previously shown to be an important predictor of both mortality and LAVV reoperation after pAVSD repair.[10] In the study by Krupickova and colleagues,[8] 29.4% (15/51) of children had an unfavourable anatomy, which is higher than would be expected in the general population of patients with pAVSD. This probably reflects the fact that children with unfavourable LAVV anatomy are more likely to present early with heart failure and require surgery during infancy.

In all of the 10 cases of reoperation for LAVVR observed by Krupickova *et al*, the mechanism was attributed to the cleft in the LAVV, either residual cleft or rupture of a previously closed cleft. Importantly, despite the young age of these patients, and the high proportion with unfavourable anatomy, 91% (10/11) of patients had their LAVV successfully repaired at reoperation. Although the repair techniques are not described in detail, we noted that the LAVV cleft was reinforced or augmented with patch material in seven patients, while in three patient, the cleft was directly closed with sutures.

The high rate of repair may be related to the use of patch material to repair the cleft. Our group has noted that LAVV regurgitation frequently occurs at the tip of the cleft, and we have also observed that incomplete cleft closure and cleft rupture often contribute to LAVVR.[3 11] As such, we have utilised a technique of cleft augmentation with a patch of

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autologous pericardium, which is then suspended with neochordae at its free edge, in order to ensure an adequate coaptation surface.[11] Following the implementation of this technique to repair the LAVV of patients with pAVSD, the rate of successful repair significantly increased from 54% to 94%.[4] Furthermore, compared with simple cleft closure, patients who underwent cleft patch augmentation had better long-term freedom from reoperation.[10] Poirier *et al* described a similar strategy of leaflet augmentation of the base of the bridging leaflets using autologous pericardium in order to allow repair of dysplastic valves in patients with AVSD, as they had also found it difficult to achieve a competent repair in patients with deficient leaflet tissue.[12]

The optimal timing for elective repair of pAVSD and tAVSD remains controversial. It might be timely to emphasise that pAVSD and tAVSD are not as benign as it might seem. Although the development of heart failure in infants with these conditions may necessitate early surgery, the trend towards elective pAVSD repair in all infants may not be wise. Such an approach of early repair in infancy may potentially increase early risk without bringing long-term benefits. Krupickova and colleagues[8] have demonstrated that although modern outcomes for infants with heart failure are much better than those in historical reports, patients who had pAVSD repair in infancy still have higher rates of reoperation and poorer long-term survival than older children undergoing elective repair. There is, certainly, a subgroup of children who would always require surgery during infancy due to developing heart failure and failure to thrive. It is also true that some children with this condition continue to thrive without any signs of heart failure beyond the infancy. It is very important to operate during infancy, when the surgery is required. It appears to be equally important not to operate during infancy when the surgery is not required. Further refinement of timing of such repair would be timely.

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CONVENTIONAL VALVE OPERATIONS

The Ross procedure in adults presenting with bicuspid aortic valve and pure aortic regurgitation: 85% freedom from reoperation at 20 years†

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Abstract

OBJECTIVES: The Ross procedure has demonstrated excellent results when performed in patients with aortic stenosis or mixed aortic valve disease [aortic stenosis and aortic regurgitation (AR)]. However, due to its reported risk of late reoperation, it is not recommended under current guidelines for patients presenting with bicuspid aortic valve and pure AR. We have analysed our own results in light of this recommendation.

METHODS: Between 1993 and 2016, 129 consecutive patients with a mean age of 34.7 ± 10.6 years (range 16–64 years) presented with bicuspid aortic valve and pure AR and underwent the Ross procedure. Patients were reviewed annually and had 2nd yearly transthoracic echocardiograms during follow-up. The unit had a liberal reoperation policy where reoperation was performed if patients developed recurrent moderate or greater AR during follow-up.

RESULTS: There was 1 inpatient death, and 3 late deaths over a mean follow-up duration of 9.6 ± 6.8 years. Late survival at 10 and 20 years post-surgery were 99% [95% confidence interval (CI) 94–100] and 95% (95% CI 85–99), respectively. Eleven patients underwent redo aortic valve replacement (AVR) and 4 patients had redo pulmonary valve replacement. Freedom from reoperation for AVR and more-than-mild AR at 10 and 20 years post-surgery were 89% (95% CI 81–94) and 85% (95% CI 74–92), respectively. Having longer aortic cross-clamp (hazard ratio 1.03, 95% CI 1.00–1.06; $P = 0.05$) and cardiopulmonary bypass times (hazard ratio 1.02, 95% CI 1.00–1.05; $P = 0.05$), and having a larger preoperative sinotubular junction diameter (hazard ratio 1.15, 95% CI 1.03–1.30; $P = 0.02$) were significant predictors of having redo AVR or significant AR at follow-up.

CONCLUSIONS: With a 20-year freedom from redo AVR and greater-than-mild residual AR of 85%, the utilization of the Ross procedure in bicuspid aortic valve patients with pure AR should be considered.

Keywords: Aortic valve replacement • Aortic regurgitation • Bicuspid aortic valve • Ross procedure • Autograft • Long-term survival • Reoperation

INTRODUCTION

Aortic valve replacement (AVR) using the Ross procedure has shown excellent results, provided the operation is performed in a centre with the necessary expertise [1–3]. Survival, in these centres, has been shown to be equivalent to an age- and sex-matched population [2]. Patients do not require anticoagulation, and haemodynamic results are excellent [4]. Despite being a 2-valve operation, it is associated with a relatively low rate of reoperation in experienced hands [1, 5].

However, results are not as good in the younger patient group presenting with pure aortic regurgitation (AR), compared to that achieved in those with aortic stenosis or mixed disease [6, 7]. Most of these patients have a bicuspid aortic valve (BAV) as the pathological basis of their valvular regurgitation. Perhaps in view of the inferior results in this group, all guidelines including the Society of Thoracic Surgeons (STS) and American Heart Association (AHA)/American College of Cardiology (ACC)

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guidelines currently recommend a mechanical valve as the optimal choice in patients younger than 60 years of age, unless there are contraindications for anticoagulation with warfarin [8, 9]. Our approach to these patients has been to offer a Ross procedure when anticoagulation is either contraindicated or deemed to be unacceptable by the patient. The current guidelines allocate the Ross procedure a Class III recommendation, stating that it should not be performed in patients with BAV and AR.

Meanwhile, the latest European Association for Cardio-Thoracic Surgery (EACTS) guidelines recommend that repair of the regurgitant valves is considered when the valve morphology permits, due to its association with lower valve-related event rates and an improved quality of life [10]. Our unit has commenced a programme of aortic valve repair in patients with BAV and AR, and has achieved good results in selected patients. However, we believe that the Ross procedure is a viable surgical option that deserves consideration. As such, we decided to review our 25-year experience with the Ross procedure in this patient cohort.

PATIENTS AND METHODS

Ethical approval for this study was obtained from the Royal Melbourne Hospital Human Research Ethics Committee for the review of outcomes of all patients undergoing the Ross procedure within the unit (HREC QA20130104). Four-hundred and twenty consecutive patients underwent the Ross procedure between 1992 and January 2017. Of these, 129 patients presented with BAV and pure AR, comprising the study cohort. Pure AR was defined as the presence of AR without any aortic stenosis.

The baseline demographics and preoperative and operative factors were collated. Preoperative aortic dimensions were mostly derived from transthoracic or transoesophageal echocardiography. In the setting of aortic dilatation, further evaluation was performed with computed tomography, and larger dimensions were reported. Follow-up data of the 129 patients were reviewed. All patients received yearly clinical review and biannual transthoracic echocardiogram during follow-up. All deaths during the follow-up period were ascertained. Patients lost to follow-up were subjected to a search in the Australian National Death Registry to confirm survival status. The primary end point of the review was all-cause mortality. Secondary end points included surgical reintervention of the aortic valve and recurrence of significant AR, defined as moderate or severe AR on follow-up transthoracic echocardiogram.

Patient selection criteria varied through the study period. Between 1992 and 1999, all patients with significant AR were offered the surgical option of a Ross procedure, regardless of their aortic root size. In the following decade between 2000 and 2009, aortic root enlargement was identified to be an important preoperative predictor of poor surgical outcomes [7]. As such, the Ross procedure was only offered to patients without significant aortic root enlargement, defined as sinotubular junction size <34 mm. From 2009 to present, a modification of the Ross procedure was introduced, where patients with larger aortic roots underwent surgery with the pulmonary autograft valve inserted within a Valsalva Dacron graft (Gelweave Valsalva; Sulzer Vascutek, Renfrewshire, Scotland), allowing for the Ross procedure to be offered even to patients with aortic root enlargement [1]. Those without significant aortic root dilation underwent the Ross procedure using the standard autologous external support

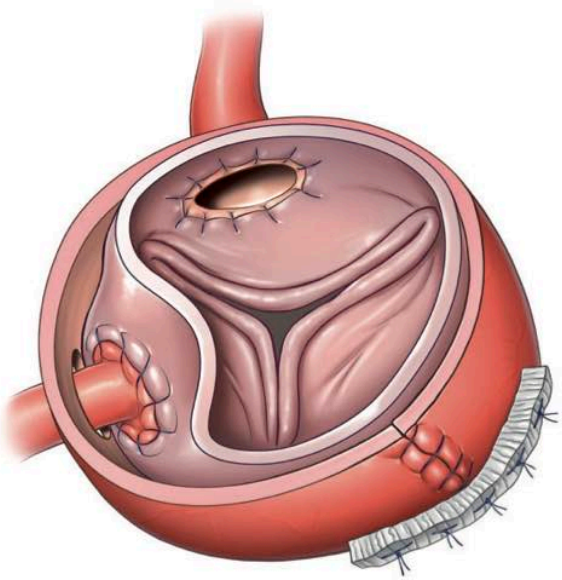

Figure 1: The autologous inclusion technique using native aortic root as the external support for pulmonary autograft.

inclusion technique (Fig. 1). This involved the implantation of their pulmonary autograft within their aortic root, which acted as an external scaffold preventing subsequent aortic root dilatation [7].

The strategy for aortic root preparation has been previously described, and aims to achieve an ideal aortic annulus size of 22–24 mm diameter in women and 24–26 mm in men [7]. Appropriate aortic root reduction in those with enlargement was performed based on pre-operative aortic annulus and sinotubular junction dimensions. Minor reduction (1–3 mm diameter reduction) was most commonly achieved with the insertion of a partial circumferential external polyester band. Greater degree of reduction (≥4 mm) required additional strategies including wedge or quadrangular resection of the non-coronary sinus tissue and plication sutures. The enlarged sinotubular junction and ascending aorta were managed with a variety of measures, including sinotubular ring, tailoring aortoplasty (if ascending aorta ≤45 mm) and Dacron graft replacement of the ascending aorta (if ascending aorta diameter >45 mm). We did not perform prophylactic replacement or repair of the non-dilated aortic root and/or ascending aorta.

Pulmonary valve replacement (PVR) was routinely performed with a cryopreserved pulmonary valve allograft. Meticulous myocardial protection was achieved throughout surgery using intermittent antegrade and retrograde tepid blood cardioplegia every 15 min. A transthoracic echocardiogram was performed biannually to monitor valve function, ventricular size and function as well as surveillance of the aortic root and ascending aorta. A liberal reoperation policy was adopted, where reoperation was recommended if patients developed moderate or severe AR post-Ross surgery, and if their left ventricular end-diastolic diameter (LVEDD) exceeded 6 cm on follow-up imaging. Pulmonary allograft function was also monitored with serial echocardiography. Indications for reoperation on the pulmonary valve were development of pulmonary allograft stenosis (mean pulmonary valve gradient >35 mmHg); and moderate or greater pulmonary regurgitation with symptoms or without symptoms but with

significant right ventricular dilation. Follow-up was deemed to be complete if patients underwent clinical review or echocardiography after January 2015 or within the year before death.

Statistical analysis

Patient baseline characteristics were summarized using mean (standard deviation) or median [interquartile range] for continuous variables and percentages for categorical variables. Survival analysis was performed using the Kaplan–Meier method. A Cox proportional hazard model was used to examine the variables, from which the hazard ratios of the chosen end point and their 95% confidence intervals were generated. The proportional hazards assumption was assessed based on the method of Harrell–Lee via diagnostic plots. Univariable analysis was performed on all variables to determine the hazard ratio for redo AVR or recurrent AR.

RESULTS

There were 129 patients with BAV and pure AR who underwent the Ross procedure during the study period. Patient characteristics are described in Table 1. The mean age at the time of Ross procedure was 34.7 ± 10.6 years (range 16–64 years). Sixty-four (50%) patients had symptoms of effort dyspnoea at the time of surgery [preoperative New York Heart Association (NYHA) class in Table 1]. Of the group, 118 (91%) patients had normal or mildly impaired left ventricular function preoperatively. Most patients had significant left ventricular dilation, with a mean LVEDD of 6.4 ± 0.6 cm. Mean aortic annulus and sinotubular junction diameters were 30.8 ± 3.3 mm and 28.9 ± 4.3 mm, respectively.

Eleven (9%) patients had the Ross procedure with external reinforcement using a Valsalva graft, and the remaining patients underwent the Ross procedure with the autologous support technique. All except 6 of the remaining patients needed adjunctive aortic root augmentation or reduction, most commonly with a Dacron partial annuloplasty ring ($n = 93$; 72%), and 74 (57%) patients needed ascending aortic reduction or replacement. All adjunctive aortic procedures are summarized in Table 2. Mean aortic annulus diameter post-augmentation was 25.0 ± 1.5 mm. The mean cross-clamp and cardiopulmonary bypass times were 178.3 ± 18.3 min and 203.7 ± 22.5 min, respectively.

Three patients had to return to theatre for bleeding, 2 patients had low cardiac output requiring insertion of intra-aortic balloon pump and there were 2 patients with new acute renal failure. All early postoperative complications are summarized in Table 3. The mean duration of postoperative invasive ventilation was 9.7 ± 3.9 h, and the mean duration of intensive care stay was 1.4 ± 0.6 days. Patients were discharged after a mean of 7.3 ± 1.7 days post-surgery. One perioperative death was reported due to myocardial infarction, with an early operative survival of 99%. The remaining 128 patients were followed up over a mean duration of 9.6 ± 6.8 years with 98% completion rate. These patients made up the cohort for subsequent analysis.

Three late deaths were reported at 4, 11 and 12 years post-surgery due to non-cardiac causes, specifically cancer (2 patients) and suicide (1 patient). Late survival at 10 and 20 years was 99% [95% confidence interval (CI) 94–100] and 95% (95% CI 85–99), respectively (Fig. 2). Eleven (9%) patients required reoperation for AVR at a median of 5.3 years (interquartile range 3.4–7.8) after the Ross procedure. All 11 patients had mechanical aortic valve implantations, and 1 of the 11 patients required concurrent ascending aortic repair with a pericardial patch. Of these, 9 (7%) patients underwent redo surgery for recurrent AR. The remaining 2 patients had infective endocarditis, of which 1 patient needed replacement of both aortic and pulmonary valves at 7 years post-surgery. An additional 3 patients had reoperation for PVR. Indications for redo PVR were pulmonary valve stenosis (2 patients) and pulmonary regurgitation (1 patient). Of the 4 pulmonary valve re-replacements, 3 utilized a porcine valve (Medtronic Freestyle valve) and 1 a pulmonary allograft. Freedom from reoperation for PVR at 5, 10, 15 and 20 years was 98% (95% CI 93–99), 97% (95% CI 89–99), 95% (95% CI 86–98) and 95% (95% CI 86–98), respectively. No mortality was reported in any of the redo operations, both aortic and pulmonary.

Freedom from reoperation for AVR at 5, 10, 15 and 20 years was 95% (95% CI 88–98), 89% (95% CI 81–94), 85% (95% CI 74–92) and 85% (95% CI 74–92). There was 1 additional patient

Table 1: Preoperative patient characteristics of the study cohort

Variables	$n = 129$
Male gender, *n* (%)	113 (88)
Age at Ross procedure (years), mean ± SD	34.9 ± 10.6
Year of Ross procedure, *n* (%)	
1993–1999	32 (25)
2000–2009	44 (34)
2010–present	53 (41)
Previous surgery/percutaneous intervention ($n = 17$), *n* (%)	13 (10)
Aortic valve repair	4 (3)
Coarctation repair	4 (3)
Open aortic valvotomy	3 (2)
VSD closure	3 (2)
Balloon valvuloplasty	2 (2)
ASD closure	1 (1)
NYHA, *n* (%)	
1	65 (50)
2	63 (49)
3	1 (1)
Severity of AR, *n* (%)	
Moderate	16 (12)
Severe	113 (88)
Bicuspid type,[a] *n* (%)	
0	7 (5)
1	103 (80)
2	19 (15)
Preoperative LV function, *n* (%)	
Normal	89 (69)
Mild	29 (22)
Moderate	9 (7)
Severe	2 (2)
Preoperative LV fractional shortening (%), mean ± SD	34.5 ± 7.1
Preoperative LVEDD (cm), mean ± SD	6.4 ± 0.6
Preoperative LVESD (cm), mean ± SD	4.2 ± 0.6
Mean aortic annulus diameter (mm), mean ± SD	30.8 ± 3.3
Mean sinotubular junction diameter (mm), mean ± SD	28.9 ± 4.3
Mean pulmonary annulus diameter (mm), mean ± SD	26.0 ± 1.5

[a]PPM bicuspid type (Sievers classification of bicuspid aortic valve).
AR: aortic regurgitation; ASD: atrial septal defect; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; NYHA: New York Heart Association; PPM: permanent pacemaker; SD: standard deviation; VSD: ventricular septal defect.

Table 2: Surgical techniques used in patients who underwent adjunctive aortic procedures during the Ross procedure

Surgical technique	*n*
Aortic annulus/sinus reduction	
Circumferential Dacron ring reduction annuloplasty	16
Partial ring reduction annuloplasty	93
Annular plication	42
Aortic sinotubular reduction	
Sinotubular ring	21
Aortic sinus adjustment	
Wedge/quadrangular resection	58
Autologous pericardial patch enlargement	6
Ascending aorta	
Tailoring aortoplasty	55
Ascending aortic replacement	19
Other cardiac surgical procedures	2
Coronary artery bypass grafting	1
Repair of right coronary artery	1

Table 3: Early postoperative complications for all 129 patients

Complications	*n* = 129, *n* (%)
Atrial arrhythmia	10 (8)
Return to theatre for bleeding	3 (2)
Low cardiac output requiring IABP	2 (2)
Acute renal failure	2 (2)
Prolonged intubation (>48 h postoperatively)	1 (1)
Stroke	1 (1)
Return to theatre for CABG	1 (1)
Insertion of permanent pacemaker	1 (1)
Antibiotics for positive homograft cultures	1 (1)
Death (myocardial infarction)	1 (1)

CABG: coronary artery bypass grafting; IABP: intra-aortic balloon pump.

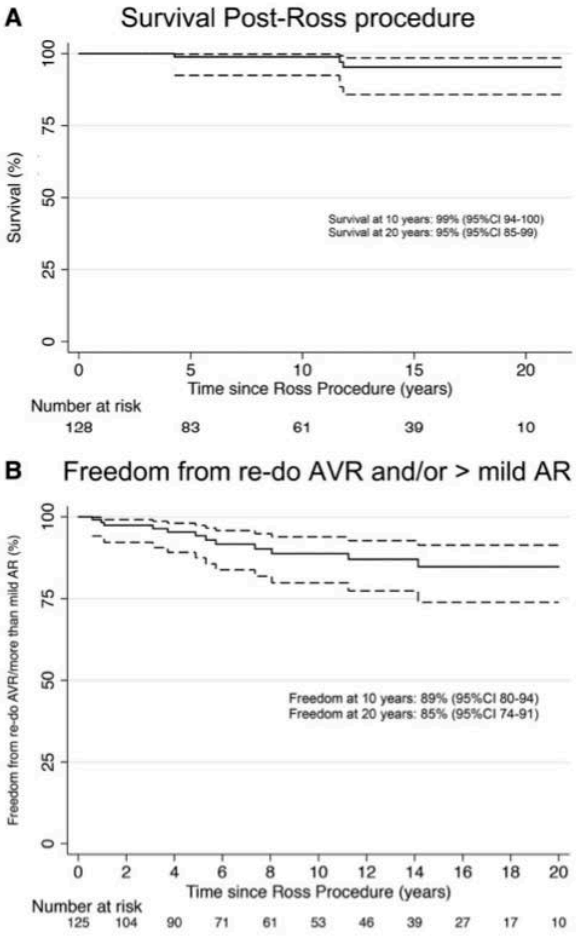

Figure 2: Kaplan–Meier curves of (**A**) survival after hospital discharge and (**B**) freedom from redo AVR and significant (more-than-mild) AR after the Ross procedure. AR: aortic regurgitation; AVR: aortic valve replacement; CI: confidence interval.

diagnosed with significant AR in his 1st year after the Ross procedure. This patient was a complex patient with a dilated aortic root and ascending aorta of 5 cm that required the use of the Valsalva Dacron graft technique and concurrent ascending aortic repair. Postoperative echocardiography demonstrated a good result with no AR. However, follow-up investigation at 1-year post-surgery demonstrated moderate AR. Overall freedom from significant (more-than-mild) AR and redo AVR at 5, 10, 15 and 20 years were 94% (95% CI 87–97), 89% (95% CI 80–94), 85% (95% CI 74–91) and 85% (95% CI 74–91), respectively (Fig. 2).

Univariable analysis identified preoperative sinotubular junction diameter [hazard ratio (HR) 1.15, 95% CI 1.03–1.30; $P = 0.02$] as a continuous variable to be a significant predictor of the recurrence of significant AR or redo AVR. In addition, having a preoperative sinotubular junction diameter ≥32 mm was strongly predictive of this end point (HR 4.22, 95% CI 1.23–14.4; $P = 0.02$). Having a longer cross-clamp time (HR 1.03, 95% CI 1.00–1.06; $P = 0.05$) and cardiopulmonary bypass time (HR 1.02, 95% CI 1.00–1.05; $P = 0.05$) were also significant predictors of the recurrence of significant AR or redo AVR (Table 4). Patients who had redo AVR or significant AR had larger preoperative aortic annulus (32.1 ± 2.5 vs 30.7 ± 3.3; $P = 0.15$) and sinotubular diameters (31.1 ± 5.2 vs 28.8 ± 4.2; $P = 0.10$), although this was not statistically significant (Table 5).

At the last follow-up, all patients were in NYHA Class I and had normal left ventricular systolic function on echocardiography (Table 6). A significant reduction in mean LVEDD was observed on follow-up echocardiogram (postoperative vs preoperative LVEDD: 5.2 ± 0.5 cm vs 6.4 ± 0.6 cm, $P < 0.001$). All except 1 patient as discussed above were free from significant AR, with mean peak and mean aortic gradients of 9.7 ± 5.6 mmHg and 5.4 ± 2.8 mmHg, respectively. None of the patients who underwent reoperation had significant regurgitation or stenosis of the reoperated aortic or pulmonary valves at follow-up. Eleven (9%) patients had moderate pulmonary regurgitation. The mean peak and mean pulmonary gradients were 20.0 ± 6.3 mmHg and 10.9 ± 6.1 mmHg, respectively.

DISCUSSION

The prevalence of significant AR in patients with BAV has been reported to vary between 11% and 32%, contributing to the high incidence of cardiovascular intervention rates of 22–57% in follow-up studies [11–13]. A recent systematic review of 11 502

Table 4: Univariable analysis of predictors of recurrent AR after the Ross procedure (redo AVR or significant AR on follow-up)

Variables	Total number of patients (n = 128)	Recurrent AR (%)	HR (95% CI)	P-value
Preoperative variables				
Age at Ross procedure (years)			1.01 (0.96–1.06)	0.79
Significant LV dysfunction				
Yes	8	1 (13)	1.12 (0.14–8.67)	0.92
No	120	11 (9)		
LVEDD (cm)			1.87 (0.71–4.92)	0.21
Aortic annulus diameter (mm)			1.13 (0.92–1.37)	0.24
Sinotubular junction diameter (mm)			1.15 (1.03–1.30)	0.02
Sinotubular junction diameter ≥32 mm	27	5 (19)	4.22 (1.23–14.4)	0.02
Ascending aorta diameter (mm)			1.08 (0.91–1.27)	0.40
Intraoperative variables				
Surgical technique				
Autologous inclusion	117	11 (9)	2.06 (0.25–16.7)	0.50
Valsalva graft	11	1 (9)		
Aortic cross-clamp time (min)			1.03 (1.00–1.06)	0.05
Cardiopulmonary bypass time (min)			1.02 (1.00–1.05)	0.05
Year of Ross procedure	32	6 (19)	0.74 (0.30–1.78)	0.50
1993–1999	44	4 (9)		
2000–2009	53	2 (4)		
2010–present				
Postoperative variables				
LVEDD on follow-up (mm)			2.18 (0.64–7.47)	0.21
Reduction in LVEDD (mm)			0.62 (0.20–1.93)	0.41

AR: aortic regurgitation; AVR: aortic valve replacement; CI: confidence interval; HR: hazard ratio; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter.

Table 5: Comparison of patients with and without recurrent (>mild) AR/redo AVR

	Patients with recurrent AR/redo AVR (n = 12)	Patients free from AR/redo AVR (n = 116)	P-value
Male, n (%)	12 (100%)	101 (87%)	0.17
Age at Ross procedure (years), mean ± SD	34.9 ± 9.1	34.8 ± 10.8	0.95
Previous surgery, n (%)	0	13 (11%)	0.45
Moderate/severe preoperative LV dysfunction, n (%)	1 (8%)	9 (7%)	0.94
Preoperative aortic annulus diameter (mm), mean ± SD	32.1 ± 2.5	30.7 ± 3.3	0.15
Preoperative sinotubular junction diameter (mm) mean ± SD	31.1 ± 5.2	28.8 ± 4.2	0.10
Preoperative LVEDD, mean ± SD	6.7 ± 0.8	6.4 ± 0.5	0.06
Postoperative aortic annulus diameter (mm), mean ± SD	25.1 ± 0.6	25.0 ± 1.5	0.96

AR: aortic regurgitation; AVR: aortic valve replacement; LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; SD: standard deviation.

Table 6: Clinical status of all patients at latest follow-up

	At latest follow-up (n = 128)
NYHA Class 1, n (%)	128 (100)
Moderate/severe LV systolic dysfunction, n (%)	0
Mean LVEDD (cm), mean ± SD	5.2 ± 0.5
Peak aortic gradient (mmHg), mean ± SD	9.7 ± 5.6
Mean aortic gradient (mmHg), mean ± SD	5.4 ± 2.8
Peak pulmonary gradient (mmHg), mean ± SD	20.0 ± 6.3
Mean pulmonary gradient (mmHg), mean ± SD	10.9 ± 6.1

LV: left ventricular; LVEDD: left ventricular end-diastolic diameter; NYHA: New York Heart Association; SD: standard deviation.

patients with BAV found an incidence of aortic valve repair or replacement of 28% [14]. The majority of these patients underwent either an isolated AVR or concomitant aortic root replacement via a Bentall procedure when there is significant aortic root dilatation. The use of the Ross procedure as a surgical option has declined to <0.5% of AVRs [15]. This is likely a result of the allocation of Class IIb indication for the Ross procedure in the 2014 AHA/ACC Guidelines for management of valvular heart disease, stating it should only be considered in young patients where anticoagulation is contraindicated or undesirable [9]. The STS guidelines support a similarly unfavourable stance with the Ross procedure having a Class III indication, particularly highlighting its inadequacy in patients with BAV and AR [8]. However, it is our belief that with appropriate aortic root stabilising strategies, the Ross procedure is a viable option in this cohort.

The ideal AVR option for young adults that provides freedom from reoperation, anticoagulation and valve-related morbidity remains elusive. Large studies have consistently demonstrated a survival disadvantage in patients who have undergone prosthetic AVRs compared to their age and gender matched counterparts, with the greatest disparity demonstrated in the younger group [16, 17]. This is due to the risk of stroke and bleeding, particularly in the setting of mechanical aortic valves [17]. However, there is great hesitation towards the Ross Procedure, due to its increased complexity and risk of perioperative complications and late reoperation. A landmark review of the STS database showed that operative mortality was twice as high after the Ross procedure as compared to propensity-matched patients who had undergone conventional AVR. They also faced an increased risk of early reoperation and renal failure. However, it is critical to note that more than half of the surgeons who performed the Ross procedure in this review were highly inexperienced, having completed only 5 or less surgeries [15]. Therefore, the results are not a representative comparison of the 2 strategies. Bioprosthetic AVR is gaining popularity in younger patients, with the prospect of having a 'valve-in-valve' transcatheter aortic valve replacement for management of late valve failure. However, the durability of bioprosthetic AVR is poor and has been associated with greater late mortality when compared to patients with mechanical AVRs [18]. The use of 'valve-in-valve' transcatheter aortic valve replacement has been demonstrated to be feasible in older patients; however, the mortality rates have been high and it has yet to be evaluated in younger patients.

The Ross procedure involves surgical intervention on 2 valves in order to address a single-valve pathology, hence accompanied by the risk of reoperation for both the autograft and homograft. Single-centre series have reported late autograft reoperation rates between 9% and 20% at a decade after the Ross procedure [19–21]. Patients with both BAV and AR are the most challenging patient group. This is a result of their propensity to develop progressive aortic root dilatation due to their underlying aortopathy. This was demonstrated in our results, with a larger preoperative sinotubular junction diameter remaining as the most important predictor of late autograft failure, despite our current surgical strategies. We have previously discussed the possible factors leading to late valve failure in an earlier publication [7]. These included uncorrected annular dilatation, the use of oversized supracoronary Dacron graft for ascending aortic replacement and presumed distortion of the autograft at implantation leading to cusp prolapse. As we routinely reduce all aortic annulus diameters to between 24 mm and 26 mm, current failures are likely due to the prolapse of the autograft leaflets. With a larger preoperative aortic root, more surgical manipulation is necessary, likely leading to more errors. Despite this, we believe that the use of an additional autologous support of the pulmonary autograft (inclusion technique) remains the key factor to our durable results.

The surgical experience in patients with BAV and AR is limited, with some studies reporting an increased rate of early autograft failure [22]. However, larger contemporary studies have demonstrated good mid-term outcomes with freedom from death and reoperation above 80% at 10 years [5, 23, 24]. As our unit had previously reported, extremely good long-term outcomes are achievable with surgical modifications to provide adequate support of the aortic root and prevent late dilatation [1]. The burden of late pulmonary homograft failure is minimal, with freedom from reintervention at over 90% 15 years later [25]. More importantly, late PVR has no impact on late survival. This is best demonstrated in patients undergoing late PVR after Tetralogy of Fallot repair [26, 27], who are in fact a higher risk group because of their chronically impaired right ventricular function from birth. Redo pulmonary valve intervention was required in 3% of our cohort, all via surgical valve replacement. Our unit has commenced a programme for percutaneous PVR using the Melody™ Transcatheter Pulmonary Valve (Medtronic Inc., Minneapolis, MN, USA) in December 2016. None of these patients had this performed, but this is a possible strategy for all future patients requiring reintervention for their pulmonary valves.

Aortic valve repair is the alternative treatment option that has been gaining recent traction, with its potential offer of freedom from anticoagulation and valve-related complications. However, the long-term results in the BAV group are not superior to that achieved with the Ross procedure. Freedom from reoperation at 10 years is between 64% and 83%, with the predominant cause of reoperation being recurrent regurgitation secondary to cusp prolapse [28–30]. Moreover, aortic valve repair has a similar learning curve as with the Ross procedure. As such, long-term follow-up data beyond the 1st decade after repair is needed before aortic valve repair can be offered as a better treatment option. Our unit has also commenced an aortic valve repair programme, although mostly for tricuspid aortic valves. We currently reserve aortic valve repairs for BAVs to older patients with larger aortic roots, in whom a valve-sparing root replacement would be performed.

In our experience, we had a total reoperation rate of 11% over 25 years, of which only 7% was for AVR secondary to autograft failure. Valve failure usually presented early - within the first 5 years of follow-up. Our results were also confounded by the higher incidence of reoperation with the 'all-comers' approach before 1999. With the modification of our patient selection and surgical strategies in 1999, our reoperation rate has reduced to 6% (6/97). Therefore, despite the current guidelines, we believe that the Ross procedure should be considered a valid treatment option for patients with BAV and AR in centres with the necessary surgical expertise.

CONCLUSION

With a 20-year freedom from redo AVR and significant residual AR of 85%, we have demonstrated that very good results are attainable with the Ross procedure in adults with BAV presenting with pure AR. These results should serve as an important benchmark for comparison of long-term results, to determine whether there is a role for aortic valve repair in this cohort. Despite the recommendations of the current guidelines, we believe that the Ross procedure, when performed with adjunctive aortic root support in centres with surgical experience in these techniques, should be considered an acceptable treatment option in these patients.

Conflict of interest: none declared.

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B.4 Naimo PS, et al. 2017;153:654-655.

EDITORIAL COMMENTARY

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

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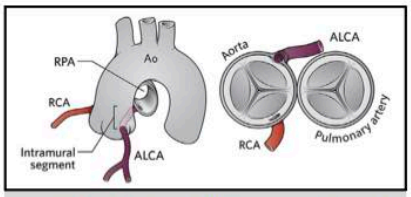

Anomalous origins of the left coronary artery from the right pulmonary artery.

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.

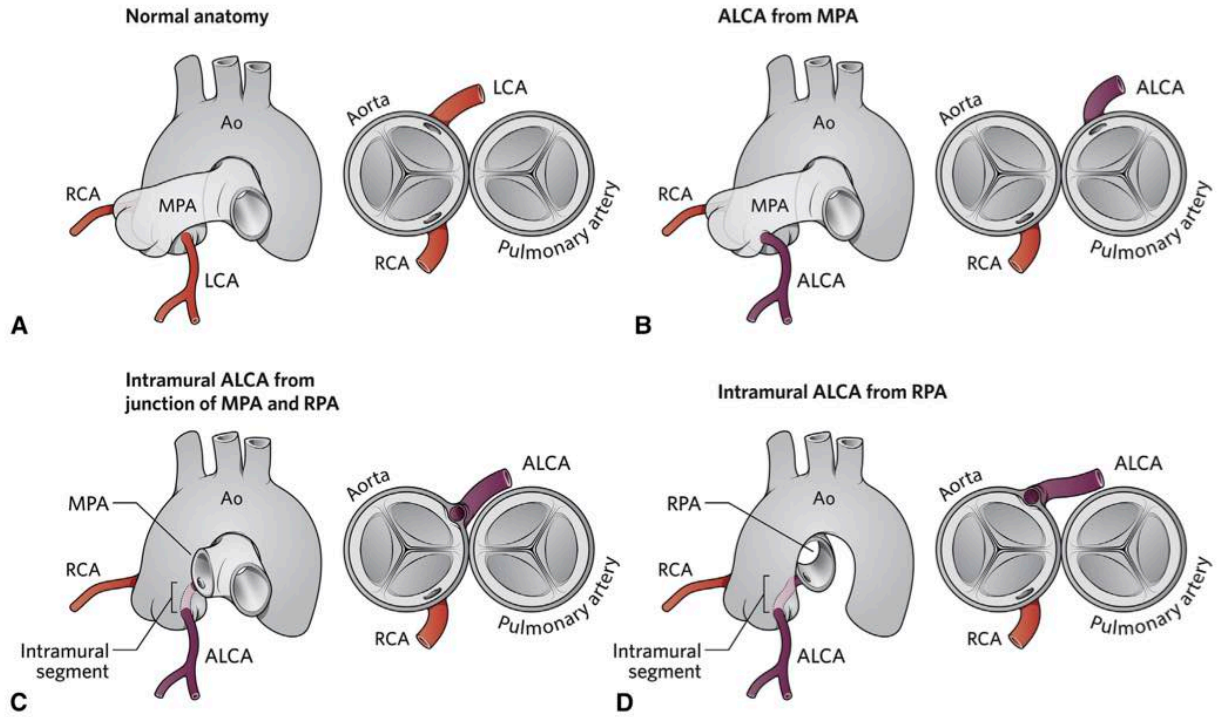

FIGURE 1. Anomalous left coronary artery origin from the pulmonary artery and its relation to normal anatomy of the great arteries. A, Normal anatomy. B, ALCA from MPA. C, Intramural ALCA from the junction of MPA and RPA. D, Intramural ALCA from RPA. *Ao*, Aorta; *RCA*, right coronary artery; *MPA*, 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 colleagues[10] 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 colleagues[10] 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 preoperative imaging. The intramural course should be suspected in all children with ALCAPA originating from the right PA[6] 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 colleagues[10] is a valuable addition to armamentarium of any cardiothoracic surgeon who deals with congenital coronary anomalies.

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B.5 Naimo PS, et al. 2016;152:211-2.

EDITORIAL COMMENTARY

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

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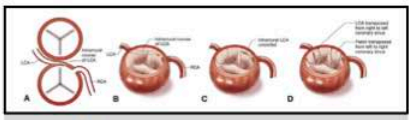

Origin of the coronary artery from the opposite sinus with an interarterial course.

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 colleagues[1] 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 prospective.

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 form 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 colleagues[1] 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

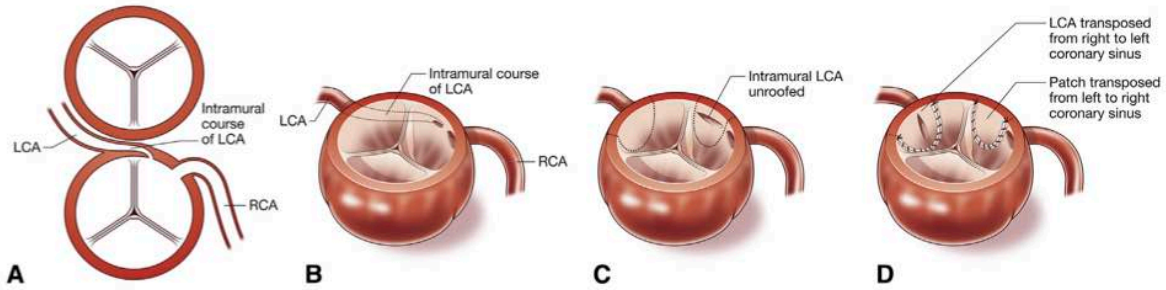

FIGURE 1. Anomalous aortic origin of the left coronary artery from the right coronary artery sinus (A and B) with a narrow origin and intramural course of the proximal interarterial portion of the coronary artery. The intramural segment of the left coronary artery is unroofed (C), and the left coronary 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 translocation[10] 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 colleagues[1] 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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