A Multi-Dimensional Outcomes Study in an Inception Cohort of Patients with Interrupted Aortic Arch

by

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Abstract

The fundamental goal of pediatric cardiac surgery is to enable patients with congenital heart disease to achieve a long and healthy life; hopefully, one comparable to that of their peers. While there is an understanding that long-term assessment is required over the course of a patient's lifetime, the manner in which the success of surgical intervention is measured in these patients should be multi-dimensional with outcomes measured in numerous domains. This thesis explores the outcomes of patients within a multi-institutional prospective inception cohort of patients with interrupted aortic arch in relation to the durability of surgical intervention, functional health status, and transition to adult care from pediatric care.

We first demonstrate that there is a persistent risk of subsequent procedures and mortality in patients after interrupted aortic arch repair. We also demonstrated that interrupted aortic arch is a chronic disease of a complex nature whereby patients often require multiple procedures after

their index repair, that the risk of aortic arch and left ventricular outflow tract procedures varies by phase (time-related), and the factors associated with both of these in addition to mortality. Our study on functional health status demonstrates that both adolescents and young adults with interrupted aortic arch primarily rated themselves the same or better than their normal peers. Our study on transition to adult care demonstrates that transition occurred in only 32% of patients by age 21, and was associated with Canadian residence. Questionnaire results also demonstrated poor levels of patient knowledge regarding their disease and strong parental involvement.

The studies presented represent the diversity of long-term outcomes that should be analyzed in order to improve patient care using a multi-dimensional approach. Future studies will focus on definitive repair techniques, ameliorating factors associated with poor functional health status, and improving transition to adult care.

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Abbreviations

IAA…….……interrupted aortic arch

22q11DS……22q11 deletion syndrome

CHD…….congenital heart disease

VSD…….ventricular septal defect

ASD……..atrial septal defect

TGA……...transposition of the great arteries

LVOT…….……...left ventricular outflow tract

CHSS……...…….Congenital Heart Surgeons' Society

FHS……..…….functional health status

CHQ-CF87……...…… Child Health Questionnaire-Child Form 87

SF-36……...……. Medical Outcomes Study Short Form-36 Health Survey version 2

U.S……..……..United States

ACHD…….…adult congenital heart disease

CACH……...……Canadian Adult Congenital Heart

Arch……...aortic arch

PCS…….…...……physical component summary

MCS…….…….mental component summary

MCID……..……minimal clinically important difference

Chapter 1

1 Introduction

1.1 Cardiac surgery and the history of interrupted aortic arch disease

Throughout time the heart has been more than just an organ within the body; it has had both spiritual and philosophical meaning for everyone from the common man, to the scholar and physician.

This importance of the heart, and its delicate irreparable nature, was echoed in numerous quotations throughout history. Aristotle (384-322 B.C.) stated "The heart alone of all the viscera cannot withstand serious injury. This is to be expected because when the main source of strength [the heart] is destroyed there is no aid that can be brought to the other organs which depend upon it"[1]. Essentially the same concept was stated by Fabricius (1537-1619), who wrote "If the heart is wounded the affair is desperate,[…]It is, therefore, unnecessary to attempt any treatment"[2]. These notions are also reflected in the statement by the French surgeon Ambrose Pare (1509-1590): "The Heart is the chiefe mansion of the Soule, the organe of the vitall faculty, the beginning of life, the fountaine of the vitall spirits, and so consequently the continuall nourisher of the vitall heate, the first living and the last dying, which because it must have a natural motion of itself, was made of the dense solide and more compact substance than any other part of the body"[3]. These sentiments reflect that the heart was believed to be the central seat of the soul, yet completely fragile throughout the majority of history, and that cardiac surgery was never anticipated as a possibility.

Even surgeons have expressed disdain, opposition and fear toward those who dared to operate on the heart. Surprisingly, as late as 1883, the renowned surgeon Theodore Billroth, widely acknowledged as the founder of modern abdominal surgery, stated that "the surgeon who should attempt to suture a wound of the heart would lose the respect of his colleagues"[4]. This sentiment was echoed in 1888 by Ferdinand Riedinger who wrote "the suggestion to suture a wound of the heart, although made in all seriousness, scarcely deserves notice"[5]. Most ironically in 1896, Stephen Paget stated in his textbook that "Surgery of the heart has reached the limit set by nature to all surgery; no new discovery can overcome the natural difficulties that attend a wound of the heart"[6]. This was the same year that Ludwig Rehn had the first reported success of repairing a stab wound in the heart of a 22 year old man. Thus was born the field of cardiac surgery, and its continued growth occurred with the advent of anesthesia, the development of cardiopulmonary bypass, the use of tissue and artificial grafts, the synthetic valve, and cardiac catheterization[7].

Congenital cardiac surgery

The anatomical dissections of Karl Freiherr von Rokitansky in the 1800's and the classification of cardiac defects of Maude Abbott in the early 1900's allowed for limited congenital cardiac surgery without the use of cardiopulmonary bypass until the 1950's[7]. In 1938, the first successful surgery for a congenital cardiac lesion was performed on 7 year old Lorraine Sweeney by Dr. Robert Gross for patent ductus arteriosus[8]. Finally, with the advent of cardiopulmonary bypass, this opened up the field of congenital cardiac surgery allowing the repair of congenital lesions that required intracardiac access, such as interrupted aortic arch (IAA) disease.

1.2 Interrupted aortic arch disease

Definition

IAA is an uncommon congenital cardiovascular malformation, wherein there is either a complete discontinuity or a nonpatent fibrous strand causing a lack of luminal continuity between the ascending and descending aortic arch.

History of interrupted aortic arch disease

IAA was first reported by Steidele in 1778, in a case where the aortic isthmus was not present[9]. In 1818, Seidel went on to describe the absence of the region between the left subclavian and the left common carotid artery[10]. In 1948, Weisman and Kesten described the absence of the region between the left common carotid artery and the innominate artery. In 1959, Celoria and Patton described the classification system we use now, which was created based on 28 cases they had amassed, and which classified IAA into three types[11].

Current classification and morphology

The classification system that we now use classifies IAA into three types based on the site of interruption: A, B, and C (Figure 1.1)[11]. Type A IAA is defined as the form where the interruption is located distal to the left subclavian artery. This form of IAA generally has a nonpatent fibrous strand of varying length (up to 3 cm) across the area of interruption[12]. Type B is the most common form of IAA, representing 60-70% of all cases, and is associated with 22q11 deletion syndrome (22q11DS)[12, 13]. In this form, the interruption is present between the left common carotid artery and the left subclavian artery. Type B IAA has 3 subtypes, based on the status of the subclavian artery: subtype B_1 occurs when there is no aberrant subclavian artery present; subtype B_2 can occur in conjunction with an aberrant right or left subclavian artery that originates from the distal descending thoracic aorta; and subtype B_3 is defined by the aberrant subclavian artery arising from the pulmonary trunk through the ductus arteriosus. Finally, the

rarest form of IAA is type C, in which the interruption is located between the innominate artery and the left common carotid artery. This type represents less than 5% of all cases[14].

Embryology

During fetal development there are up to 6 aortic arches; all of which are not present at the same time[15]. Between the 6th and 8th week of gestation, the adult arterial arrangement is present in the fetus[15]. Arches 1-3 ultimately become vessels supplying the face and skull[15]. As the 5th aortic arch is usually rudimentary and regresses, or never develops, it is the 4th and 6th arches that ultimately result in the aortic arch[15]. The left 4th aortic arch forms part of the arch, where the proximal part (between the innominate and left common carotid) of the aortic arch develops from the aortic sac, and the distal part (between the left common carotid and left subclavian artery) comes from the left dorsal aorta[15, 16]. The distal part of the left 6th aortic arch forms the ductus arteriosus, and the segment of aortic arch between the left subclavian artery and the ductus arteriosus[15, 16]. The site of interruption varies based on which specific abnormality occurs during the development of these aortic arches, whereby segments persist or regress in a complex fashion (Figure 1.2)[15, 16].

Prevalence and natural history

The prevalence of IAA is estimated to be 0.003 per 1000 births[14, 17]. It is estimated that 1.4% of autopsy cases of congenital heart disease (CHD) and 1.3% of infants with CHD are patients with IAA. If IAA is left untreated, the median age to death ranges from 4-10 days, and the disease has a 75% mortality by 1 month[18, 19]. As patients with IAA are dependent upon having a patent ductus for lower body perfusion, death is primarily the result of closure of the ductus arteriosus and loss of systemic perfusion. Consequently, survival can be longer if the ductus arteriosus remains patent; however ultimately mortality is 90% by 1 year[20].

Associated cardiac anomalies

Other than a patent ductus arteriosus, which is necessary to sustain life by providing blood flow into the aortic arch beyond the site of interruption, IAA has many associated lesions and is commonly associated with the presence of a ventricular septal defect (VSD). IAA is also commonly associated with a spectrum of hypoplasia of left sided heart structures and atrial septal defects (ASD), in addition to anomalies such as truncus arteriosus, transposition of the great arteries (TGA), double-outlet right ventricle, and aortopulmonary window[19, 21-25]. A large concomitant VSD is present in approximately 75% of cases[25]. The VSD, often with a malaligned outlet septum that is displaced posteriorly, can create a muscular ridge known as the muscle of Moulaert (hypertrophy of the anterolateral muscle bundle on the left side of the ventricle), which may jut into the subaortic region causing left ventricular outflow tract (LVOT) obstruction[19, 25, 26]. In combination with a bicuspid or dysplastic aortic valve, a narrowed aortic annulus, and hypoplasia of the arch, this creates a physiology similar to hypoplastic left heart syndrome. Hypoplasia of the left side of the heart results from a lack of outflow from the left heart during the fetal period[12]. The aortic valve is bicuspid in 30-50% of patients. In addition, subaortic stenosis can be present at birth or develop later in life, with a high proportion occurring in type B_2 IAA[25]. Subaortic stenosis or obstruction can occur as a result of decreased flow through the left ventricular outflow tract secondary to leftward deviation of the conoventricular septum causing malalignment[19]. ASDs found in association with IAA, are usually at the fossa ovalis, at times resulting in large defects which are hemodynamically significant[25]. Lastly, anomalies of the brachiocephalic vessels are common, as described in the subtypes of type B IAA above.

Associated syndromes

DiGeorge syndrome, velocardiofacial syndrome (Shprintzen syndrome), and conotruncal anomaly face syndrome (Takao syndrome) were identified individually, but almost all cases are caused by deletions within the 22q11.2 chromosome segment, and represent the various presentations of 22q11DS (with varying severity) that occur in individual patients[27-31]. Although a patient may have 22q11DS (a specific genotype), they can have varying phenotypes, some with many associated morbidities (severe) and some with few associated morbidities (mild). The syndromes mentioned above are identified by unique clusters of phenotypic features.

Haploinsufficiency of 3 genes (TBX1, CRKL, and ERK2) on chromosome 22q11.2 cause neural crest cell and anterior heart field dysfunction, in addition to the associated anomalies of 22q11DS[31]. Approximately 80% of infants with 22q11DS have cardiovascular anomalies[31]. Almost all types of congenital heart defects have been described in the context of this deletion syndrome[31]. This deletion syndrome is most commonly associated with anomalies of the conotruncus, including tetralogy of Fallot, tetralogy of Fallot with pulmonary atresia, truncus arteriosus, and IAA. More than 25% of patients with IAA have 22q11DS[21]. The presence of DiGeorge syndrome, in which there is the absence of thymic tissue and related immunodeficiency, should be routinely assessed for, as it is a frequent associated finding in patients with IAA[14, 17, 32]. In addition to immunodeficiency, the problems associated with DiGeorge syndrome include cardiac abnormalities, abnormal facies, cleft palate, hearing deficits, and hypocalcemia/hypoparathyroidism[27]. In a 1984 publication by Van Mierop et al., DiGeorge syndrome was found to be primarily associated with type B IAA[33]. Velocardiofacial syndrome has similar findings, but is not associated with an absent thymus[30, 34-36]. Kinouchi and colleagues first described conotruncal anomaly face syndrome in 1976[37], which has even fewer requisite features characterizing the diagnosis and is described as consisting of dimorphic facial features in association with conotruncal heart defects[38].

Clinical presentation

Presentation of IAA can occur with or without prenatal diagnosis. As a result of prenatal ultrasound examinations, prenatal diagnosis has become more common than in the past. In cases where a prenatal diagnosis has been made, prostaglandin E_1 treatment can be instituted at birth to keep the ductus arteriosus open[12]. However, when a prenatal diagnosis has not been made, a diagnosis may not become evident until closure of the ductus arteriosus[12]. At this time patients can present with severe systemic acidosis secondary to tissue malperfusion, which can ultimately result in end-organ damage such as gut ischemia, liver dysfunction, kidney failure, myocardial damage, and neurological injury[12]. Tissue malperfusion occurs because when the duct closes, the flow provided from the pulmonary artery via the ductus arteriosus into the aorta beyond the site of interruption is no longer present, and the tissues beyond the interruption have a significantly decreased blood supply. In patients where the ductus arteriosus does not close immediately,

congestive heart failure may be the presenting symptom as a result of dropping pulmonary vascular resistance, leading to increasing shunting of blood from left to right across a VSD, pulmonary overcirculation, and ventricular volume and pressure overload[12, 39].

On examination, patients may have abnormal pulses based on the location of the lesion, in addition to several signs that may not always be present and are therefore not conclusive. These include differential cyanosis between upper and lower limbs, heart murmurs, electrocardiogram abnormalities, and radiographs of the chest that may demonstrate cardiomegaly and/or pulmonary edema.

Diagnosis

Echocardiography is the gold standard with regard to diagnosis of IAA prior to surgical management[12]. An alternative form of imaging is cardiac catheterization, which is only required when there are anatomic features present that require further characterization[12]. o be easily delineated during transthoracic echocardiography include the location of interruption, and presence of associated anomalies[12]. Other features that are useful in deciding upon management are the length of interruption, inner aortic diameter, LVOT dimensions, aortic valve anatomy (number of leaflets), and the presence of thymic tissue[12]. Computed tomography and magnetic resonance imaging may play a role in complex cases[12].

Treatment

Medical management

There are several strategies involved in the medical management of patients with IAA. The initial resuscitation and stabilization of patients with IAA requires reestablishing flow through the ductus arteriosus. The introduction of prostaglandin E_1 therapy in 1976 by Elliott et al. dramatically transformed the care of patients with IAA by helping to keep the ductus arteriosus open[40]. An open duct allows for the blood to be supplied to tissue beyond the area of interruption

via blood from the pulmonary circulation. Increasing systemic perfusion can be achieved by also increasing pulmonary vascular resistance, which can be accomplished by limiting oxygen administration and instituting a ventilatory strategy of hypoventilation with permissive hypercapnea[12]. It is also important to manage acidosis and maintain appropriate volume status, using inotropes if required for temporization prior to surgery[12].

History of surgical management

The first repair of this lesion was reported by Merrill in 1955, who described direct repair in a 3 year old female patient with a short interruption, and without closure of the commonly associated VSD[41]. In this case, the absent region was located between the left subclavian artery and a patent ductus arteriosus; the ductus arteriosus was consequently divided and anastomosed to the left subclavian artery[41]. Four years later, the 2 concomitant VSDs were repaired[41]. Two years later, a similar repair was reported by Mustard in a patient who was 7 months old[42]. In the early 1960s, 2 successful cases of repair were reported. Both Ruiz et al. (1961) and Blake et al. (1962) used prosthetic material to repair the aortic arch[43, 44]. This was followed in 1968 by a report of 3 infants who underwent a new repair by Sirak et al., in which the arch vessels were turned downwards to reconstruct the aortic arch[45]. The branches that were turned down and used to repair the arch were either the left subclavian artery, the left common carotid artery, or both[45]. This report included the first successful repair done in a neonate[45]. Repair in a patient who was 18 hours old was reported by Norton et al. in 1970, and repair in an 11 day old patient was published in 1976[46, 47]. Repair using a polyester graft between the pulmonary trunk and descending aorta with simultaneous pulmonary artery banding was done in another 11 day old patient by Litwin and colleagues in 1972[48]. Also in 1970, the first arch repair with concomitant VSD closure was reported by Barratt-Boyes et al., in a patient who also had total anomalous pulmonary venous connection[49]. This procedure required both a median sternotomy and a thoracotomy, and was done under deep hypothermic circulatory arrest in an 8 day old patient with an interruption distal to the left subclavian artery[49]. Through a left thoracotomy a 12 mm polyester conduit was attached to the distal end of the descending aorta, and then a median sternotomy was used to attach this to the proximal ascending aorta, while also repairing the VSD and the total anomalous pulmonary venous connection[49]. In 1973 Murphy et al. reported

complete repair in a 3 day old patient who had interruption proximal to the left subclavian artery with concomitant VSD, using a segment of basilic vein taken from the father of the patient[50]. The repair used this vein segment as a conduit between the descending and ascending aorta through a median sternotomy, with extension of the incision into the 3rd left intercostal space[50]. In 1975, Trusler et al. reported concomitant IAA and VSD repair using circulatory arrest via a median sternotomy alone, using the direct repair technique[51]. The repair used an end-to-side anastomosis of the descending aorta to the ascending and transverse aortic arch after excision of the ductal tissue, and included closure of the VSD[51]. In 1996, Asou et al. reported performing repair through a median sternotomy using continuous perfusion cardiopulmonary bypass methods[52]. The same was reported in 1997 by McElhinney et al.[53].

It should be noted that with the advent of prostaglandin E_1 in the 1970s, which allowed the immediate preoperative stabilization of these patients by preventing closure of the ductus arteriosus, the surgical care of these patients was revolutionized[54-57].

Current surgical management

The changes that have occurred in cardiac surgery, with respect to cardiopulmonary bypass and cerebral perfusion, have changed the operative techniques used to manage patients with IAA[12]. Various repair strategies are used to treat the different types of IAA. Type A IAA, without any associated intracardiac lesions, is generally treated using an extended end-to-end anastomosis, without the use of cardiopulmonary bypass[12]. The choice of repair (single versus staged) is more complex in type B IAA, type C IAA, and those forms with associated cardiac anomalies[12]. The strategy presently employed by most centres is single stage repair under profound hypothermia using a direct anastomosis without circulatory arrest, although moderate hypothermia or circulatory arrest are also sometimes used (Figure 1.3)[39, 58]. Continuous low flow perfusion via innominate artery cannulation is also often used[59]. Two other approaches include a staged repair with direct repair of the interruption and concomitant pulmonary artery banding for temporization of the VSD (through a left thoracotomy) followed by VSD closure at a later time, and a left carotid artery turn down technique with pulmonary artery banding in patients with

associated VSDs (Figure 1.4)[12, 21]. Repair through a left thoracotomy is also often employed in patients without a VSD[12]. Staged repair occurs when the arch is repaired via a left thoracotomy (with a possible concomitant pulmonary artery banding), and the VSD is closed during a subsequent operation[60]. The VSD can be closed via the right atrium or pulmonary artery based on its location[59]. Of note, adequate mobilization of the vessels is required to achieve a tension free repair, with possible ligation of the anomalous right subclavian artery if present[12]. In addition, patch augmentation of hypoplastic regions of the aorta may be considered based on individual patient anatomy[12]. LVOT obstruction can be treated with isolated subaortic resection, or in more severe cases, with complex repairs such as the Damus-Kaye-Stansel repair, or a Damus-Kaye-Stansel type anastomosis with a modified Blalock-Taussig shunt and right ventricle to pulmonary artery conduit insertion. Although initially a staged approach was thought to produce better outcomes[60-62], primary repair is now the favored approach[63-65], with selective use of staged repair[66].

Postoperative management

During the postoperative period after IAA repair, particular attention should be given to residual hemodynamic lesions, the presence of 22q11DS, and undiagnosed pathologies, which may result in the requirement for prolonged intensive care management with possible inotropic therapy[12]. While a VSD may be identified by analyzing whether there is a step up in saturation in the pulmonary arterial line (uncommon), echocardiography is the mainstay in diagnosis. Due to the fact that there may be some residual degree of LVOT obstruction, there may be significant left-to-right shunting across either a VSD or an ASD, and this must be diligently assessed in the setting of any hemodynamic compromise[25]. Cardiac catheterization post-operatively is used more judiciously, but is especially important in delineating LVOT obstruction[12]. In addition, if DiGeorge syndrome is present, particular attention needs to be given to monitoring for hypocalcemia[25].

Outcomes

Morbidity and mortality

There are multiple sources of morbidity related to the initial repair. Morbidity related to the primary or index repair is highly dependent upon the subtype and associated anomalies. Due to the extensive mobilization that needs to occur to ensure a tension free repair, damage can occur to the left recurrent laryngeal nerve resulting in vocal cord paralysis or the thoracic duct resulting in a chylothorax[12]. In addition, because of the location of the left mainstem bronchus, which is under the arch of the aorta, tension of the repair may result in compression of the bronchus, leading to airway obstruction and pulmonary atelectasis[12, 25]. Reoperation may be indicated for these consequences of aggressive or inadequate mobilization[25]. Reoperation may also be required for inadequate resection of ductal tissue[67].

There are several acute causes of death after the primary repair. Death primarily results from acute or subacute heart failure, but may also result from multi-organ failure. Another group of deaths is the result of residual aortic or LVOT obstruction. While these can occur acutely after the primary repair, these can also recur late after initial repair. Recurrence is discussed further below.

Early time-related survival

Prior to the work done by the Congenital Heart Surgeons' Society (CHSS), most early reports of mortality were based on a small number of cases, and reported mortality ranged from 20-85% at time points from 30 days to 12 years after surgery[13, 18, 50, 51, 66, 68-76]. In the experience by Sell et al. of 63 patients with IAA who underwent surgery, early mortality was 39%[13]. Sell et al. demonstrated that patients operated on more recently, during their experience, were shown to have improved survival at 2 weeks[13]. Death within two weeks of repair for neonatal single stage repair of IAA was 7%, as reported in the same manuscript[13]. Other publications also demonstrated that mortality could be 10% or less[77, 78]. An earlier work by the CHSS (n=174) on the same cohort used in this study, solved a multivariable equation for a 7 day old neonate,

which was risk-adjusted and demonstrated 30 day mortality for patients with type A IAA to be 4%, while type B IAA with concomitant VSD was higher at 11%[58].

Late time-related survival

Because many patients are critically ill shortly after birth and prior to surgery, survival from time of birth, with inclusion of the deaths that occur prior to surgery, strongly demonstrate how treatment can affect the natural history of IAA[25]. From the CHSS study, we demonstrated that 5-year survival calculated from the time of birth was predicted to be 45%, while the hazard is immediately high but declines by 1 year[58]. In comparison, survival after repair in patients with IAA with concomitant VSD repair was 63% 4 years after surgery[58]. More recent work suggests even greater improvement with survival at 5 years greater than 70%[73-75, 79]. Five-year survival after repair in type A IAA with or without left sided obstruction was 93%, while type B had an 83% survival[58]. Similarly, Oosterhof et al. demonstrated that 5-year survival in patients with uncomplicated IAA, who had repair between the years of 1993-1999, was 83%[76].

Risk factors for death

There are multiple risk factors that have been found to be associated with death. One important factor that can affect the risk of death is the location of the interruption, with type C having the greatest risk, while the difference between type A and type B is much smaller[13, 58]. Concomitant cardiac anomalies are important risk factors, with isolated VSDs and those rare cases of IAA with no concomitant lesions having the least risk[25]. Jonas et al. found that the smaller the left ventricular-aortic junction diameter, the lower the survival at 6 months after repair[58]. In addition, a complex repair, such as a left ventricular-aortic conduit, or a repair which leaves residual lesions within the LVOT also has increased the risk of death[58]. Another risk factor for death is the patient's condition just prior to surgery, with acidosis prior to surgery associated with an increased risk of death within 2 weeks of the index repair[13]. Oosterhof et al. found that independent risk factors for death prior to repair included the following: absence of a VSD, the

presence of a non-cardiac anomaly, a complex cardiac anomaly, an episode of acidosis, and earlier birth cohort[76].

A 2005 CHSS study demonstrated that subsequent arch and LVOT procedures are common after IAA repair[80]. Additionally, it was found that: 1) patients with a low birth weight, immediate presentation, type B IAA, and major associated cardiac anomalies remain at increased risk of death and initial LVOT procedures; 2) index arch repair using direct anastomosis with a non-polytetrafluoroethylene patch augmentation was associated with reduced mortality; 3) patients whose index operation included an LVOT procedure were at greater risk for death and more complex subsequent management; and 4) LVOT obstruction managed with catheter-based techniques was associated with increased recurrence rates and the need for an additional subsequent procedure[80].

1.3 Residual or recurrent lesions after the primary repair and subsequent procedures

Late morbidity is often secondary to pathology in one of two anatomic regions. The first is within the aortic arch, and the second is within the LVOT. Both can have persistent obstruction because these patients often have a spectrum of hypoplastic left heart physiology[12, 13].

In a study of 65 patients with 55 early survivors, Brown and colleagues found that 20 patients underwent 27 reoperations between 1 week and 9 years post-operatively; 15 patients had a subsequent arch procedure, 13 surgical and 2 catheter-based[21]. The 15-year actuarial freedom from subsequent arch, LVOT, or any type of procedure was 74%, 92%, and 60%, respectively[21]. They could not identify any factors associated with subsequent procedures[21]. Tlaskal and colleagues studied 50 patients undergoing IAA repair using direct arch anastomosis between 1990 and 2009[81]. Of the 40 early survivors, 17 required subsequent procedures[81]. Hussein and

colleagues studied 112 patients with IAA undergoing index repair between 1985 and 2007[82]. There were 11 early deaths, and 12 early and 19 late subsequent arch procedures[82]. An additional 16 patients had significant arch obstruction at the time of the study[82].

Aortic arch

Recurrence of aortic obstruction is a significant problem following the index repair. Gradients across the aorta can occur either at the anastomotic sites or where synthetic material, which does not have the potential for growth, has been used. For this reason, circumferential interposition grafts in particular have fallen out of favor[12]. Sell et al. reported that patients with direct arch anastomosis have up to 60% obstruction (gradient greater than 30 mmHg) within 18 months after surgery[13, 83]. Percutaneous balloon dilatation is often used to relieve residual or recurrent obstruction. In 1996, Asou et al. reported that freedom from reintervention due to gradients across the aorta was 86% at 3 years[52]. As reported by Hussein et al., there were 12 early and 19 late subsequent arch procedures, and an additional 16 patients had significant arch obstruction at the time of the study after their index repair[82]. The factors associated with subsequent arch procedure were an index repair technique other than direct anastomosis and the need for subsequent LVOT procedure[82].

Left ventricular outflow tract

Of a more complicated nature are reinterventions for LVOT obstruction. It remains unclear whether this develops after the index repair, or whether it is present from the time of birth, but only becomes apparent at some time point after the primary repair[25]. It is likely that both phenomena occur[25]. It has been argued that because the hazard function (risk) for the presence of LVOT obstruction decreases in the 5 years after the index repair, that there is some suggestion that this may be present at birth[25, 58]. Therefore, it has been suggested that LVOT bypass procedures should be left until presentation, at which time an aggressive strategy should be employed[25]. Fulton et al. reported reinterventions to be as high as 77% 3 years after the primary surgery[73].

There are several groups of patients in whom LVOT obstruction is thought to develop. In patients with certain forms of univentricular atrioventricular connections, if a LVOT obstruction gradient is defined as a gradient greater than 40 mmHg between the left ventricle and descending thoracic aorta (not including the suture line), this may present after IAA repair [25]. In addition 40% of patients with a conoventricular VSD or a VSD in the outlet of the right ventricle develop LVOT obstruction[13]. There are also a small proportion of patients with IAA and concomitant VSDs in whom the LVOT is too small in size, and as a result, arch repair with closure of the VSD leaves residual obstruction. It is important to preoperatively identify these patients with low flow across the LVOT while the ductus remains open[25]. Surgical repair in these individuals included an arch repair with a concomitant Ross-Konno or a Damus-Kaye-Stansel anastomosis, in addition to closure of the VSD with the goal of lining up the left ventricle with the aortic and pulmonary valves (not in the case of a Ross-Konno)

, and an right ventricular to pulmonary artery conduit [25]. It has been found that reoperation, while well tolerated, has not always resulted in the elimination of obstruction as defined by residual gradients. Intermediate-term survival of IAA patients who have had reoperation for LVOT obstruction, have had good survival[13].

Conclusion

Late morbidity from recurrent aortic arch and LVOT pathology is common, yet the risk factors for related reinterventions have yet to be clearly defined within the literature. Therefore, using innovative statistical techniques, the CHSS sought to assess the recurrence of subsequent procedures on patients after IAA repair and the variables associated with repeated arch and LVOT procedures.

1.4 Functional health status

Definition of functional health status

There are many interrelated definitions for the term "functional health status' (FHS) that are currently used interchangeably and without a clear definition[84-86]. Some of these terms include quality of life, health related quality of life, health status, or functional status[86, 87]. Due to the lack of an accepted meaning, Gill and Feinstein suggest that authors include a definition in their work, in addition to the concepts or dimension (also known as domains) that they are studying[86]. They found that only 11 of 75 articles studying these concepts included a definition, and that only 35 of 75 clearly delineated the domains being studied[86].

In this work, the theoretical framework for FHS was conceptualized as the amount of bother (i.e., impact) a patient experiences secondary to their health care condition with regard to any domain in their life. In other words, FHS is the impact of disease and morbidities on a patient's ability to function in various setting and roles. In comparison, the term "quality of life" defines their overall life satisfaction that is positively or negatively influenced by their perception of certain aspects of life which are important to them, including matters both related and unrelated to health.

This concept is mirrored by the definition of the term "medical outcome", has come to include the patient's perception of their well-being; something that was well expressed in 20th century medical literature[88, 89]. The definition of health as stated by the World Health Organization is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[90]. This describes two separate ideas: 1) that health has multiple facets; and 2) that health is not simply a lack of disease[91]. Consequently, children's health is conceptualized to have physical and psychosocial (emotional, behavioral, and social) dimensions, and deficits in either may affect the ability to perform important social roles[92].

Importance and relevance of measuring functional health status

The reason that we operate on children with IAA is because, without surgery, the outcome for these children is almost certainly death. Surgery offers longevity; however it does not prevent morbidity, nor does it necessarily make these children identical to their peers who have never had any health problems. In the past, outcomes in children with IAA had been measured using the traditional dimensions of morbidity and mortality. As outcomes in children with IAA have improved, survivors now have a long remaining lifespan after repair. Therefore, morbidity and mortality measurements alone are no longer adequate, and non-medical factors may now have increased significance (including 22q11DS). However, while CHD patients have a confirmed reduction in mortality, they also have increasing morbidity (arrhythmia, heart failure, etc.) with age, and thus measuring FHS has become increasingly important[93-96]. There has also been a shift in thinking, which has placed increased importance on the patients' perspective in measuring outcomes[97].

Reasons for measuring FHS include: 1) discrimination (i.e., identification of the level of morbidity in an individual or a group at a specific point in time), 2) evaluation (i.e., gauging changes over time in patients, such that may occur with treatment), and 3) prediction (i.e., prognostication of clinical outcomes in patients)[98]. Measurement offers the opportunity to reduce the impact of poor FHS, change policy, assess or determine problems, and thus ultimately improve the delivery of service to patients[99]. Measurement can also help guide the allocation of resources as it can predict outcome[100]. It can also give us a greater understanding of the disease experience, which is especially important in chronic disease, which gives us the potential to improve it through services, and intervention or the lack thereof[100].

As FHS has become an increasingly important outcome measure, we are faced with the question of "how critically ill children with IAA fare as adolescents and adults". In addition, researchers have increasingly understood the importance of assessing this directly from the patient, and have developed multiple assessment tools[101]. Despite this interest, FHS (quantitatively assessed using questionnaires) has had limited examination in IAA patients, and we are left wondering if we

have in fact helped these patients who were critically ill as children, beyond correction of their CHD.

Quantitative assessment of functional health status

FHS can be assessed using multiple methods. These include quantitative, qualitative and mixed methods. This section will focus on the use of quantitative measures to assess FHS.

Quantitative assessment primarily utilizes a questionnaire-based methodology to obtain information from patients or proxies who complete these forms. A questionnaire (or index) is a collection of items which may be divided into domains[86]. A domain is an area of focus (related to a concept or dimension) and, in the context of a questionnaire, it may consist of a single or multiple related questions (also known as items)[86]. Finally, depending on the questionnaire being used, the results are often reported as summary or domain scores that are created from the available data. This allows the data from the multiple domains and items to be presented in a format which can be easily communicated and compared[86]. Patients are also often asked to give a global impression of how they feel they are doing, which is assessed outside of the summary scores. This single question can give investigators additional information, as it reports data related to various patient preferences and values[86].

Stemming from the fact that the definition of terms related to FHS are still unclear, one issue that has resulted is that many questionnaires assess various conceptual domains using terms that have been defined differently[86]. Consequently, results vary when using different tools. It is also imperative to keep in mind the content and definitions used when choosing an assessment tool or interpreting the results, and most importantly when changing therapies and health policy[86, 102]. It should also be noted that the variability from one questionnaire to the next is often related to the use of age group specific questions.

One must also always assess the psychometric (mathematical) and clinimetric (non-mathematical) properties of a questionnaire. The primary psychometric properties that should be assessed include: 1) reliability; 2) validity; and 3) responsiveness. Reliability can be related as the precision of a tool, that is, whether it produces the same answer with every use[103]. The scores produced by any questionnaire should aim to have low associated random error when repeated measurements are made under conditions which have not changed[104]. The different types of reliability that are included within this are internal consistency and test-retest reliability (reproducibility)[105]. Validity can be defined as whether the tool measures what it is supposed to measure (i.e., accuracy)[103, 104]. The types of validity include content, construct, and criterion validity[105]. Responsiveness can be explained as the ability of an instrument to detect change, although there is still controversy about whether it should detect statistically or clinically significant change, or change due to the effect of a treatment[98, 104-109]. The primary clinimetric property that should be assessed is sensibility. Sensibility is a multi-dimensional property which encompasses the areas of: 1) purpose and framework; 2) comprehensibility; 3) replicability; 4) suitability of scale; 5) face validity; 6) content validity; and 7) ease of usage[110].

Questionnaire assessment of functional health status

Generic and disease-specific tools

Generic and disease-specific tools are very different, both with their pros and cons, and often capturing the data from both has is advantageous[111].

Generic tools provide a complete summary of the different dimensions of health[111]. The advantage of general measures is that one can use them to compare the group of interest to different populations (i.e., disease groups) or to their normal counterparts[111, 112]. They can also relate data pertaining to benefits and side effects, as the calculation used subtracts the side effects from the net benefits[111]. However, it has been suggested that generic instruments may not have adequate sensitivity to detect small differences in particular symptoms that can affect FHS[113].

Disease-specific tools aim to capture the particular symptoms and problems of an illness or its treatment (i.e., the disease-specific dimensions)[113]. In comparison to generic tools, tools that are disease-specific may not capture adverse side effects or may over-value the effect of a treatment. However, they may also be able to provide a reliable assessment of an aspect particular to a disease[111, 114]. Disease-specific tools do not allow evaluation of the outcomes that are not specific to the disease[111]. Of note, tools that are disease-specific are primarily appropriate for patients with only one chronic condition[114].

Patient and parent proxy tools

While assessment in adults is always done by the patient themselves, this is not always the case with children, as they may be too young, unwell, or have a cognitive impairment that prevents them from completing the questionnaire themselves[105]. When a patient cannot complete the tool themselves, a researcher may turn to a proxy (usually a parent or guardian) to obtain data that the patient is unable to provide for themselves[105]. While the individual completing the questionnaire may have familiarity with the patient and the medical care the patient is receiving, the proxy can only provide what they perceive to be the child's perspective[105]. There is no assurance that these data are an accurate reflection of the child's perspective, and therefore the validity and reliability of the data can be called into question[105]. While proxy views may simply be different than that of the patient, they may also be affected by the cultural and social views of the proxy, the educational level attained by the proxy, and the relationship between the patient and the proxy[115]. In addition, the report of the proxy will likely be influenced by factors such as the medical history of the patient, what they expect for the patient, their awareness of normal childhood development, whether there are other children within the household, and how aware they are of the child's development as assessed by others[115]. The report of the proxy (who may be healthy) may reflect their reservations or worries, and not be a true reflection of the patient[105]. This may be a result of the distress that proxies (who are usually parents) feel with regard to the assessment of the patient (usually their child). Large discrepancies between proxy and patient assessment have been noted in cases when the patient had an illness and was compared to a normal child, when the patient was receiving treatment when the questionnaire was completed, and when there was a long period of time between treatment and questionnaire completion[116-118].

Finally, the method used for data collection may also influence the amount of difference seen between patient and proxy questionnaires[119].

Despite the fact that patient and proxy reports may not always be equivalent, valuable information can be obtained from questionnaires completed by the proxy[120]. As young patients are often dependent on their proxy, it is important to understand the impact of the child's illness on the family, and vice versa[115]. Therefore, while both the patient and the proxy may provide important information, it is critical to determine what information is needed for the study.

Patient age

Tools created for completion by children must be appropriate for the level of development of the patient; primarily with regards to cognition and emotion, if cognitive impairment is not a concern[121]. Questions must be age-appropriate in relation to the issues and concerns children face at particular ages; otherwise, if the tool is used over a larger age range, it may not be sensitive to various age-specific problems[105]. The terminology used must also be age-appropriate[105]. In addition, children at different developmental stages may have different interpretations of the same questions, based on the expectations placed on them and based on context[105]. Age can also present a problem with regard to the proxy completion of questionnaires, whereby the same question has very different meaning based on the age of the patients (i.e., social functioning in a toddler vs. an adolescent)[105]. Consequently, different questionnaires are generally required for different age ranges[105].

Selected questionnaires

Two self-report questionnaires were selected for use in this study by the CHSS, to evaluate IAA patients. As the population of IAA patients used had not completely transitioned to adulthood (the population straddled the age of 18), both a child and an adult questionnaire were required.

As a first step in evaluating the population of patients with IAA, who had never had their FHS evaluated before, we thought it would be important to use generic measures that were highly validated within the literature to gain an overall appreciation of the current FHS of these patients. Therefore, we chose two questionnaires which have had their psychometric properties of reliability, validity, and responsiveness assessed in prior publications, as detailed below. The selection of a generic measure also allowed us to compare the results with published normative data. We decided to use the Child Health Questionnaire-Child Form 87 (CHQ-CF87) because we had previously used it in a population of patients with TGA with success, and it would also allow us to draw comparison with another group of patients with CHD. We also chose the Medical Outcomes Study Short Form-36 Health Survey version 2 (SF-36) questionnaire, which is perhaps the best known generic adult questionnaire assessing FHS. Both questionnaires also contained similar domains, although the items within each domain varied. The primary practical difference between these 2 questionnaires is that while the SF-36 only has 36 questions, the CHQ-CF87 has 87 questions, making the CHQ-CF87 less practical with regard to administration.

Child Health Questionnaire-Child Form 87

The CHQ-CF87 is a generic tool, that assesses FHS in children between the ages of 10 and 18[92]. It is a questionnaire that was developed by Landgraf, and evaluates multiple personal domains, in addition to the relationship of the patient to the family. Therefore, in addition to asking a single global question regarding current patient health in comparison to 1 year ago, it also creates scores for the following domains: 1) Global Health; 2) Physical Functioning; 3) Role/Social Limitations-Emotional; 4) Role/Social Limitations-Behavioral; 5) Role/Social Limitations-Physical; 6) (freedom from) Bodily Pain; 7) Behavior; 8) Global Behavior; 9) Mental Health; 10) Self Esteem; 11) General Health Perceptions; 12) Family Activities; and 13) Family Cohesion[92]. The definitions of these domains can be seen in Table 1.1. This questionnaire was modeled on the SF-36[121], and its completion takes approximately 25-30 minutes[122].

The CHQ-CF87 has been widely tested. From the CHQ Scoring and Interpretation Manual, it can be seen that the alpha coefficients were above the standard 0.70 for group level analysis in 9/10

domains (all except General Health) in the 3 disease populations tested (attention deficit hyperactivity disorder, cystic fibrosis, and end stage renal disease) amongst school based population[92]. The reliability estimates ranged from 0.73-0.97 in all categories (except General Health)[92]. Hosli et al. demonstrated good internal consistency of both items and scales, in addition to discriminant and concurrent validity when using the CHQ-CF87 in a Dutch adolescent population[123]. However, this study also demonstrated ceiling effects (physical functioning, role/social limitations-emotional, role/social limitations-behavioural, role/social limitations-physical)[123], and this result was mirrored in an Australian study that also demonstrated ceiling effects for the Physical Functioning and Role/Social domains[124]. Ceiling and floor effects occur when measures have distinct upper and lower limits and a large proportion of subjects have scores at one of these limits[125]. Helseth et al. demonstrated that the reliability scores based on Cronbach's α were generally acceptable for the CHQ, that again this measure may demonstrate ceiling effects, and that the alpha coefficients were high in all but Role/Social Limitations-Behavioral (however this was not demonstrated in all studies)[126, 127]. Raat et al. demonstrated that the average retest scores demonstrated better scores for 5 scales, and also displayed good discrimination between healthy children and those with 2 or more self-reported chronic illnesses[127].

Short Form-36 Health Survey version 2

The SF-36 assesses FHS in adults aged ≥ 18 years. The SF-36 was developed by Ware et al. in the 1990s, and was developed for self-administration, administration by telephone, or administration during a face to face interviews[128]. Self-administration of the questionnaire takes approximately 7-10 minutes, resulting in low respondent and administrative burden[129]. This questionnaire is likely the best known example of a health index, meaning that it is composed of multiple questions, with each group representing a domain, with a format similar to the CHQ-CF87[112]. It too can be used in virtually any group of individuals[112], and therefore some have suggested its use routinely to assess patient improvement[130]. As with the CHQ-CF87, the SF-36 asks one question regarding current health in comparison to 1 year ago. Scoring produces 2 component summary scores related to physical and mental state (each created from 4 domain scores), and 8 scores for the following multi-item domains: 1) Physical Functioning; 2) Role-

Physical; 3) (freedom from) Bodily Pain; 4) General Health; 5) Vitality; 6) Social Functioning; 7) Role-Emotional; and 8) Mental Health. The SF-36 does not include important domains related to sleep, health concerns, family, and sexual and cognitive function. In this regard, other tools, such as the Sickness Impact Profile, the complete Medical Outcomes Study, and the Health Insurance Experiment are more complete with regard to the inclusion of these concepts or dimension, but have 4 times greater respondent burden[128]. The applications of this questionnaire are broad and include: 1) the evaluation and monitoring of individuals, 2) the monitoring of populations, 3) estimating burden of illness, 4) the evaluation of treatment effects, 5) the management of disease, 6) the prediction of risk and cost-effectiveness, 7) the improvement of patient-provider relationships, and 8) providing consumers with information directly[131].

There have been multiple studies assessing the SF-36, of which some of the results are presented here. The SF-36 was created to achieve two goals of comprehensiveness: 1) to be multi-dimensional regarding the two major concepts of physical and mental health; and 2) to measure a complete selection of health states[132]. In order to accomplish this, the domains most frequently assessed in other tools were included, and multi-item domains were developed from items that were known to best recreate a validated full-length scale[132]. In one of the primary studies by McHorney et al., the validity of the SF-36 as tested using psychometric and clinimetric tests was demonstrated by the creators[132]. In addition, they have shown that while the SF-36 is a generic tool that can be used in many populations, making it subject to floor and ceiling effects, floor effects were found to be rare for this questionnaire, even in those with chronic disease[133]. Multiple studies have also demonstrated that the SF-36 is able to distinguish between multiple moderate and severe diseases, and that the internal consistency-reliability coefficients are high (0.80-0.90)[131, 132, 134-137]. A study by Garratt et al. demonstrated the internal consistency (using item-scale correlations and Cronbach's α) and validity of the tool[130]. Item-scale correlations should be >0.4, and evaluate the degree to which an item is related to the rest of its scale[130]. Cronbach's α is a measure of the correlation between items in a scale (internal consistency), and is thought to be acceptable once it is greater than 0.7[130]. The paper by Garratt et al. found the item-scale correlations to range from 0.55-0.78, and Cronbach's α to range from 0.80-0.92[130]. Validity in this paper was assessed using confirmatory factor analysis for psychometric validation, in addition to the comparison of 4 health conditions to assess construct validity[130].

Confirmatory factor analysis evaluates the degree of agreement between hypothetical factors that form the measure and the scales created to assess those factors[130]. An eigenvalue of >1.1 is considered to demonstrate that a factor is relevant, and in this study the eigenvalues ranged from 1.3-12.8[130]. A review of the SF-36 detailed the multiple studies that demonstrated strong validity for the SF-36 in groups with different demographic and disease profiles, in addition to test-retest reliability and the reliability estimates of the summary scores[129]. This same review also detailed the validity studies done for the SF-36, which demonstrated validity in multiple disease states using statistical methods such as the area under the receiver operating characteristic curve and the Mann-Whitney U-test[129]. Finally, the SF-36 has also been validated in multiple languages[138-140].

Results of functional health status assessment in patients with congenital heart disease

FHS is poorly understood in patients with CHD. While there has been very limited assessment of FHS in patients with IAA, there have been studies in patients with other forms of CHD. Prior studies have had variable results with some showing that patients with CHD had poorer FHS[141-143], others showing no difference when compared to others[144-147], and one study even showing that patients with CHD had FHS better than normal children[148]. However, many of these studies were based on parent reported FHS, rather than the self-reported FHS of patients which has become a more recent focus in the literature[142, 144, 145, 147].

As the outcomes of children with IAA have improved, it has now become increasingly important for us to understand what kind of FHS these children will have as they transition to adulthood. The quality of this population's survival and the functional limitations they experience are unclear. Quantifying the self-reported psychosocial aspects of well-being and determining the patient-specific factors associated with scores in each domain in children with IAA are areas of importance. This should be done with an increased focus on non-medical factors, as these often play an important role in FHS.

Conclusion

FHS assessment instruments allow us to measure domains of health and assess the impact of disease on a patient's daily life. Using instruments designed for patient completion, the CHSS therefore sought to assess the late self-reported FHS of patients after IAA repair and the factors associated with it.

1.5 Transition to adult congenital heart disease care

Since the advent of cardiac surgery, there has been a growing population of patients with CHD who now survive into adulthood due to advances in medical and surgical therapy. It is now estimated that approximately 85% of neonates with CHD currently survive beyond 18 years of age[149-151]. The current estimate is that there are approximately 100,000 adults with CHD in Canada, and 1,000,000 in the United States (U.S.)[152, 153]. However, despite this increase in survival, complete cure in patients with more complex CHD is rare, as they often have late complications and require further therapy for residual or recurrent lesions[154]. This has led to increased importance being placed on the transition of care for patients moving from the pediatric to adult life stage, in order to prevent them from being lost to follow-up. Transition is defined as the "purposeful and planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented health care systems"[155]. Up to 70% of patients are lost to follow-up or have lapses in their care when they leave pediatric cardiology[156, 157]. Therefore, transition to adult care is an area requiring more investigation in order to improve the rates of transition.

Current guidelines

Current guidelines vary in their recommendations regarding the follow-up of patients with CHD. Some recommend that just over half of adult congenital heart disease (ACHD) patients should be seen every 12 to 24 months due to the possibility of further complications (2001)[152, 158-161].

However, simple lesions with little residua can undergo follow-up every 3-5 years, and those with the most complex lesions, every 6-12 months[158]. The guidelines by the Canadian Cardiovascular Society, attempt to detail the features of each lesion that require follow-up, and in some cases, the frequency of follow-up required after repair (2010)[162-166]. In comparison, the guidelines of the European Society of Cardiology (2010) provide detailed follow-up requirements for the majority of lesions, while the guidelines of the British Cardiac Society (2002) provide none[167, 168]. These varying recommendations need reconciliation and must also be clearly provided to patients during their care, in order to prevent patients becoming lost to follow-up.

Transition patterns from other studies

While there have been very few studies regarding transition to ACHD care in the literature, these studies have provided us with some important information. A 2002 publication of 104 patients demonstrated that referral to an adult centre was primarily made by pediatric cardiologists (53%), medical cardiologists (25%), and general practitioners (11%)[169]. This study also showed the average age at referral was 28+/- 11 years (range 16-72, median 24 years), and the time from the last cardiology visit varied greatly with a range of 1 month-25 years (median 3 years). It was noted that 29 patients had no follow-up for more than 5 years, and of these, 14 had no follow-up for more than 10 years. Six patients were referred due to complications related to their cardiac problems. Another more recent study demonstrated that only 47% of CHD patients achieved a successful transition to adult care[170]. From these studies we can see the varied referral pattern, the high proportion of patients who are lost to follow-up, and the low rates of transition previously reported. It should, however, be noted that transition patterns are highly dependent on the health care delivery systems in which they occur, and it is the structure and process of these systems that facilitate successful transition.

Parental involvement and patient knowledge

There is very little literature on the effect of parental involvement on a patient's care. While parental involvement can have a profound influence on a patient's ability to manage their care, a study by Clarizia et al. demonstrated that increased parental involvement has been found to leave children unsure of their diagnosis, and unable to communicate directly with their health care providers[171]. This study also found these parents often did not encourage independence, even in tasks that were age-appropriate[171]. This was compounded by patients' lack of knowledge regarding their own health. Similarly, Reid et al. found that attending cardiac appointments without parents or siblings also correlated with successful transition to adult care (OR: 6.59; 95% CI: 1.61-27.00)[170].

Clarizia et al. found that patients with more knowledge about their diagnosis had a better understanding about transition to adult care (100% vs. 7%, $p<0.01$), and were more likely to directly communicate with their health care providers that those patients who were less knowledgeable or had no knowledge (88% vs. 33% $p=0.03$)[171]. Adults with CHD have a low level of knowledge regarding their heart condition. In a study of 104 patients by Dore et al., the clinical diagnosis was completely unknown by 36/104 (35%) patients, only 79% had knowledge of antibiotic prophylaxis, and 66% of women have ever discussed the risks of pregnancy with their doctor[169]. Confidence was found to be improved through having knowledge about their heart condition, and gave patients the ability to manage their health care independently from their parents[171]. Reid and colleagues found that patients who had undergone more pediatric cardiac surgeries, and who had more comorbid conditions had a higher rate of transition, which one could speculate may be related to having more knowledge of their condition[170]. Scal et al. found that those patients with more complex needs were more likely to have addressed the importance of transition, which may also relate to having increased knowledge[172].

As such, preparing young patients to transition to adult care is important to successful transition[155, 173, 174], and central to this is the awareness of the roles of the patient, the parent, and the health care provider[170, 171, 173-179]. Patients must be taught about their diagnosis, management,

and general and disease-specific preventative measures[170, 174, 176]. In addition, patient skills must be built to ensure they can manage their care, and understand the importance of continued care for their disease although they may feel well. It is of prime importance that patients with CHD be informed that they need life-long follow-up and are at increased risk for complications due to residual lesions and sequelae. Increasing the structure, number, and importance of transition programs may in part help improve transition.

Health system infrastructure

One of the main issues that may be causing the lack of transition, especially in the U.S. is a lack of appropriate care facilities with ACHD trained caregivers. In countries such as Canada, the United Kingdom, the Netherlands, and Switzerland, clinics focused on care for ACHD patients have been longstanding[180]. Fifteen ACHD centres exist in Canada (Canadian Adult Congenital Heart (CACH) Network), of which 5 are multi-disciplinary centres of excellence to varying degrees, and serve a wide catchment[181]. Although there are some exceptions, most patients ≥ 18 years are required to be seen at an adult facility in Canada's government funded universal health care system. In the U.S., there is a diverse practice, and the age of transition varies greatly because of the differences in available health care coverage. It has been recommended that transition to ACHD care occur at age 18, or by the end of high school[182, 183]. Held in 2000, the goals from the 32nd Bethesda Conference were to have 30-50 regional centres of excellence across the U.S. However, no adequate plan exists to train the staff required to take care of these patients[184, 185]. More formal training programs are required to train the personnel in cardiology, sonography, and adult congenital cardiology to staff existing and future centres of ACHD care.

Conclusion

Transition to adult care is imperative to maintaining the health of patients with IAA, yet currently is not adequate. The CHSS sought to determine patterns and factors associated with the transition to adult care. To accomplish our objectives, we examined the transition to adult care of young adults with repaired IAA.

1.6 Congenital Heart Surgeons' Society Data Center

The CHSS is a group of approximately 100 pediatric cardiac surgeons, representing 65 centres. The history of the group dates back to the mid 1950s when a group of 16 surgeons met annually to discuss their early experience of operating on children with congenital heart lesions. This group was then formalized in 1985 by Dr. John Kirklin and Dr. Eugene Blackstone who proposed the creation of a society of surgeons who would pool their data on congenital cardiac surgeries, and the CHSS Data Center was born. This formalization occurred as a result of the fact that the prevalence of congenital heart lesions is low, and that the data from multiple institutions would be required if any meaningful analysis was to be done in order to make an impact when treating these children.

The CHSS Data Center does not follow all patients with congenital heart disease from each institution, but instead follows patients based on inception cohorts with lesions or procedures of interest. Cohorts are started by the members of the CHSS generally based around questions of interest in populations that often have high morbidity or mortality. In order to collect the data required for each cohort, the CHSS Data Center was established, which was initially located in Birmingham, Alabama, but was subsequently relocated to the Hospital for Sick Children in Toronto (Sick Kids Hospital) in 1997. The CHSS Data Center is a fully staffed facility where patient data are collected, entered, stored, and analyzed. In addition, annual follow-up of all living patients in each cohort is conducted by the CHSS Data Center.

Since 2001, a surgeon-in-training has been involved at the CHSS Data Center as the primary research fellow of the data housed here. This fellowship teaches data management and analysis while earning a post graduate degree from the University of Toronto. This work was completed during my time as the CHSS Data Center John W. Kirklin/David A. Ashburn research fellow (2008-2011).

1.7 Cohort

The CHSS inception cohort of patients with IAA includes 447 patients who underwent an index repair at 32 institutions in Canada (3), the U.S. (28), or Brazil (1), and who were enrolled between the years of 1987 and 1997. This is the largest multi-institutional inception cohort of patients with IAA. All patients with IAA admitted to a CHSS institution within 30 days of birth were eligible to be included. Participation by member institutions and patients was voluntary and confidential. Follow-up data has been collected on an annual basis for this cohort since inception, and includes a yearly questionnaire sent to patients regarding current physician, current medications, hospitalizations, interventions they have undergone (surgical and catheter-based), and current symptoms. The CHSS Data Center then annually collects information from the patient's hospital regarding the procedures each patient has undergone (operative reports from surgeries and catheterizations), and hospitalizations. Data was also collected in a cross-sectional fashion using questionnaires when desired to obtain more detailed data to answer specific questions (CHQ-CF87, SF-36, transition questionnaire, 22q11DS questionnaire). Numerous aspects regarding this cohort have been studied, and this has led to 5 publications prior to the studies presented in this dissertation[22-24, 58, 80].

1.8 Ethics statement

As this cohort was established in 1987, ethics approval from Sick Kids Hospital was already obtained at the start of this study, and has been renewed on an annual basis. In addition, research ethics board approval was obtained and is renewed yearly according to local requirements at each participating institution. Ethics approval was also obtained for the distribution of the questionnaires used in this study, as an amendment. Data collection and analysis for this thesis were conducted only after obtaining research ethics board approval at both Sick Kids Hospital and the University of Toronto.

1.9 Chapter previews and study questions

Preview to chapter 2 and study questions

In order to determine the outcomes of patients with IAA beyond their index procedure, we examined the procedures these patients underwent following their index repair using the same cohort that had been previously studied by the CHSS Data Center[22-24, 58, 80]. One of our primary goals was to take this cohort, which we had previously studied, and determine the risk of subsequent procedures using two novel statistical techniques, nested competing risks and modulated renewal, to answer the study questions below. Data for this project were obtained from the 32 institutions which had patients with repaired IAA within the cohort. Data were obtained from initial and annual follow-up of these patients.

Study questions

a. What is the spectrum of subsequent procedures that patients with IAA undergo after index repair?
b. What is the time-related probability of transition to mutually exclusive outcomes?
c. What is the time-related probability of repeated subsequent arch procedures, LVOT procedures, and mortality, in addition to their associated factors?

Preview to chapter 3 and study questions

The focus of this chapter is to determine the FHS of patients with IAA. As our cohort had just begun to cross the age boundary of 18 and move into adulthood, we assessed the FHS of both the adolescents and young adults in this cohort using the CHQ-CF87 (patients aged < 18 years) and the SF-36 (patients aged ≥ 18 years), in addition to using a CHSS developed questionnaire to assess 22q11DS status. This questionnaire was developed because there is a spectrum of disease, and patients may not have a genetic diagnosis. Data for this project were taken from patients from 29 institutions with repaired IAA within the cohort who returned their FHS questionnaire.

Data were obtained from initial and annual follow-up of these patients in addition to the cross-sectional FHS and 22q11DS questionnaires.

Study questions

a. What is the current FHS of patients with IAA, and how does it compare to normative data?
b. Is there a difference between adolescent (aged <18 years of age) and young adult (aged ≥ 18 years) FHS?
c. What is the proportion of patients demonstrating features related to 22q11DS status?
d. What is the association of disease and treatment on the FHS of patients with IAA? That is, what are the patient, clinical (including features related to 22q11DS status), and socioeconomic characteristics that are associated with different domains of the FHS questionnaires?

Preview to chapter 4 and study questions

In the fourth chapter, transition to adult care in patients with IAA is investigated. In those patients within our cohort ≥ 18 years of age, we requested the completion of another CHSS developed questionnaire that assessed multiple facets associated with transition to adult care, with the goal of providing answers to the study questions below. Data for this project was taken from patients from 23 institutions with repaired IAA within the cohort who returned their transition questionnaire. Data was obtained from initial and annual follow-up of these patients in addition to the cross-sectional transition and 22q11DS questionnaires.

Study questions

a. What is the proportion of young adults with IAA who have successfully transitioned from pediatric to adult care? What are the correlates of successful transfer?
b. What are the current sources of care for these patients?
c. What is the effect of country of residence (i.e., health care system) on care received?

Preview to chapter 5

In the final chapter of this dissertation, the findings presented in Chapters 1 through 4 are synthesized, and the implications are presented as a comprehensive approach to the care of patients with IAA. There is a focus on limiting the number of subsequent procedures that these patients undergo, improving their FHS, and finally increasing their transition to ACHD care. There is also discussion of the limitations of this work, and future directions for studies which can enhance the care of patients with IAA.

Tables for chapter 1

Table 1.1: Summary of concepts in the Child Health Questionnaire-Child Form 87: Definitions of low and high scores in a completed questionnaire. Reproduced with permission from The Child Health Questionnaire (CHQ) Scoring and Interpretation Manual © 2008 HealthActCHQ, Inc., Boston, MA. All rights reserved. Page 21-22[186].

Concepts	Number of items	Low score	High score
Physical Functioning	9	Child is limited a lot in performing all physical activities, including self-care, due to health.	Child performs all types of physical activities, including the most vigorous, without limitations due to health.
Role/Social-Physical	3	Child is limited a lot in schoolwork or activities with friends as a result of physical health.	Child has no limitations in schoolwork or activities with friends due to physical health.
General Health Perceptions	12	Child believes their health is poor and likely to get worse.	Child believes their health is excellent and will continue to be so.
(freedom from) Bodily Pain	2	Child has extremely severe, frequent and limiting bodily pain.	Child has no pain or limitations due to pain.
Role/Social-Emotional	3	Child is limited a lot in schoolwork or activities with friends as a result of emotional problems.	Child has no limitations in schoolwork or activities with friends due to emotional problems.
Role/Social-Behavior	3	Child is limited a lot in schoolwork or activities with friends as a result of behavior problems.	Child has no limitations in schoolwork or activities with friends due to behavior.
Self Esteem	14	Child is very dissatisfied with abilities, looks, family/peer relationships and life overall.	Child is very satisfied with abilities, looks, family/peer relationships and life overall.
Mental Health (well-being)	16	Child has feelings of anxiety and depression all of the time.	Child feels peaceful, happy and calm all of the time.
Behavior (getting along)	17	Child very often exhibits aggressive, immature, or delinquent behavior.	Child never exhibits aggressive, immature, or delinquent behavior.
Family Activities	6	The child's health very often limits and interrupts family activities or is a source of family tension.	The child's health never limits or interrupts family activities nor is a source of family tension.
Family Cohesion	1	Family's ability to get along is rated "poor".	Family's ability to get along is rated "excellent".
Change in Health	1	Child's health is much worse now than 1 year ago.	Child's health is much better now than 1 year ago.

Table 1.2: A summary of Table 7.1 'Composition and Interpretation of the Lowest and Highest Scores for the SF-36v2 Health Survey Component Summary Measures and Health Domain Scales'. Reproduced with permission from User's Manual for the SF-36v2® Health Survey (2nd ed.) © 2007, page 76, OptumInsight, Lincoln, RI[131]. SF-36v2® is a registered trademark of the Medical Outcomes Trust and is used under license. The SF-36v2® Health Survey is copyrighted © 1992, 1996, 2000, by Medical Outcomes Trust and QualityMetric Incorporated.

Scale/Measure	Number of items	Lowest possible score	Highest possible score
Physical Component Summary	All	Limitations in self-care, disabilities, or decrements in well-being; severe bodily pain; frequent tiredness; health rated *poor*	No physical limitations, disabilities, or decrements in well-being; high energy level; health rated *excellent*
Mental Component Summary	All	Frequent psychological distress; social and role disability due to emotional problems; health rated *poor*	Frequent positive affect; absence of psychological distress and limitations in usual social/role activities due to emotional problems; health rated *excellent*
Physical Functioning	10	Very limited in performing all physical activities, including bathing and dressing	Performs all types of physical activities, including the most vigorous activities, without limitations due to health
Role-Physical	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities as a result of physical health
(freedom from) Bodily Pain	2	Very severe and extremely limiting pain	No pain or limitations due to pain
General Health	5	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality	4	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
Social Functioning	2	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role-Emotional	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities as a result of emotional health
Mental Health	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time
Reported Health Transition	1	Health much worse than one year ago	Health much better than one year ago

1.10 Figures for chapter 1

Figure 1.1: Celoria and Patton classification of interrupted aortic arch. Original diagram taken from Celoria and Patton classification of interrupted aortic arch (IAA). Fig. 3. – Type A IAA with interruption distal to the left subclavian artery. Fig. 4. – Type B IAA with interruption between the left common carotid and left subclavian arteries. Fig. 5. – Type C IAA with interruption between the innominate and left common carotid arteries. Art. – artery. L. – left. R. – right. Reprinted from the American heart journal, Vol. number 58, Celoria GC and Patton RB, Congenital absence of the aortic arch, Page 409, Copyright 1959, with permission from Elsevier[11].

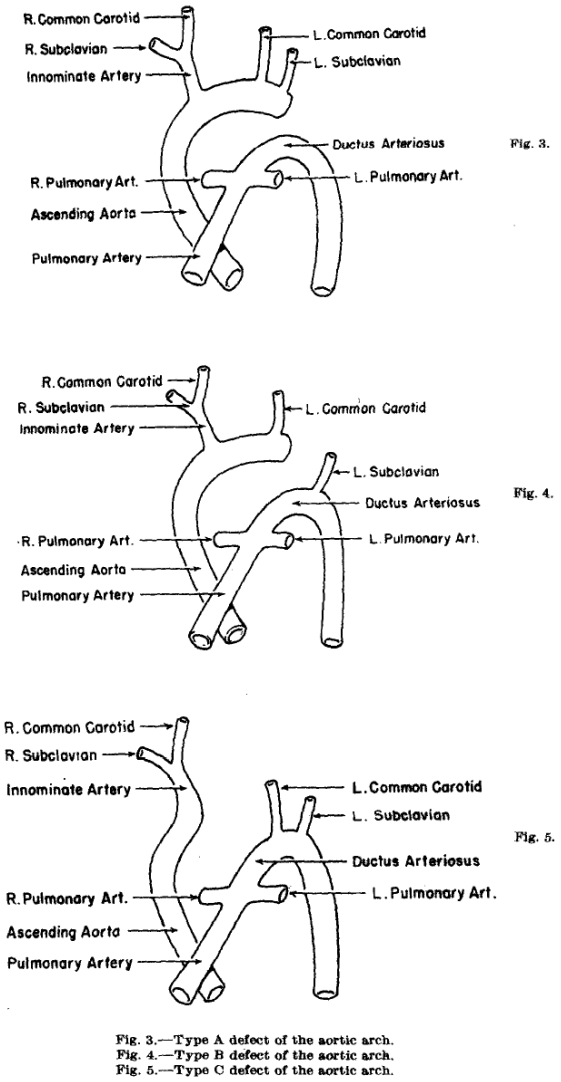


Fig. 3.—Type A defect of the aortic arch.
Fig. 4.—Type B defect of the aortic arch.
Fig. 5.—Type C defect of the aortic arch.

Figure 1.2: A schematic representation of the aorta and pulmonary artery originating from a fetal heart. The primitive aortic arches from which both are derived are shown in roman numerals. Fig. 6. – Site of a type A and type B interrupted aortic arch defect are demonstrated. Fig. 7. – Site of a type C interruption is demonstrated. Ext. – external. Int. – internal. L. – left. P.A. – pulmonary artery. R. – right. Reprinted from the American heart journal, Vol. number 58, Celoria GC and Patton RB, Congenital absence of the aortic arch, Page 411, Copyright 1959, with permission from Elsevier[11].

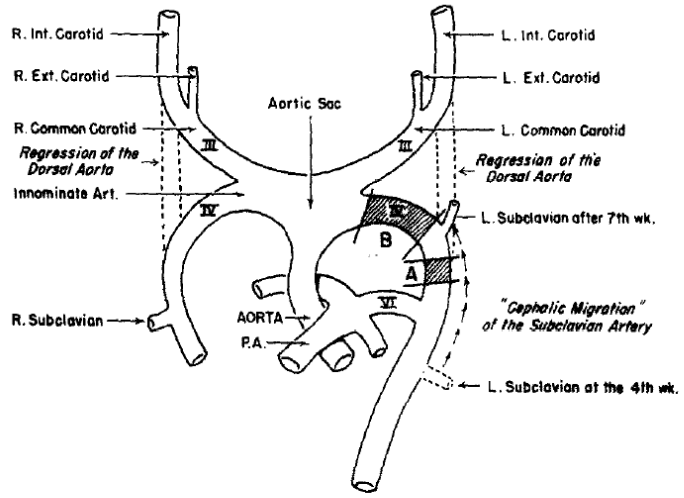


Fig. 6.

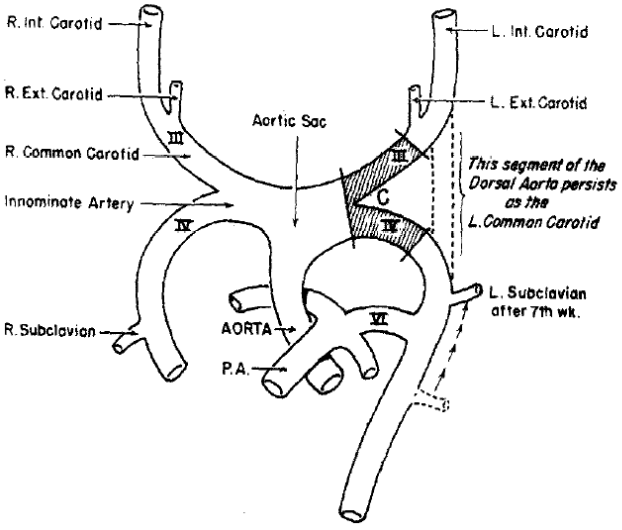


Fig. 7.

Figure 1.3: Direct repair of interrupted aortic arch. Direct end-to-end anastomotic repair before (A) and after (B) surgical correction. Dotted circle represents ventricular septal defect. Ao – aorta. LCA – left carotid artery. LSCA – left subclavian artery. PA – pulmonary artery. RCA – right carotid artery. RSCA – right subclavian artery. Content is reproduced from Brown JW et al., Outcomes in patients with interrupted aortic arch and associated anomalies: a 20-year experience, European journal of cardio-thoracic surgery, 2006, Volume 29, Issue 5, page 668, by permission of Oxford University Press[21].

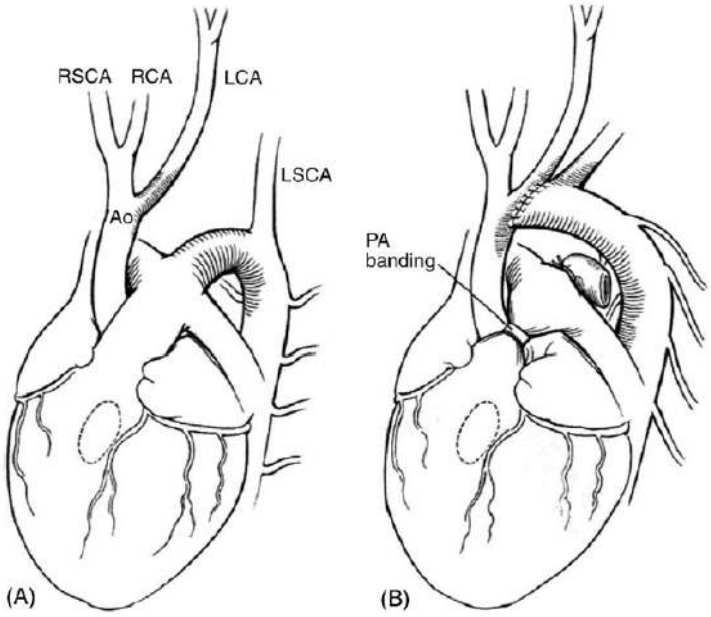
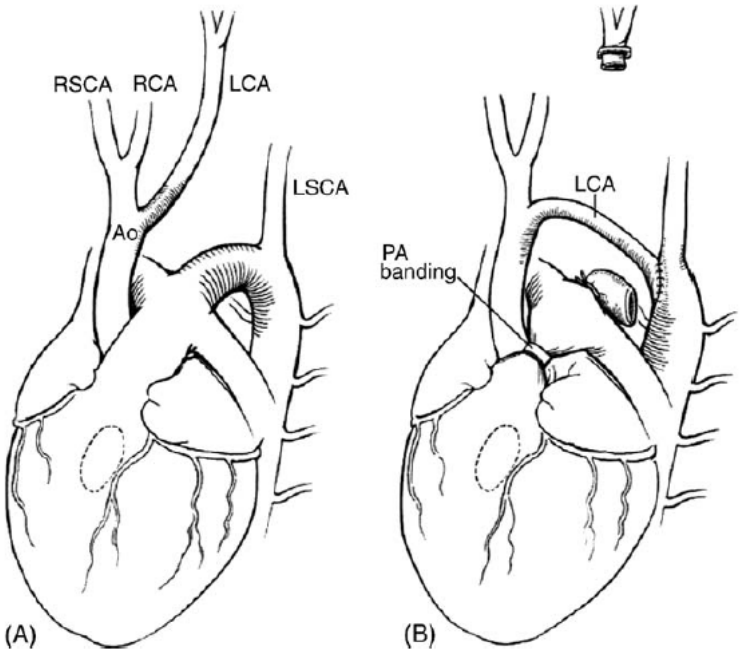


Fig. 3. Direct end-to-end anastomosis of interrupted aortic arch repair; before (A) and after (B) correction.

Figure 1.4: Left common carotid artery turn down repair of type B interrupted aortic arch. (A) Type B interrupted aortic arch. (B) The left common carotid artery is divided distally and end-to-side anastomosis is performed to the descending aorta. Dotted circle represents ventricular septal defect. Ao – aorta. LCA – left carotid artery. LSCA – left subclavian artery. PA – pulmonary artery. RCA – right carotid artery. RSCA – right subclavian artery. Content is reproduced from Brown JW et al., Outcomes in patients with interrupted aortic arch and associated anomalies: a 20-year experience, European journal of cardio-thoracic surgery, 2006, Volume 29, Issue 5, page 668, by permission of Oxford University Press[21].



Chapter 2

2 Persistent risk of subsequent procedures and mortality after interrupted aortic arch repair[187]

2.1 Abstract

Objectives: Multiple subsequent procedures directed at the arch and/or the left ventricular outflow tract, are frequently required after interrupted aortic arch repair. We investigated patterns and factors associated with these subsequent procedures and mortality.

Methods: We reviewed the data from a prospective inception cohort of patients, which included 447 patients with interrupted aortic arch at 32 institutions enrolled from 1987 to 1997. We classified the subsequent procedures by type (catheter-based or surgical) and focus (arch, left ventricular outflow tract, and ‘‘other’’ cardiovascular lesions).We used competing risks and modulated renewal analysis to explore subsequent procedures. Both of these methods allow us to mathematically define the phases after an event (acute or early, chronic or constant, and late), and then search for factors affecting these phases.

Results: There were 158 subsequent arch and 100 left ventricular outflow tract procedures. Freedom from death at 21 years was 60% overall. The risk of additional subsequent arch procedures decreased after the first subsequent arch procedure in the acute phase, but did not significantly change in the chronic phase. The risk of additional subsequent left ventricular outflow tract procedures increased after the first subsequent left ventricular outflow tract procedure in the chronic phase. The risk factors for subsequent arch procedures and mortality, but not for subsequent outflow tract procedures, were related in a complex way to previous procedures and their timing.

Conclusions: Interrupted aortic arch is a chronic disease in which patients often undergo multiple subsequent procedures with persistent risk for additional intervention and mortality. The

risk factors are related to the type of procedure and timing of previous procedures, to the morphology of the initial lesion, and details of the index procedure. Interrupted aortic arch should be considered a chronic disorder.

2.2 Background

For survivors of neonatal repair of an IAA, subsequent procedures, particularly for aortic arch (arch) or LVOT obstruction, are common and are associated with mortality. One question is whether repeated subsequent procedures on the arch or LVOT are a continuing risk after repair of IAA. Given the current excellent operative survival after the initial neonatal repair, this question emerges as one addresses the longer term morbidity and FHS of patients with this infrequently encountered anomaly. Two previous studies by the CHSS examined the outcomes of patients with IAA, but they did not address repeated or subsequent arch or LVOT procedures and their associated factors[58, 80]. This report builds on the previous 2005 CHSS report by adding 5 additional years of follow-up and adding evaluation of the time-related rates of and associated factors for subsequent arch procedures, LVOT procedures, and mortality after the index IAA repair[80].

2.3 Methods

Between January 1987 and December 1997, 472 neonates with IAA admitted within 30 days of birth were enrolled by 32 CHSS member institutions (Appendix 2.1) using a prospective inception cohort design. IAA was defined as either a complete discontinuity or a nonpatent fibrous strand in the transverse arch or aortic isthmus, as described in the operative report. The 25 patients who did not undergo arch repair after enrolment were excluded, leaving 447 patients in the study. The ‘‘index procedure’’ was defined as the initial procedure, consisting of repair of the arch discontinuity with or without simultaneous repair of the VSD, LVOT obstruction, or other cardiovascular anomalies (‘‘other’’). A ‘‘subsequent procedure’’ was defined as one that occurred after the index procedure. The characteristics of the patients and cardiac morphology are summarized in Table 2.1, A. Institutional and patient participation was voluntary and confidential. The patients provided informed consent, and approval was obtained according to

the local requirements. Ethics approval for the CHSS Data Center was obtained annually from the Research Ethics Board of the Sick Kids Hospital, Toronto, Ontario, Canada.

Data collection

The data were abstracted from copies of medical records submitted to the CHSS Data Center annually, for initial and subsequent assessments, hospitalizations, and procedures, and entered into a database by CHSS Data Center staff and member surgeons. The variables recorded have been defined and described in our previous work, and are presented in Table 2.1[80]. The most recent annual cross-sectional follow-up was performed between January and October 2008. These data were included with data from all previous annual follow-up of patients. Of the 447 patients, 169 were known to have died and 278 were presumed to be living. Follow-up was obtained from the patient and corresponding institution for 151 of the 278 presumed survivors (54%). Thus, current vital status was known for 320 of the 447 patients in the cohort (72%). It should be noted that while follow-up was only considered complete if patients returned their annual questionnaire (151). However, the most recent follow-up date possible was obtained for the remaining 127 patients who were not known to be dead (Social Security Death Master File search, home institution/relatives contacted, etc.). As such, we have some, but not current follow-up on these patients. The median follow-up was 13.5 years (range, 13 days to 21.4 years) for surviving patients.

Statistical analysis

The goals of the analysis were to describe: 1) the spectrum, frequency, and timing of subsequent arch and LVOT procedures; 2) the time-related occurrence of mutually exclusive outcomes after a first or second subsequent arch or LVOT procedure using a nested competing risks methodology; 3) the time-related probability of repeated subsequent arch and LVOT procedures using a modulated renewal methodology that incorporated or adjusted for all procedures as time-varying covariates; and 4) the factors associated with subsequent arch procedures, LVOT procedures, and mortality. Both the nested competing risks and modulated renewal methods used

multiphase parametric modeling of the hazard function, as previously described[188]. Data are expressed as the frequency, median with the range, or mean and standard deviation, with the number of missing values indicated. All analyses were performed using Statistical Analysis Systems software, version 9.2 (SAS Institute, Inc, Cary, NC). The statistical methods are described in greater detail in Appendix 2.2.

2.4 Results

Overall status after index repair

The characteristics of the index repair are described in Table 2.1, B. Of the 447 patients undergoing index IAA repair, 44 had their first LVOT procedure at the index repair. Of 447 patients undergoing index repair, 133 died with no subsequent arch or LVOT procedure (21 having undergone some ‘‘other’’ procedure), and 154 patients were alive at the most recent follow-up, with no subsequent arch or LVOT procedures. Fifty of these 154 patients had undergone an ‘‘other’’ procedure. A total of 160 patients have had one or more subsequent arch and/or LVOT procedures, with or without ‘‘other’’ procedures. Of these, 119 patients had 158 subsequent arch procedures and 69 patients had 100 subsequent LVOT procedures (not mutually exclusive). Of these 160 patients, 36 (23%) were alive. A display of cumulative risk of subsequent procedures over time is shown in Figure 2.1, illustrating not only a high risk of early procedures after index repair but also a continuing non-zero rate of subsequent procedures 1 to 2 decades after repair. The most common subsequent arch procedures were transcatheter balloon dilations and surgical patch augmentation (Appendix 2.3, A). The most common subsequent LVOT procedures were fibromuscular resection, the Konno procedure, and transcatheter balloon dilation (Appendix 2.3, B). Appendix 2.3, A-D, list the types of procedures stratified by the subsequent procedure number.

Competing risks for first and second subsequent arch procedures and death

Competing risks showed that 15 years after the index repair, 32% had died without a first subsequent arch procedure, 29% had undergone a first subsequent arch procedure, and 39% remained alive without a first subsequent arch procedure (Figure 2.2, A). Of those patients who had undergone a first subsequent arch procedure; 15 years later, 22% had died without a second subsequent arch procedure, 31% had undergone a second subsequent arch procedure, and 47%remained alive without a second subsequent arch procedure (Figure 2.2, B).

Competing risks for first and second subsequent LVOT procedures and death

Competing risks showed that 15 years after the index repair, 33% had died without a first subsequent LVOT procedure, 18% had undergone a first subsequent LVOT procedure and remained at risk, 1% had undergone a first subsequent LVOT procedure and were no longer at risk of additional procedures, and 48% remained alive without a first subsequent LVOT procedure (Figure 2.3, A). For those patients having a first subsequent LVOT procedure, 15 years later, 13% had died without a second subsequent LVOT procedure, 44% had undergone a second subsequent LVOT procedure, and 43%remained alive without a second subsequent LVOT procedure (Figure 2.3, B).

Subsequent arch procedures and their associated factors

The overall hazard function for any subsequent arch procedures showed 2 phases, an early or acute phase, accounting for 102 events, and an ongoing or chronic phase accounting for 56 events. Stratification of the overall hazard function into each subsequent arch procedure (first, second, third, and so forth) showed that the acute phase risk decreased between the first and second subsequent procedures and showed a trend for the lowest risk for the third subsequent procedure. The chronic phases showed no statistically significant change in the risk with subsequent arch procedures (Figure 2.4, A). The final multivariable model is shown in Appendix 2.4. Associations that significantly increased risk of any subsequent arch procedure in the early (‘‘acute’’) and late (‘‘chronic’’) hazard phases are listed in Table 2.2.

Subsequent LVOT procedures and their associated factors

The overall hazard function for any subsequent LVOT procedures showed 2 phases, an early or ‘‘acute’’ phase accounting for 50 events, and an ongoing or ‘‘chronic’’ phase accounting for 50 events. Stratification of the overall hazard function into each subsequent LVOT procedure (first, second, third, and so forth) showed that the early phase risk increased slightly between the first and second subsequent procedures, although the difference was not statistically significant. The ongoing or chronic phase risk of a second subsequent LVOT procedure was significantly greater than that for a first subsequent procedure (Figure 2.4, B). The final multivariable model is shown in Appendix 2.4. Associations that were significantly associated with an increased risk of subsequent LVOT procedures are listed in Table 2.2. Although the risk was increased when the immediately preceding procedure was the index procedure, the presence of an immediately preceding subsequent LVOT procedure was not a risk factor. This finding is in contrast to that for subsequent arch procedures (see above).

Mortality and its associated factors

Of the 447 patients, 169 have died. The hazard function for time-related mortality was characterized by a more prolonged early phase only, with survival at 21 years of 60% (70% confidence interval, 57%-62%) (Figure 2.5). The final multivariable model is shown in Appendix 2.4. Associations that significantly increased the risk of mortality are listed in Table 2.2.

2.5 Discussion

Previous studies

Past studies have reported widely ranging estimates of survival for patients with IAA, with more recent studies reporting improvements. These include 47% at 10 years (n = 63, dates of operation 1974-1987)[13], 85% at 12 years (n = 72, dates of operation 1985-1997)[73], 70% at 5 years (n = 82, dates of operation 1985-1995)[74], 67% at 10 years (n = 94, dates of operation 1975-1999)[75], 50% at 30 days (n = 40, dates of operation 1977-1997)[66]. Although initially a staged approach was thought to produce better outcomes[60-62], primary repair is now the favored approach[63-65], with selective use of a staged repair[66].

Our previous 2005 CHSS study demonstrated that subsequent arch and LVOT procedures are common after IAA repair[80]. Additionally, we found that 1) patients with a low birth weight, immediate presentation, type B IAA, and major associated cardiac anomalies remained at increased risk of death and initial LVOT procedures, 2) index arch repair using direct anastomosis with a non-polytetrafluroethylene patch augmentation was associated with reduced mortality, 3) patients whose index operation included an LVOT procedure were at a greater risk of death and more complex subsequent management, and 4) LVOT obstruction managed with catheter-based techniques was associated with increased recurrence rates and the need for an additional subsequent procedure[80].

Recent studies have corroborated our previous and current findings that subsequent arch and LVOT procedures are common after IAA repair. In a study of 65 patients with 55 early survivors, Brown and colleagues found that 20 patients underwent 27 reoperations between 1 week and 9 years postoperatively; 15 patients had a subsequent arch procedure, 13 surgical and 2 catheter-based[21]. The 15-year actuarial freedom from subsequent arch, LVOT, or any type of procedure was 74%, 92%, and 60%, respectively[21]. They could not identify any factors associated with subsequent procedures[21]. Hussein and colleagues studied 112 patients with IAA

undergoing the index repair between 1985 and 2007[82]. There were 11 early deaths, and 12 early and 19 late subsequent arch procedures[82]. An additional 16 patients had significant arch obstruction at the time of the study[82]. The factors associated with subsequent arch procedure were the index repair technique other than direct anastomosis and the need for subsequent LVOT procedure[82]. Tlaskal and colleagues studied 50 patients undergoing IAA repair using direct arch anastomosis between 1990 and 2009[81]. Of the 40 early survivors, 17 required subsequent procedures[81]. Mishra recently reviewed the extant published data on IAA[189]. None of these reports focused on the risk factors for subsequent procedures after the first intervention, which was the focus of the study presented in this chapter.

Present Study

The present study focused on estimating the hazard for subsequent arch and LVOT procedures (after the index procedure). In the present study (in contrast to the previous CHSS work), we added the use of a statistical technique, modulated renewal with adjustment for as time-varying covariates, to examine the inter-relationships of such procedures. In this renewal model, the baseline hazard function for a subsequent procedure was assumed to be dependent only on the time since the nearest previous procedure of its kind, modulated by other risk factors that might be dependent on the time since the index repair. The classic analogy is that of a refrigerator, which usually fails because its compressor motor fails. The risk of failure depends primarily on the interval since the most recent motor replacement (‘‘subsequent procedure’’), rather than on the interval since the original motor was installed (‘‘index procedure’’). Additionally, other characteristics of the refrigerator (‘‘anatomic factors’’) or how it is repaired (‘‘procedures’’) might contribute to the risk, some of these factors appearing between motor changes and ‘‘modulating’’ the renewal.

Principle Findings

Our first finding was that multiple procedures after index repair are common. IAA is often a chronic disorder and not a structural anomaly definitively treated by a single operation in the

newborn period. Of the 447 index procedures, the cohort experienced 158 subsequent arch procedures, 100 subsequent LVOT procedures, and 192 subsequent ‘‘other’’ procedures. Many patients underwent multiple subsequent procedures, with 2 patients each having undergone 11.

Our second finding was that although the acute risk of subsequent arch procedures decreased after each subsequent arch procedure, the chronic risk showed no significant trend. In comparison, the acute risk of subsequent LVOT procedure showed no significant trend, and the chronic risk increased after each subsequent LVOT procedure. This finding underscores the chronicity of the disorder, because the hazards show no long-term tendency to decrease. The different patterns we found between the subsequent arch and LVOT procedure hazards might reflect the differences in how the arch and LVOT respond to subsequent procedures. The arch, for example, will normally grow, except perhaps in discrete areas of recurrent stenosis. Subsequent procedures directed at the more discrete areas will generally be long lasting in the older child, and the hazard will plateau. In contrast, certain LVOT anatomic configurations have a propensity for recurrence (as in the subaortic membrane), and local resection or patching might be inadequate for long-term relief or might actually stimulate fibromuscular proliferation. In addition, LVOT obstruction might be multi-level (supravalvar, valvar, subvalvar discrete or tunnel-like), with different levels becoming significantly obstructive at different times. Such a trend has been demonstrated after a variety of operations associated with the risk of LVOT obstruction[190]. Therefore, we can conclude that with each subsequent procedure of the aortic arch we are more likely to solve the problem (in the acute phase), while we are less likely to solve LVOT problems with subsequent procedures (in the chronic phase).

Our third finding was that factors associated with subsequent arch procedure were related to previous procedures, as well as to characteristics of the anatomy and the index repair. Most of the anatomic factors and factors related to the index repair found in this study, have been found to increase risk in previous studies[189]. The present study is the first to demonstrate risk factors related to previous procedures (Table 2.2). At any time, the likelihood of a subsequent arch intervention was greatest when the most recent procedure was a catheter-based arch procedure, followed (in descending order of magnitude of risk) by a surgical arch, LVOT, and ‘‘other’’

procedure in the acute phase. These risks were also present in the chronic phase, although in somewhat different order (see Figure 2.6). This implies that, at least in the era under consideration, catheter-based arch intervention might be less durable than surgical intervention for arch obstruction. The most recent procedure being an arch procedure was also a significant risk factor for subsequent arch procedures. This might be accounted for by patients with more complicated arch problems, with increased chance of failure of a previous attempt at correction (particularly at the index procedure). This rationale is further supported because the shorter interval from the index procedure to the most recent arch procedure is also a risk factor, the shorter interval reflecting the inadequacy of repair, the limited tissue growth within that short interval, or the complexity of the arch pathology (Figure 2.6). Other factors associated with a chronic risk of subsequent arch procedure were similar to those associated with acute risk, with the addition of greater cumulative number of arch procedures. The latter risk factor, again, most likely reflects the complexity of the residual arch problem. As in the acute phase, in the chronic phase, the most recent procedure being an ‘‘other’’ procedure was a risk factor. This finding might reflect nothing more than the relative prevalence of ‘‘other’’ procedures (e.g., conduit changes or staged operations) in the chronic phase.

In contrast to subsequent arch procedures, we could not identify the risk factors for subsequent LVOT procedures that were related to previous procedures. This is perhaps due to the heterogeneous morphology of LVOT obstruction, institutional variability in the indications for reoperation, or the tendency to take a stepwise approach to potentially complex LVOT obstruction. We found anatomic and index procedural risk factors to be commensurate with those of previous studies, and the associated factors included anomalous right subclavian artery, a small or medium VSD, and the use of a polytetrafluroethylene graft to repair the arch at index repair. That patch augmentation of the arch at index repair is an association might be owing to the necessity to patch a hypoplastic arch, which, in turn, was associated (pathophysiologically or morphologically) with LVOT obstruction. The immediate preceding procedure, being the index procedure, might be a risk factor because of the relatively high prevalence of ‘‘borderline’’ LVOTs that were left unrepaired at the index operation, which then required repair as the next procedure. Only 44 patients (10%) underwent an LVOT procedure at the index repair, but 100 more LVOT procedures were subsequently performed. In contrast, LVOT repair at the index

repair might not reduce the risk of subsequent LVOT procedure. In the series by Morales and colleagues, 20 for example, 43% of patients underwent LVOT repair at the index operation, but the 5-year freedom from a subsequent LVOT procedure was only 66%.

Our fourth finding was that subsequent procedures adversely affected survival. This effect might have been due to the procedure itself or to the clinical conditions that necessitated the procedure. This is illustrated by the associations that increased the risk for death listed in Table 2.2. The procedural risk factors included a subsequent procedure that involved VSD closure, circulatory arrest, or an arch procedure done without patch augmentation. The risk factors related to the timing and interaction of the subsequent procedures included a greater cumulative number of arch or ‘‘other’’ procedures, a shorter interval between the index repair and the most recent arch or ‘‘other’’ procedure, and a longer interval between the index repair and the closest preceding LVOT procedure. Most of these risk factors have plausible explanations. Subsequent VSD closure indicates a staged approach to repair that might be associated with increased mortality. Other than excision and primary anastomosis, arch procedures done without patch augmentation might be more palliative procedures, such as left ventricular to descending aortic bypass, interposition tube graft placement, or balloon dilatation, all of which could increase the mortality hazard. The cumulative number of arch or ‘‘other’’ procedures being a risk factor is consistent with each successive arch or ‘‘other’’ procedure being associated with an early phase risk of mortality, adding to the cumulative risk. The short interval between the index repair and the closest preceding arch or ‘‘other’’ procedure, as stated previously, indicates the rapidity of recurrence and/or the severity of residual lesions, which might be the most challenging and thus associated with greater risk operations or subsequent procedures. The relationship between mortality risk and the longer interval between the index repair and the closest preceding LVOT procedure might reflect delays in operative relief of recurrent LVOT obstruction, with resulting left ventricular dysfunction and greater mortality risk. None of these risk factors related to subsequent procedures has been previously elucidated. Our ability to identify them was a result of the large cohort, the long duration of follow-up, and the use of the statistical technique of modulated renewal.

Of particular interest was that patch augmentation, as a part of the index arch repair, was not associated with improved survival, although it was in the previous CHSS analysis. Although this was found to be a salutary factor in some studies[21, 80], in other studies, direct anastomosis without a patch conferred better survival[82]. Morales and colleagues reported excellent results with direct anastomosis in a series of 60 patients, but that study did not include a comparison group (with patch augmentation)[191]. In the present study, patch augmentation of the arch at the index operation was associated with a subsequent LVOT procedure (see above), which indirectly might have indicated a greater mortality risk and thus neutralized the advantage of patch augmentation. In our view, the complex interplay of these risk factors leaves the question of the advantage of patch augmentation unanswered.

Study Limitations

The present study had several important limitations. First, because this was an observational inception study, we were unable to serially and consistently measure the morphologic characteristics (e.g., LVOT diameter) that might have helped us to explain the associations among subsequent procedures that we observed. Second, enrollment at participating institutions was voluntary, allowing for the possibility of selection bias, as we are unaware of the number of patients at any given institution who had the diagnosis (the denominator) and their baseline characteristics. Third, the enrollment period (1987-1997), although it afforded impressive long-term follow-up, represented an ‘‘early era’’ in the techniques of the index repair. Outcomes have significantly improved in the more recent era. For example, Morales and colleagues, examining a cohort undergoing repair between 1995 and 2005, reported 100% freedom from a subsequent arch procedure at 5 years[191]. In the latter study, it will be interesting to determine how the hazard for subsequent arch and LVOT procedures develops beyond a decade of follow-up. Fourth, our study focused on an analysis of subsequent procedures rather than on variables measuring the evolving pathologic features and pathophysiology (which might have helped us explain the pattern of subsequent procedures). As with the morphologic data, the latter would require a prospective study designed with the intent to measure these variables.

For a complete discussion of study limitations, please see Chapter 5 (pages 116).

2.6 Conclusions

Patients undergoing IAA repair are at persistent risk of subsequent procedures and mortality. Complex interrelationships exist among these subsequent procedures. IAA is a chronic disorder and not a structural anomaly definitively treated in the newborn period, a message that should be made clear to practitioners, patients, and their families alike.

2.7 Tables for chapter 2

Table 2.1: Patient characteristics and characteristics of index interrupted aortic arch repair. Data are presented as numbers (%) or mean±standard deviation. Part A. – Patient characteristics. Part B. – Characteristics of interrupted aortic arch repair. IAA – interrupted aortic arch. No. – Number. SD – standard deviation. VSD – ventricular septal defect.

VARIABLE	No. (Missing)	Value
A. PATIENT CHARACTERISTICS		
Demographic Characteristics		
Age at admission (days, mean ± SD)	447 (0)	4.41±5.28
Birth weight (kilograms, mean ± SD)	198 (249)	2.55±1.29
Gender (female/male)	222/225	50%/50%
Non-cardiac anomaly	155 (0)	35%
DiGeorge syndrome	81 (0)	18%
Morphologic Characteristics		
Type of IAA	446 (1)	
Type A	125	28%
Type B	318	71%
Type C	3	1%
Major associated cardiac anomalies	447 (0)	
None (with isolated VSD)	326	73%
None (with no VSD)	6	1%
Aortopulmonary window	19	4%
Complete atrioventricular septal defect	3	1%
Atrioventricular discordance	2	.4%
Double-outlet right ventricle	8	2%
Partial anomalous pulmonary venous drainage	1	.2%
Single ventricle	13	3%
Taussig-Bing	5	.1%
Transposition of the great arteries with VSD	20	4%
Truncus Arteriosus	45	10%
Bicuspid aortic valve	143 (230)	66%
Anomalous right subclavian artery	103 (42)	25%
Left superior vena cava	33 (31)	8%
Large patent ductus arteriosus	239 (174)	88%
Large VSD	308 (71)	82%
Multiple VSDs	29 (84)	8%
Malalignment of VSD	221 (0)	49%

B. CHARACTERISTICS OF INTERRUPTED AORTIC ARCH REPAIR

Demographic Characteristics		
Age at operation (days, mean ± SD)	447 (0)	9.81±19.74
Weight at index IAA repair (kilograms, mean ± SD)	361 (86)	3.18±0.86
Technique of arch repair		
Approach	447 (0)	
Median sternotomy	323	72%
Thoracotomy	122	27%
Both sternotomy and thoracotomy	2	.4%
Augmentation of aortic arch	114 (0)	26%
Type of IAA Repair	447 (0)	
Direct anastomosis with no patching	265	59%
Direct anastomosis with patching	122	27%
Interposition graft	58	13%
Main pulmonary artery-aorta bypass conduit	2	.4%
Use of graft material	447 (0)	
Polytetrafluoroethylene	57	13%
Pulmonary artery homograft	52	12%
Other	28	6%
Pericardium	23	5%
Aortic homograft	16	4%
Xenograft	4	1%
Unspecified homograft	3	1%
Subclavian artery	447 (0)	
None	385	86%
Left divided	39	9%
Right divided	23	5%
Both divided	6	1%

Table 2.2: Associations that increase risk. Arch – aortic arch. LVOT – left ventricular outflow tract. PA – pulmonary artery. PTFE – polytetrafluoroethylene. VSD – ventricular septal defect.

For subsequent arch procedures

Acute risk

Variables related to demographics and morphology

1. Diagnosis of aortopulmonary window
2. Younger age at time of index procedure

Variables related to index procedure

1. Index procedure included a concomitant LVOT procedure
2. Left subclavian artery used to repair arch in index procedure
3. VSD left open at index procedure

Variables related to subsequent procedures

1. Shorter time interval from index procedure to the most recent arch procedure
2. Longer time interval from index procedure to the most recent LVOT procedure
3. Longer time interval from index procedure to the most recent "other" procedure
4. In decreasing order of risk:
    a. Most recent procedure is a catheter-based arch procedure
    b. Most recent procedure is a surgical arch procedure
    c. Most recent procedure is an LVOT procedure
    d. Most recent procedure is an "other" procedure

Chronic risk

Variables related to demographics and morphology

1. Diagnosis of truncus arteriosus
2. Patient born earlier in the study enrollment interval

Variables related to index procedure

1. PTFE interposition graft used to repair arch during index procedure

Variables related to subsequent procedures

1. Shorter time interval from index procedure to most recent arch procedure
2. Longer time interval from index procedure to most recent LVOT procedure
3. Shorter time interval from index procedure to most recent "other" procedure
4. In decreasing order of risk:
    a. Most recent procedure is an "other" procedure
    b. Most recent procedure is an arch procedure
    c. Most recent procedure is an LVOT procedure
5. Greater cumulative number of arch procedures

For subsequent LVOT procedures

Acute risk

1. Presence of anomalous right subclavian artery
2. Pulmonary homograft used to repair arch during index procedure
3. Most recent procedure is the index procedure

Chronic risk

1. Small or medium size VSD
2. PTFE interposition graft used to repair arch during index procedure

For mortality (all acute risks)

Variables related to demographics and morphology

1. Female gender
2. Patient born earlier in the study enrollment interval
3. Diagnosis of truncus arteriosus
4. Small or medium size VSD
5. Hypoplastic left heart class greater than class I.

Variables related to index procedure

1. Lower weight at time of index procedure
2. Index repair done via sternotomy
3. PA band performed at time of index procedure
4. Systemic-to-pulmonary shunt performed at time of index procedure

Variables related to subsequent procedures

1. Subsequent procedure includes VSD closure
2. Subsequent procedure done with circulatory arrest
3. Subsequent surgical arch procedure performed without patch augmentation
4. Greater cumulative number of arch procedures
5. Greater cumulative number of “other” procedures
6. Shorter time interval from index procedure to most recent arch procedure
7. Longer time interval from index procedure to most recent LVOT procedure
8. Shorter time interval from index procedure to most recent “other” procedure

2.8 Figures for chapter 2

Figure 2.1: Cumulative hazard for subsequent procedures of any type. This graph demonstrates the cumulative number of events per patient at any given point since the index procedure. *Circles* represent any subsequent procedure (n = 436). IAA – interrupted aortic arch.

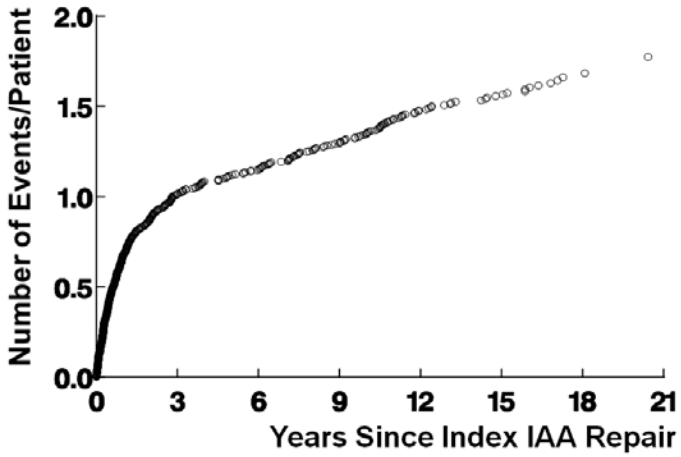


Figure 2.2: Competing risks for first and second subsequent aortic arch procedures. A, All patients started at index interrupted aortic arch repair (n = 447) and could transition to either subsequent aortic arch procedure for residual or recurrent obstruction at aortic arch repair site or death. B, All patients began at time of first subsequent aortic arch procedure (n = 119) and could transition to either subsequent aortic arch procedure for residual or recurrent obstruction at arch repair site or death. Y-axis, proportion of patients (expressed as a percentage of total) in each category at any given time. *Solid lines* represent parametric point estimates; *dashed lines* enclose 70% confidence intervals; *circles with error bars* represent nonparametric estimates. Arch – aortic arch. IAA – interrupted aortic arch. SP – subsequent procedure.

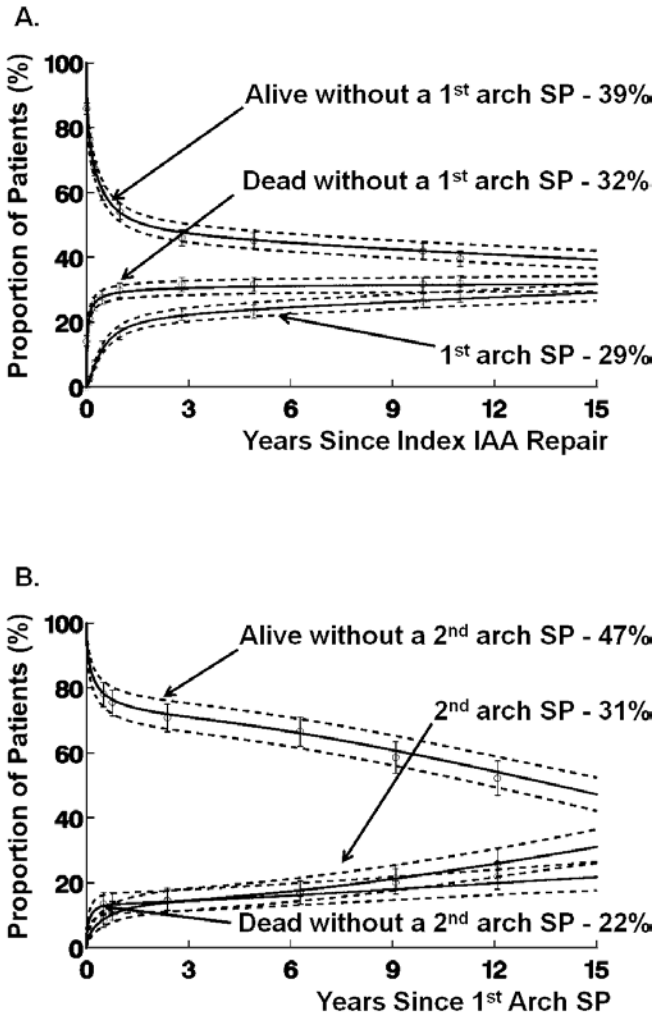


Figure 2.3: Competing risks for first and second subsequent left ventricular outflow tract procedures. A, All patients began at index interrupted aortic arch repair (n = 423) and could transition to either subsequent left ventricular outflow tract (LVOT) procedure (still at risk or no longer at risk of additional LVOT procedures) for residual or recurrent obstruction at LVOT or death. B, All patients began at time of first subsequent LVOT procedure (n = 67) and could transition to either subsequent LVOT procedure for residual or recurrent obstruction at LVOT or death. Patients considered no longer at risk of LVOT procedures underwent repairs such as the Damus-Kaye-Stansel procedure or heart transplantation and were censored at that point. Y-axis, proportion of patients (expressed as percentage of total) in each category at any given point. *Solid lines* represent parametric point estimates; *dashed lines* enclose 70% confidence intervals; *circles with error bars* represent nonparametric estimates. IAA – interrupted aortic arch. SP – subsequent procedure.

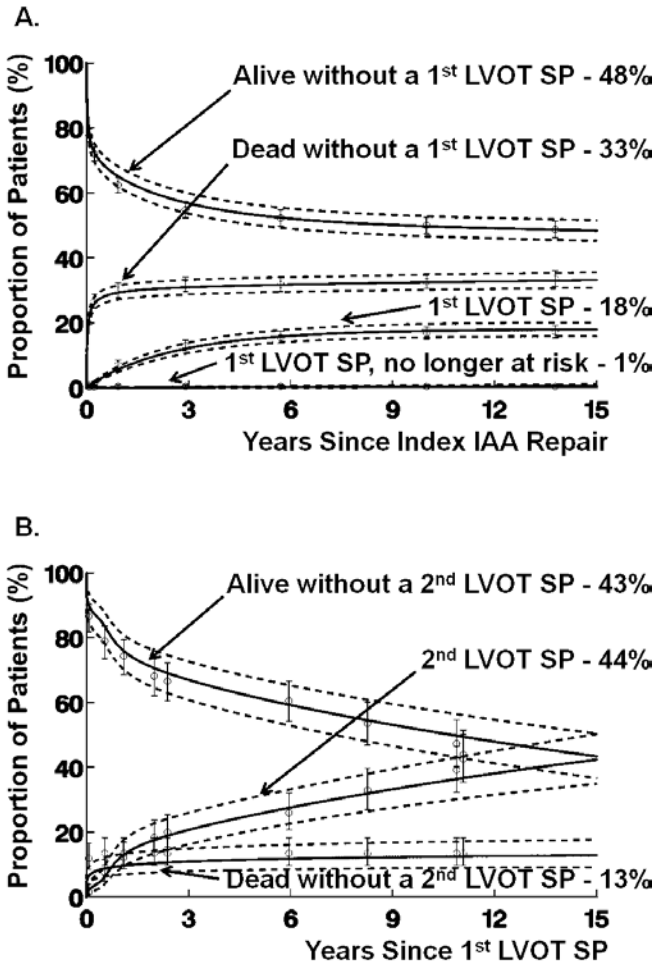


Figure 2.4: Modulated renewal for subsequent aortic arch and left ventricular outflow tract procedures. A, All patients began at previous aortic arch (arch) procedure (n = 447). B, All patients began at previous left ventricular outflow tract (LVOT) procedure (n = 423Each curve represents number of patients undergoing successive repair. Each curve was truncated at the last event. Proportion of patients at risk expressed as percentages. Number of patients alive and at risk at 5, 10, and 15 years for each renewal listed across top of graph. Patients considered no longer at risk of LVOT procedures, who underwent repairs such as Damus-Kaye-Stansel or heart transplantation, were censored at that point.). *Solid lines* represent parametric point estimates; *dashed lines* enclose 70% confidence intervals; *circles* represent events. SP – subsequent procedure.

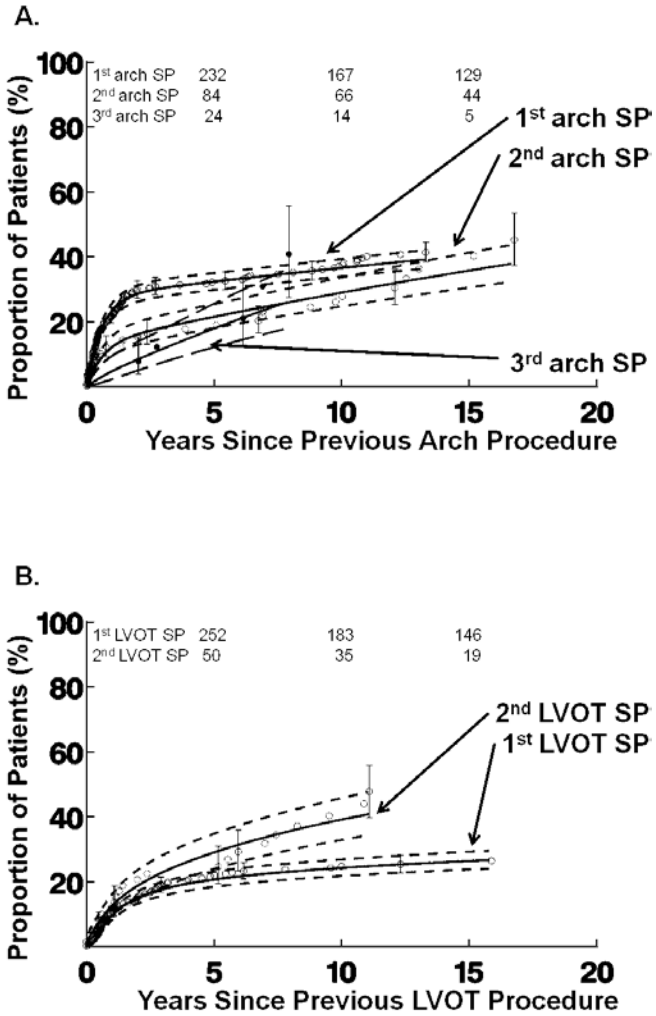


Figure 2.5: Overall time-related survival of 447 neonates since index interrupted aortic arch repair. All patients began at the time of index interrupted aortic arch (IAA) repair at a Congenital Heart Surgeons' Society member institution. The overall survival at 1, 3, 6, and 9 years was 66%, 64%, 63%, and 62%, respectively. *Solid lines* represent parametric point estimates; *dashed lines* enclose 70% confidence intervals (CI); *circles with error bars* represent nonparametric estimates.

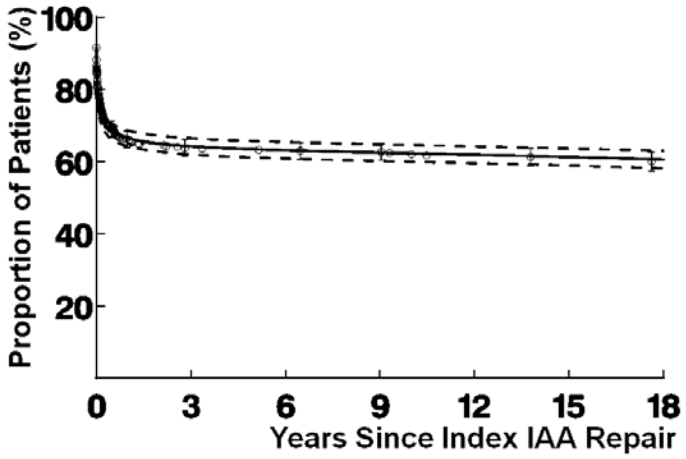
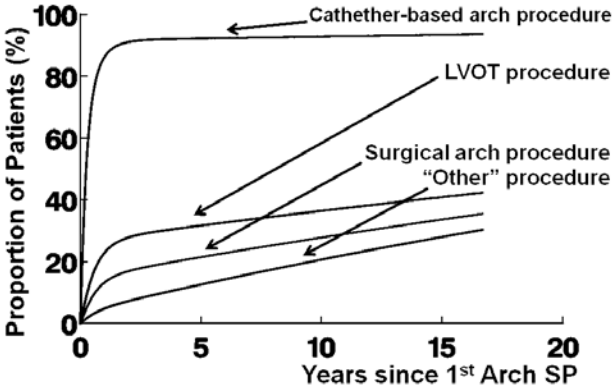
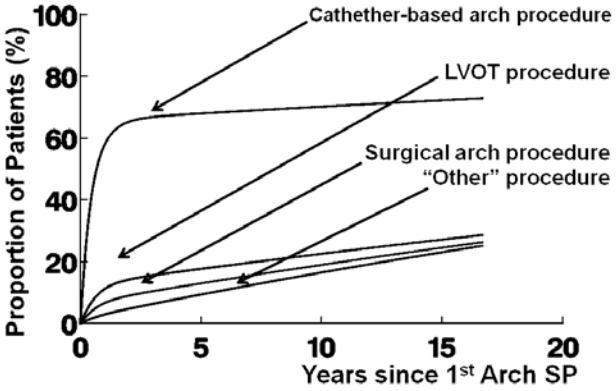


Figure 2.6: Risk of a second subsequent aortic arch procedure stratified by type of most recent procedure (catheter-based aortic arch, ‘‘other,’’ surgical aortic arch, left ventricular outflow tract procedure) and interval (1 month, 2 months, and 4 months) from the index procedure to the most recent aortic arch procedure (in this case the first subsequent aortic arch procedure) for a patient with a particular risk profile. This graph serves to illustrate ‘‘risks related to previous procedures’’ 1 and 4 (A-D), Table 2.2, for subsequent aortic arch (arch) procedure. A ‘‘typical’’ patient profile was assumed (i.e., one who had interrupted aortic arch without an additional cardiac diagnosis, a birth date near the middle of the study era, an index repair at an average age for patients in the second renewal, an index repair without concomitant left ventricular outflow tract (LVOT) resection, without the use of polytetrafluroethylene or subclavian artery for arch repair, and without concomitant ventricular septal defect closure, and 1 subsequent arch procedure). These 3 graphs demonstrate that as the interval from the index procedure to the most recent arch procedure (in this case, the first subsequent arch procedure) increases (from 1 to 2 to 4 months), the risk of a second subsequent arch procedure decreases, independent of what the most recent procedure had been. This finding is tantamount to risk 1 in Table 2.2. Furthermore, the risk of a second subsequent arch procedure is generally greatest when the most recent procedure was a catheter-based arch procedure, followed by an LVOT procedure, a surgical arch procedure, and an ‘‘other’’ procedure. This finding illustrates the complex, time dependent interrelationships among the subsequent procedures (also shown in Table 2.2). The exact order of risk of the 4 types of most recent procedures differs between Table 2 and A, B, and C because the former risks were calculated separately for the acute and chronic risk phases, and those in A, B, and C were calculated as a composite risk. *Solid lines* represent parametric point estimates. Arch – aortic arch. LVOT – left ventricular outflow tract. SP – subsequent procedure.

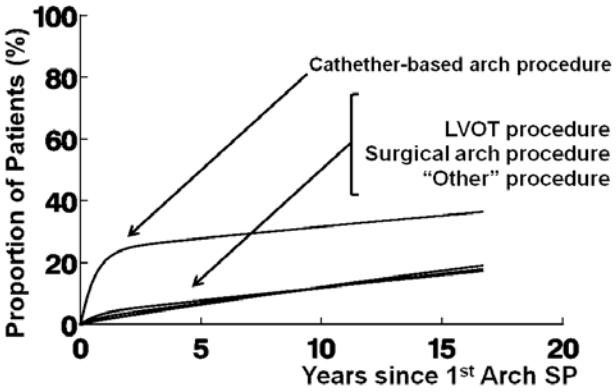
A. 1 month



B. 2 months



C. 4 months



Chapter 3

3 Factors associated with self-reported functional health status in a multi-institutional cohort of young adults with interrupted aortic arch

3.1 Abstract

Objectives: Improved survival after congenital heart surgery has increased the interest in long-term functional health status. We sought factors associated with the self-reported functional health status of adolescents and young adults with repaired interrupted aortic arch.

Methods: Follow-up of survivors (aged 13-24 years) from a 1987-1997 inception cohort of neonates with interrupted aortic arch was completed in 2010. This follow-up included completion of a functional health status questionnaire [Child Health Questionnaire-CF87 (CHQ-CF87) (age <18, n = 51) or the Medical Outcomes Study Short Form-36 (SF-36) (age >=18, n = 66)], and completion of a questionnaire regarding 22q11 deletion syndrome (22q11DS) (n = 141 survivors), as few patients had undergone genetic testing for 22q11DS due to the lack of availability at the time of their surgeries. Patient characteristics (including features potentially consistent with the presence of 22q11DS), medical history, and psychosocial factors associated with functional health status domains were determined using multivariable linear regression analyses.

Results: When reviewing the data from adolescent and young adult respondents in comparison to normative data, domain scores were significantly higher in 2/9 CHQ-CF87 and 4/10 SF-36 domains, and only lower in the SF-36 Physical Functioning domain. Factors most commonly associated with lower domain scores included: features suggestive of 22q11DS (low calcium levels, recurrent childhood infections, genetic testing/diagnosis, abnormal facial features, hearing deficits); the presence of self-reported behavioral/mental health problems; and a higher number of procedures. Lower functional health status scores were less commonly associated with

specific anatomy, higher number of medications, lower family income, lower weight and age at index repair, shorter procedure free interval, and having other medical problems. Depending on the functional health status domain, factors explained 10% to 70% of the score variability (R2=0.10-0.70, adj-R2=0.09-0.66). Of note, functional health status was minimally related to IAA morphology and repair type.

Conclusions: Morbidities potentially related to 22q11DS, psychosocial and recurrent medical problems affect functional health status in interrupted aortic arch survivors, and dominate over cardiac history (morphology and repair). Nonetheless, survivors generally perceive themselves to have higher functional health status than their peers – a seemingly paradoxical association that may reflect known phenomena (response shift, disability paradox, sense of coherence). Evaluation, surveillance, and strategies aimed at definitive surgical treatment, mental health, and genetic issues might be important program components of cardiac care in the transition from adolescence through early adulthood. Ongoing assessment of functional health status in this cohort will be required to detect deteriorations related to increasing medical complexity, variations from further interventions, and stress associated with mature adult roles and responsibilities.

3.2 Background

In the past, outcomes in children with IAA had been measured using the conventional values of morbidity and mortality. As outcomes in children with IAA have improved, survivors now have a long remaining lifespan after repair, and morbidity and mortality measurements alone are no longer adequate. Therefore, FHS has become an increasingly important outcome measure. We are faced with the question: "How do critically ill children with complex heart disease fare as adolescents and adults?". This question is reflected in the comment written in 1952 by Lembcke: The best measure of quality is not how well or how frequently a medical service is given, but how closely the result approaches the fundamental objectives of prolonging life, relieving distress, restoring function and preventing disability[88]. In addition, the definition of health as stated by the World Health Organization is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[90]. Health is conceptualized to have physical and psychosocial (emotional, behavioral, and social) dimensions, and therefore deficits in either may affect the ability to perform important social roles[92]. Finally, the term *medical outcome*, has now evolved to include the patient's perception of their well-being, a notion that was well expressed in 20th century medical literature[88, 89]. As the outcomes of children with IAA have improved, it has now become vital for us to understand what kind of FHS these children will have as they transition to adulthood.

FHS can be defined as the amount of bother a patient experiences secondary to their health care condition with regard to any domain in their life. Prior studies of FHS in patients undergoing cardiac surgery have had varied results, with some showing poorer FHS[141-143], others showing no difference[144-147], and even some showing that these patients had FHS better than normal children[148]. However, many of these studies were based on parent reported FHS, rather than self-reported FHS, which has become a more recent focus in the literature as it is based on the perceptions of the patient, and not a proxy[142, 144, 145, 147]. With an increased focus on non-medical factors that often play a significant role in FHS, we aimed to quantify the self-reported

psychosocial aspects of well-being and physical functioning, and determine the patient-specific factors associated with scores in each domain.

FHS assessment instruments allow us to measure these domains of health and assess the impact of disease on a patient's daily life. Using these instruments designed for patient completion and having noted from a prior CHSS study that these patients often undergo multiple subsequent procedures after their primary repair, the CHSS sought to assess the late self-reported FHS of patients after IAA repair and the variables associated with it[187]. The IAA cohort was chosen for study in order to allow us to evaluate the effects of multiple reinterventions, in addition to allowing us to compare this cohort to our previously evaluated TGA cohort[148].

3.3 Methods

Patients

Between January 1987 and December 1997, 472 neonates with IAA admitted to a CHSS institution within 30 days of birth were prospectively enrolled by 29 CHSS member institutions (Appendix 3.1). IAA was defined as either a complete discontinuity or a nonpatent fibrous strand in the transverse arch or aortic isthmus, as described in the operative report. The 25 patients who did not undergo arch repair after enrolment were excluded, leaving 447 patients in the study. Treatment was non-randomized and selected by the enrolling institution based on surgeon and institutional knowledge, experience, and preference. The characteristics of the patients and cardiac morphology are summarized in Table 3.1.

Data Collection and Measurements

The data were abstracted from copies of medical records submitted to the CHSS Data Center annually, for initial and subsequent assessments, hospitalizations, and procedures, and entered

into a database by CHSS Data Center staff and member surgeons. The variables recorded have been defined and described in our previous work[80]. Cross-sectional follow-up was performed between August 2009 and August 2010. Of the 447 patients, 169 were dead and 278 were alive.

A copy of the CHQ-CF87 was sent to all surviving patients < 18 years of age, and the SF-36 was sent to all surviving patients ≥ 18 years of age. All patients also received a questionnaire developed by the CHSS related to current 22q11DS status and features associated with 22q11DS. Patients were sent this short questionnaire, because most of them had never undergone genetic testing due to the lack of availability of genetic testing at the time of enrollment. If no response was received within 6 weeks of initial mailing, a reminder was sent, followed by 2 attempts to complete follow-up by telephone, in addition to reminder emails if email addresses were available.

Consent

Institutional and patient participation was voluntary. Patients provided informed consent, and approval was obtained at each participating centre according to the local institutional requirements. Ethics approval for the CHSS Data Center was obtained annually from the Research Ethics Board of the Sick Kids Hospital, Toronto, Ontario, Canada.

Child Health Questionnaire and Short Form Health Survey

The CHQ-CF87 was chosen for our study because it is an 87-item validated questionnaire that assesses self-perceived physical and psychosocial well-being of children aged 10-18 years[92]. The children in our population were age ≥ 11 years of age at follow-up. Most pediatric FHS instruments focus on parents' perception of children's disease, such as the Child Health Questionnaire Parent Form-50[192-194]. In contrast, the CHQ-CF87 focuses on an individual's subjective perception of his or her health. The CHQ-CF87 is designed for completion by the child. The CHQ-CF87 measures 13 child health domains, with each scored on a scale from 0 to

100. Higher scores indicate better self-perceived function. Published scores obtained from 278 healthy children aged 10 to 15 years from a middle school in northeast U.S. were used as normative reference[195]. Although the ethnic and gender distribution of the reference population may not be similar to our population (it is not provided), the sample size and age distribution are similar.

The SF-36 is a similar generic health survey (i.e., it is not disease-specific) which captures data regarding FHS from patients ≥ 18 years of age. As with the CHQ-CF87, higher scores indicate better self-perceived function, but for this survey scores are calibrated such that 50 is the average score or norm. The SF-36 measures 8 health domains and also provides 2 psychometrically-based scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Normative data used for comparison was taken from the User's Manual for the SF-36v2 Health Survey and matched for age[131].

22q11DS questionnaire

The 22q11DS questionnaire (see Appendix 3.2) was developed by the CHSS as a qualitative assessment tool. At the time when many patients were initially diagnosed and evaluated for IAA, genetic testing for this deletion syndrome was not widely available. As a result, because of the spectrum of varying severity, many patients may not have been diagnosed with this condition, although more than 25% of patients with IAA have been reported to have 22q11DS[21]. This tool was conceptualized to assist us in determining whether patients potentially exhibited the features of 22q11DS, despite the lack of diagnosis. This questionnaire was developed by first determining the features of 22q11DS from the literature, followed by the development of the questions with a focus on content and wording, placing the questions in a meaningful order and format, followed by testing within the CHSS Data Center with feedback, and final revision. The questionnaire assessed patients in the following domains for potential features of 22q11DS: genetic conditions, learning, behavior, mental health, hearing, health issues related to calcium or thyroid problems, and other medical problems (speech related, infections, and abnormal facial features).

Statistical Analysis

The goals of the analysis were to 1) compare the FHS of patients with IAA to normative data, 2) determine whether adolescent or adult IAA populations have more deviation from normal, 3) determine the proportion of patients demonstrating features related to 22q11DS status, and 4) determine the patient, clinical (including features related to 22q11DS status), and socioeconomic characteristics associated with different domains of the FHS questionnaires.

Data are expressed as the frequency, median with the range, or mean and standard deviation, with the number of missing values indicated. Response bias was sought by comparing categorical data for responders versus non-responders using $\chi 2$ or Fisher's exact tests, and continuous variables using the Wilcoxon two-sample test. CHQ-CF87 and SF-36 domain scores were z-scored using normative data to look at deviations from normal. FHS scores of IAA patients were compared to normative data, using single sample t-tests against a hypothesized mean. Multivariable linear regression was performed for scores on each of the CHQ-CF87 and SF-36 scales using variables listed in Table 3.1, along with data taken from the 22q11DS questionnaire. To identify the demographic, socioeconomic, lifestyle, morphologic, and procedure related factors associated with the domains of the FHS questionnaires (i.e., Physical Functioning, General Health, etc.), a bootstrap bagging algorithm (1000 samples) was used that included all potential variables associated with the outcomes, with the exception of variables with an unacceptable amount of missing data (>40% missing) or <5 events (Table 3.1). The variable 'elapsed time on bypass' (minutes) and the corresponding transformations were included in multivariable analysis although it had 43% of data missing for the CHQ-CF87 (SF36, missing=36%). We elected to include this variable as it had a borderline amount of missing data only for one questionnaire, and it was previously found to be of interest in another publication[73]. Factors selected in at least 50% of the bootstrap samples were selected for further modeling. The final multivariable model was obtained not through bootstrapping, but rather through stepwise multivariable regression modeling, with backward selection of variables to obtain the final model for each risk factor. Reliability indicates the percentage of bootstrap samples in which a given factor was selected. All regression models used a maximum likelihood algorithm to determine

parameter estimates. All analyses were performed using Statistical Analysis Systems software, version 9.2 (SAS Institute, Inc., Cary, NC).

3.4 Results

Of the 278 patients sent questionnaires, 120 were sent to patients < 18 years of age (CHQ-CF87), and 158 were sent to patients ≥ 18 years of age (SF-36). The response rate was as follows: 51/120 patients (43%) returned a CHQ-CF87 (69 non-responders) and 66/158 (42%) returned a SF-36 (92 non-responders). An additional 22 questionnaires (CHQ-CF87 and SF-36) were returned from patients with cognitive impairment, and therefore could not be included as they were primarily completed by caregivers. As a result, our study included 117/278 patients (42%) with a median age of 19.0 (range 13.2-23.7, and mean age 18.7±2.7). We also had 141/278 (51%) patients return a 22q11DS questionnaire (2 patients who completed the CHQ-CF87 and 3 who completed the SF-36, did not complete the 22q11DS questionnaire).

Comparison to non-responders

While there were not many differences between responders and non-responders for the CHQ-CF87, responders were less likely to have “other” medical problems (27% vs. 51%, p=0.01), had greater total number of surgical procedures (1.98±1.05 vs. 1.51±0.72, p=0.01) and were more likely to have redo procedures with circulatory arrest (27% vs. 10%, p=0.01). The only difference between SF-36 responders and non-responders, is that responders were younger (20±2 vs. 20±1, p=0.05). See Table 3.1 for a complete list of the variables compared, including demographic data, data at time of questionnaire completion, morphologic data, characteristics of index repair, procedural sequence and timing data, data regarding subsequent procedures, and data from 22q11DS questionnaire.

Change in health status compared to 1 year ago

One question on both the CHQ-CF87 and SF-36 questionnaires asks patients to report their change in health in comparison to one year ago, with responses ranging from much better than 1 year ago to much worse than 1 year ago. This is the only question from both questionnaires that is reported using the raw data. For both the CHQ-CF87 and the SF-36, the majority of patients report that their health is about the same now as 1 year ago (55% and 72% respectively), with more CHQ-CF87 patients doing worse in comparison to last year (36% (18/49)), and more SF-36 patients doing better (25% (16/65)) (See Table 3.2).

Comparison to normative data

The CHQ-CF87 scores of children with IAA were significantly different in 2/9 categories when compared to normative data, with a higher score in Mental Health (p=0.03) and in (freedom from) Bodily Pain (p <0.0001) (see Table 3.3). When SF-36 patients were compared to normative data, values were compared to patients aged 18-24 (although a small number of responders was >24 years of age), as we thought this was the most appropriate match. When compared to normative data, SF-36 responders were found to have higher scores in 4/10 domains; specifically the Mental Component Summary (p=0.04), (freedom from) Bodily Pain (p=0.0002), Vitality (p=0.0002), and Mental Health (p=0.01). Patient scores were only significantly lower in the Physical Functioning domain of the SF-36 (p=0.02). From this data, we can see that the only domains in which IAA patients score poorer than norms relate to physical status.

Z-scored comparisons to normative data

As both the CHQ-CF87 and SF-36 are measured on different scales with the CHQ-CF87 scored out of 100, and the SF-36 centred on a score of 50, we created Z-scores from the data using the normative values, in order to allow comparison between the adolescents and adults. When we look at the Z-scored values, we see that there are 2/9 categories in which the z-scored values with regard to the CHQ-CF87 are negative (Physical Functioning and Role/Social Limitations-

Emotional), while the remainder are positive (7/9). However, only 2 of these have significant p-values ((freedom from) Bodily Pain and Mental Health). In contrast, when we look at the SF-36, the majority of categories (6/10) have a slight trend to being below the normal values, and only 5 are significantly different with respect to p-values (with all but one of these having a positive Z-score) (See Table 3.3).

Domain associations for FHS questionnaires

Multivariable regression analyses were performed for scores on each CHQ-CF87 and SF-36 domain (Table 3.4). Although statistically significant, the percent variation in CHQ-CF87 and SF-36 domain scores explained by the factors was highly variable, with adjusted R^2 values ranging from 13-66% for the CHQ-CF87, and 9-51% for the SF-36. Of note, FHS was minimally related to IAA morphology and repair type.

CHQ-CF87 domain associations

Three main groups of variables were predominantly associated with the domains of the CHQ-CF87 (Table 3.4). The first of these groups were variables related to mental health status taken from the 22q11DS questionnaire, and in all domains (except for Global Health, (freedom from) Bodily Pain, and General Health Perceptions), either the presence of mental health counselling or having taken medications for mental health problems decreased scores. The next group of variables relate to genetic testing or the presence of a genetic condition and were also taken from the 22q11DS questionnaire. These variables also adversely affected scores and were associated with the domains of (freedom from) Bodily Pain, Behavior, Self Esteem, and Family Activities. The third group of variables was the total number of procedures ("other" or catheter-based interventional), with more procedures being associated with lower domain scores. This was found to be associated with Global Health, Role/Social Limitations-Physical, Mental Health, and Self Esteem.

Multiple other variables were found to be significantly associated with CHQ-CF87 domain scores (see Table 3.4). Of note was having a lower median neighbourhood family income (calculated in US dollars), which was adversely associated with the domains of Family Activities and Family Cohesion (i.e., this was found to be associated with lower scores). Also found to be important were several variables related to features of 22q11DS (abnormal facial features, taking calcium supplements, having low calcium levels, having had speech therapy, having abnormal hearing, and having recurrent infections).

SF-36 domain associations

When we examine the results presented in Table 3.4 with regard to the SF-36, 2 of the 3 groups of variables above were again found to be widely associated with many domains of the SF-36 questionnaire (variables related to poor mental health and higher total number of procedures). Variables related to mental health taken from the 22q11DS questionnaire were associated with 4 of the domains (freedom from Bodily Pain, Vitality, Social Functioning, and Mental Health), and the Mental Component Summary score. As with the CHQ-CF87, a higher total number of procedures (arch, left ventricular outflow tract, or procedure of any type) was again associated with poorer scores in many domains. We also found that a shorter time to the last procedure was associated with poorer domain scores for Social Functioning and the Mental Component Summary score.

Several other features taken from our 22q11DS questionnaire were also found to have association with lower scores such as having recurrent childhood infections requiring medication or admission to hospital with the General Health domain, patient having had a low calcium level with the (freedom from) Bodily Pain domain, and having had behavioral problems in school with the Role-Emotional domain.

Finally, several other variables were associated with lower scores in various domains of the SF-36. These include the association of: a lower median family income with the Physical

Functioning and Role-Physical domain; presence of uncomplicated IAA with (freedom from) Bodily Pain and Social Functioning domain; having had a lower weight at index repair with the Social Functioning domain; having a higher total number of medications with the Role-Emotional domain; and finally a younger age at questionnaire completion was adversely associated with the Mental Component Summary.

Summary of findings from 22q11DS questionnaire

Of the 278 patients who were presumed alive and were eligible to complete the questionnaire, 141 (51%) patients completed the 22q11DS questionnaire. Of the patients who completed the questionnaire, 52% (72/141) reported having undergone genetic testing. Of those who had genetic testing, 48/70 (69%) had this genetic testing to assess for a possible problem. The percentage of patients who answered the questionnaire reported having been diagnosed with a genetic condition was 36% (48/135). This is in comparison to 20% of patients (28/141) who were listed as having DiGeorge according to our database. However, many patients may not have been genetically tested secondary to the lack of testing available in the late 80s and early 90s, or may not have been clinically suspected of having the syndrome due to the wide spectrum of disease (some cases being very mild). Therefore, in the remainder of the questionnaire we attempted to determine the prevalence of associated features, regardless of a 22q11DS diagnosis, based on self-report using the 22q11DS questionnaire we developed.

In the second section of the questionnaire, we asked patients about their learning, behavior, and mental health, as patients are often known to have medical problems in these areas when 22q11DS anomalies are present. We found that 71% (99/140) of patients who responded to the questionnaire reported having difficulties with learning in school. Of those who further described their learning problem, 12% (9/75) reported issues related to concentration/attention deficit disorder/attention deficit hyperactivity disorder, and 21% (16/75) reported requiring special education. We also found that 19% (27/139) self-reported behavioral problems, and the reasons varied widely. Finally, 36% (50/140) of respondents reported having had mental health counseling for a wide variety of reasons, including mood/fear/anxiety/depression/suicide

(24%=8/33), family related issues (12%=4/33) and behavior/anger (12%=4/33). In addition, 21% (29/140) of patients reported having taken medications for mental health issues, 14% (20/140) had been diagnosed with anxiety, 6% (8/139) with depression, and 1% (2/139) had been diagnosed with schizophrenia, which has a reported association with 22q11DS.

In the third section of the questionnaire, we assessed other medical problems that are known to be associated with 22q11DS defects. The percentage of patients who reported having had their hearing tested and having abnormal results was 22% (31/139), and 4% of patients (6/135) reported the need to use hearing aids. Another commonly associated feature is low calcium levels, and 20% (27/139) of patients self-reported this, with the same number reporting having taken calcium supplements or medications to correct their calcium levels. The last two questions of this section related to thyroid problems, which were self-reported by 9% (12/137).

In the last section of the questionnaire, we assessed speech therapy, recurrent childhood infections and abnormal facies. With regard to speech therapy, this was self-reported by 63% (87/139) of patients, with 37% (19/51) of these patients undergoing speech therapy for articulation and pronunciation. It was also found that 22% (30/137) reported recurrent infections requiring medication or admission to hospital. Surprisingly, 23% (32/137) of patients reported having been told they had abnormal facial features by a doctor.

The changing denominator in the above results is due to missing responses. See Appendix 3.2 for the responses from the entire 22q11DS questionnaire.

3.5 Discussion

Summary

FHS is becoming an increasingly important measure in patients with congenital heart defects due to improvements in life expectancy over the last several decades. This study of FHS in patients with IAA demonstrates that these patients generally perceive themselves to do the same or better than their normal counterparts in multiple domains of their lives. The presence of factors related to the total number of procedures, time since last procedure, mental health, genetic testing or diagnosis, features potentially related to 22q11DS, and lower family income dominated over anatomical details, repair type, and other variables. This suggests that variables which have more immediacy to the patient have a stronger influence on patient FHS. One finding that helps to confirm this, is that shorter time since last procedure, and more procedures (which may be a surrogate for more recent procedures), are associated with poor domain scores.

Comparison to normative data

The only domain from both questionnaires where patients had significantly lower scores than their normal counterparts was Physical Functioning in the SF-36. All other domains showed no difference, or our patients had higher scores. As in other studies, our patients had higher scores in the (freedom from) Bodily Pain domain (i.e., less pain)[142, 148, 196]. These improved scores could be secondary to many factors, including the notion that these children have increased resiliency and strength after having an operation for CHD, or that having CHD gives children a different reference point with regards to their notions of function in different domains of their lives. These same findings have also been shown in children with cancer and chronic disease[197, 198].

IAA patients generally perceive themselves as having the same or higher FHS than their peers, possibly attributed to several concepts reported in the literature: the disability paradox; response shift; and sense of coherence[199, 200]. Moons et al. define good quality of life as a life which is

associated with acknowledgement of impairment, preservation of control over a body, mind and life, being able to perform expected roles, and feeling satisfied when comparing one self and one's capabilities with the conditions of others in similar situations[199]. In comparison, poor quality of life is associated with having pain, experiencing frequent or continued fatigue, and losing control over one's bodily functions[199]. The disability paradox results from a conflict in perception about these individuals with IAA. While they are often perceived by external observers to have an undesirable daily life, they feel that they experience good FHS as demonstrated by their scores. Response shift is the change in internal standards and values due to a redefinition of "good FHS"[201, 202]. It is possible that patients with IAA have developed internal values of health that are significantly different from healthy individuals, allowing their FHS scores to be the same or higher than their normal peers[199]. Finally, a sense of coherence can be defined as a gauge of an individual's view on the world, which is improved by a sense of being highly comprehensible, manageable, and meaningful[199, 203]. Patients who grow up with CHD may have learned to cope with their disease (i.e., have made it more manageable), and have an increased appreciation and meaningfulness associated with their life as they have had it threatened by an illness which required major surgery[199].

Comparison to other groups

While the FHS of the patients in this study was primarily the same or better than their normal counterparts, the results from other studies are variable when we examine patients with other congenital heart conditions, and a small subset of these results will be presented below. When FHS was evaluated in patients with TGA, the study patients were found to have significantly higher scores in all domains of the CHQ-CF87 (mean age 13±1)[148]. A recent study of patients with pulmonary atresia with intact ventricular septum conducted by the CHSS (using the CHQ-CF87, the teen report and young adult report forms of the Pediatric Quality of Life Inventory 4.0, and the Congenital Heart Adolescent and Teenager Questionnaire) similarly found that patients generally scored themselves better than age- and sex-matched controls (median age 18.6 years, range 9.1-23.7)[204]. When a group of patients with tetralogy of Fallot was evaluated using the SF-36, it was found that patients did more poorly than healthy men with regards to Physical Functioning, General Health, and the Physical Component Summary score, and that they had

higher scores than female patients with tetralogy of Fallot in (freedom from) Bodily Pain (median age 32.2, range 18.4-60.0)[205]. In comparison, another study of FHS in patients with tetralogy of Fallot using the SF-36, and providing comparison with healthy siblings, reported that patients had scores worse than their siblings for Physical Functioning, General Health, and Role-Physical, and that their SF-36 z-scores were worse than Canadian norms in the domains of Physical Functioning, General Health, and Vitality (median age 33, range 18-60)[206]. There is a large amount of variability with regard to how patients do in comparison to their healthy norms. Repeated evaluation (to ensure the reproducibility of results and determine the effect of life events on results), and further elucidation of explanatory variables is required.

Demographic and clinical factors

In our multivariable analyses, we found adjusted R^2 values that ranged from 9-66% (R^2=0.10-0.70), which indicates that in some cases a large part of the variation in different domain scores can be explained by the variables we have tested, while in other cases, this is not true. Values for the CHQ-CF87 ranged from 0.024-0.26 in a past publication by Culbert et al where each domain was evaluated for associations[148]. In a study by McCrindle et al., the R^2 for the parent reported CHQ psychosocial and physical functioning summary scores were 0.34 and 0.40 respectively[142]. In another study that examined bivariate analyses for the physical function and physical limitations domains, for the parent and child CHQ, all R^2 were found to be <0.05[207]. We could not find R^2 values for the SF-36. In most domains, we found that the variables we have tested place the scores we have reported above what is reported in past publications or toward the upper values of this previous range. However, we still have not been able to find the combination of explanatory variables allowing us to explain more variation. We would likely benefit from including other information in our dataset which we did not have, possibly related to current symptoms and exercise capacity[204, 208].

Adolescents compared to adults

Comparing the scores from the CHQ-CF87 and the SF-36 allowed us the opportunity to look at how FHS changes across the movement of patients to adulthood (i.e., with age ≥ 18).

When we compare the health status of adolescents and young adults, now versus 1 year ago, we found that while a small proportion of patients seemed to be getting worse (somewhat worse or much worse) in adolescents, in young adults a small proportion was doing better (somewhat better or much better). In both groups the majority thought their health was about the same now as 1 year ago (55% vs. 72%), and the proportion was higher in young adults. In the adolescents who completed this questionnaire (12.9-17.8 years of age) we speculate a small proportion feel that their condition is getting worse as at their age they are more aware of differences when compared to their normal peers. We speculate that more young adults who completed the questionnaire (18.0-23.2 years of age) feel they are doing better for a similar reason of increased stability as they mature into their adult roles.

We found that the results from the CHQ-CF87 show only significant differences in two domains ((freedom from) Bodily Pain and Mental Health), in both of which IAA patients score higher than their normal counterparts. In comparison, on the SF-36, IAA patients score higher in one component score (Mental Component Summary), and three domains ((freedom from) Bodily Pain, General Health, and Mental Health), with only Physical Functioning having a significantly lower score. These results may demonstrate that adult IAA patients tend to feel they are doing even better compared to their adolescent counterparts, although these results are not compared using the same questionnaire, preventing us from directly comparing results. Only with respect to Physical Functioning do young adults fare worse; however, this may be the result of multiple causes, and should therefore be the focus of future work. From the work we present in the next chapter, we can speculate that this may be a result of fewer U.S. patients transitioning to adult care, with transition at a later age. We can also hypothesize that their poorer Physical Functioning scores may be secondary to patients not being medically optimized because they have not transitioned and are not receiving appropriate care. This may also be related to a change in perception as patient's age, with patients over 18 having a different perspective than their younger counterparts with regard to normal physical functioning once they become more independent, and are able to better compare themselves to their peers.

Study limitations

There are several limitations associated with our study. The first is that our assessment of FHS is based on cross-sectional data. While we have captured the FHS of our study patients at a particular date in time, we are unable to be certain whether this is highly variable from day to day, or whether it is stable over longer periods of time.

Another limitation is that the response rate was suboptimal. Due to various logistical issues, it was hard to establish contact with a large population of patients primarily dispersed across Canada and the U.S. and this may contribute to undetected response bias. Although we are using a denominator of 278 living patients, it should be noted that 6 patients had refused participation at some time in the past, and 56 were patients whom the CHSS Data Center could not directly contact. We were reliant upon the institution to contact this last group of patients, and as a result have had none to minimal follow-up on these patients. Although we detected very few differences to non-responders when all variables were compared, non-responders may differ in other ways that may impact FHS that we were unable to capture. Also, although there were only a few differences found in the CHQ-CF87 responders (more "other" medical problems, greater total number of surgical procedures, and redo procedures with circulatory arrest), the differences found may suggest these patients were sicker in comparison to non-responders.

This cohort of patients was enrolled between the years of 1987 and 1997, and there may consequently be some component of era effects that are demonstrated through their FHS based on treatment received at that time. We did not assess era effect in this cohort due to the limited number of respondents for each questionnaire. However, as FHS is gaining importance it will be interesting to see whether patients treated in the current era will have different FHS profiles than this historic cohort, and it will be important to clarify this.

By selecting questionnaires that were generic, disease-specific measures may have been overlooked which would have been important to our assessment of FHS in this population. The

reason we nonetheless chose to do so was because both the CHQ-CF87[92, 123, 127, 209] and SF-36[130, 132-134, 137] are widely validated questionnaires and allowed comparison with normative data. A drawback of the questionnaires is that there is no established consensus on how large the difference in domain score must be in order to achieve clinical significance, as opposed to statistical significance alone. This difference in domain scores should also not be due to chance, and is known as minimal clinically important difference (MCID)[131]. While the manual for the SF-36 does provide MCIDs, many of the MCIDs have qualifications and were also created based on the assumption that the baseline score for the group being evaluated is lower than the average for the general population, which does not appear to be the case in our study[131]. No data regarding MCID values for the CHQ-CF87 could be found in the literature. It is thought that a difference is important when it is associated with changes in clinical factors, changes in events related to health (e.g. disability, loss of work, productivity at work, hospitalization, death), and a change in a patient's evaluation of their own health[131].

There are also several other limitations with regard to this study. One limitation to the study is that since the CHQ-CF87 and SF-36 questionnaires are self-report questionnaires, those patients who were so cognitively impaired that they were unable to complete the questionnaire were not reflected in the assessment. Due to a lack of data on the social, demographic, and economic characteristics of the normative populations we utilized in the comparison, there may be population differences that account for an undetermined bias in the analyses. In addition, because medical record review was the source for patient data outside of the questionnaires, the inherent limitations with regards to reliability and completeness of this method should be noted. Finally, a large number of variables were tested, which can increase the risk of spurious results associated with multiple comparisons. In order to minimize the risk of this, we only included variables that had a bootstrap or bootstrap cluster reliability greater than 50%, and which obtained significance in the final multivariable model. In order to minimize the number of variables tested and to create simplicity in explaining variables, we did not test for interactions.

For a complete discussion of study limitations, please see Chapter 5 (pages 116).

3.6 Conclusions

FHS in IAA is predominantly affected by morbidities related to 22q11DS, psychosocial issues, and recurrent medical problems, rather than cardiac history (details related to morphology and repair). IAA patients generally perceive themselves as having the same or higher FHS than their normal peers, possibly attributed to: response shift, the disability paradox, sense of coherence. Evaluation and surveillance strategies aimed at definitive surgical treatment, mental health, and genetic issues may be an important component of care in the transition from adolescence to early adulthood. FHS is dynamic and changes can be expected during the course of a lifetime. Therefore, longitudinal FHS assessment is needed to detect deteriorations related to increasing medical complexity, fluctuations related to further interventions, and stress associated with mature adult roles and responsibilities. In order to identify normal changes, and changes associated with the high risk time intervals surrounding admissions and procedures, prospective studies with repeated measurements are needed.

3.7 Tables for chapter 3

Table 3.1: Patient demographic, morphologic, and procedure related variables for responders and non-responders. Data are presented as numbers (%) or mean ± standard deviation. Note only variables with more than 5 events and < 40% missing data were included in multivariable analysis. * The variable 'elapsed time on bypass' (minutes) and the corresponding transformations were included in multivariable analysis although it had 43% of data missing for the CHQ-CF87 (SF36, missing=36%) (see explanation in Methods – Statistical analysis). CHQ-CF87 – Child Health Questionnaire-Child Form 87. IAA – interrupted aortic arch. SF-36 – Medical Outcomes Study Short Form-36 Health Survey version 2. USD – United States dollars. VSD – ventricular septal defect.

	CHQ-CF87, n = 51		CHQ-CF87 non-responders, n = 69			SF-36, n = 66		SF-36 non-responders, n = 92		
Variable	**Number (missing)**	**Value**	**Number (missing)**	**Value**	**p-value**	**Number (missing)**	**Value**	**Number (missing)**	**Value**	**p-value**
Patient demographic information										
Male	28 (0)	55%	34 (0)	49%	0.5	34 (0)	52%	53 (0)	58%	0.4
DiGeorge syndrome	9 (0)	18%	19 (0)	28%	0.2	9 (0)	14%	15 (0)	16%	0.6
Other cardiac anomalies	12 (0)	24%	13 (0)	19%	0.5	9 (0)	14%	19 (0)	21%	0.3
Other medical problems	14 (0)	27%	35 (0)	51%	0.01	22 (0)	33%	25 (0)	27%	0.4
Patient data at time of questionnaire completion										
Age (years)	51 (0)	15.6±1.5, 15.8 (12.9-17.8)	69 (0)	15.7±1.39, 15.9 (13.2-18.0)	0.9	66 (0)	19.9±1.3, 19.6 (18.0-23.2)	92 (0)	20.5±1.7, 20.3 (18.0-23.6)	0.05
Total medications being taken	51 (0)	1.0±1.3, 0.0 (0.0-5.0)	N/A	N/A	N/A	65 (1)	0.9±1.4, 0.0 (0.0-9.0)	N/A	N/A	N/A
Median neighborhood family income from last census adjusted for inflation (USD)	49 (2)	64306.2±26676.0, 58786.5 (18143.8-128666.8)	N/A	N/A	N/A	63 (3)	70319.2±27540.0, 64111.3 (16633.1-140766.4)	N/A	N/A	N/A

Patient morphologic information										
Type A IAA	19 (0)	37%	19 (0)	28%	0.3	23 (0)	35%	32 (0)	35%	1.0
Type B IAA	31 (0)	61%	50 (0)	72%	0.2	43 (0)	65%	60 (0)	65%	1.0
Isolated VSD	38 (0)	75%	55 (0)	80%	0.5	54 (0)	82%	68 (0)	74%	0.2
Large VSD size	32 (0)	63%	49 (0)	71%	0.3	47 (0)	71%	67 (0)	73%	0.8
Presence of an anomalous right subclavian	12 (0)	24%	12 (0)	17%	0.4	14 (0)	21%	24 (0)	26%	0.5
Presence of a bicuspid aortic valve	13 (0)	25%	14 (0)	20%	0.5	26 (0)	39%	37 (0)	40%	0.9
Characteristics of index repair										
Weight at index IAA repair (kilograms)	40 (11)	3.42±0.94, 3.39 (2.20-8.00)	52 (17)	3.14±0.44, 3.20 (2.20-4.00)	0.09	59 (7)	3.35±0.81, 3.20 (2.00-8.00)	79 (13)	3.29±0.90, 3.10 (1.20-7.00)	0.3
Thoracotomy	9 (0)	18%	14 (0)	20%	0.7	26 (0)	39%	34 (0)	37%	0.8
Direct arch repair	30 (0)	59%	49 (0)	71%	0.2	39 (0)	59%	53 (0)	58%	0.9
Arch repair using patch	19 (0)	37%	17 (0)	25%	0.1	12 (0)	18%	25 (0)	27%	0.2
Goretex interposition graft	2 (0)	4%	3 (0)	4%	1.0	11 (0)	17%	10 (0)	11%	0.3
Arch repair using homograft pulmonary artery	7 (0)	16%	7 (0)	10%	0.4	5 (0)	8%	10 (0)	11%	0.5
Cardiopulmonary bypass used	42 (0)	82%	55 (0)	80%	0.7	42 (0)	64%	60 (0)	65%	0.8
Elapsed time on bypass at index repair (minutes)*	29 (22)	81.31±73.05, 70.00 (0.00-227.00)	46 (23)	82.80±73.84, 79.50 (0.00-326.00)	0.8	42 (24)	44.69±59.91, 0.00 (0.00-190.00)	55 (37)	52.31±71.71, 0.00 (0.00-306.00)	0.8
Total circulatory arrest used	41 (0)	80%	55 (3)	83%	0.7	42 (0)	64%	60 (0)	65%	0.8
Total circulatory arrest time at index repair (minutes)	35 (16)	36.40±27.84, 46.00 (0.00-104.00)	47 (22)	41.51±28.49, 46.00 (0.00-105.00)	0.5	42 (24)	24.57±31.23, 0.00 (0.00-90.00)	63 (29)	25.73±30.08, 0.00 (0.00-109.00)	0.7
Procedural sequence and timing										
Total number of surgical procedures	51 (0)	1.98±1.05, 2.00 (1.00-5.00)	69 (0)	1.51±0.72, 1.00 (1.00-4.00)	0.01	66 (0)	2.03±1.05, 2.00 (1.00-4.00)	92 (0)	1.79±0.97, 2.00 (1.00-6.00)	0.2
Total number of interventional catheter-based procedures	51 (0)	0.27±0.60, 0.00 (0.00-3.00)	69 (0)	0.42±0.79, 0.00 (0.00-3.00)	0.4	66 (0)	0.56±1.36, 0.00 (0.00-8.00)	92 (0)	0.40±0.85, 0.00 (0.00-6.00)	1.0
Total number of other procedures	51 (0)	0.49±0.92, 0.00 (0.00-5.00)	69 (0)	0.41±0.93, 0.00 (0.00-5.00)	0.4	66 (0)	0.64±1.25, 0.00 (0.00-9.00)	92 (0)	0.58±1.19, 0.00 (0.00-9.00)	0.5
Total number of arch procedures	51 (0)	1.45±0.64, 1.00 (1.00-3.00)	69 (0)	1.32±0.65, 1.00 (1.00-4.00)	0.1	66 (0)	1.56±1.01, 1.00 (1.00-7.00)	92 (0)	1.46±0.75, 1.00 (1.00-4.00)	0.7
Total number of LVOT procedures	51 (0)	0.43±0.85, 0.00 (0.00-3.00)	69 (0)	0.28±0.59, 0.00 (0.00-3.00)	0.5	66 (0)	0.50±0.88, 0.00 (0.00-3.00)	92 (0)	0.26±0.66, 0.00 (0.00-4.00)	0.06
Time since last procedure (years)	51 (0)	12.63±4.18	N/A	N/A	N/A	64 (2)	15.49±5.15	N/A	N/A	N/A
Time since last surgical procedure (years)	51 (0)	12.93±4.10	N/A	N/A	N/A	64 (2)	16.27±4.74	N/A	N/A	N/A

Redo procedures										
Redo with total circulatory arrest	14 (0)	27%	7 (0)	10%	0.01	12 (0)	18%	19 (0)	21%	0.7
Circulatory arrest at any time	16 (10)	39%	57 (0)	83%	0.8	49 (0)	74%	73 (0)	79%	0.5
22q11DS variables										
Genetic or DNA testing	27 (8)	63%	N/A	N/A	N/A	24 (8)	41%	N/A	N/A	N/A
Diagnosed with a genetic condition	19 (8)	44%	N/A	N/A	N/A	17 (9)	30%	N/A	N/A	N/A
Difficulties with learning in school	34 (2)	69%	N/A	N/A	N/A	38 (3)	60%	N/A	N/A	N/A
Behavioral problems in school	9 (3)	19%	N/A	N/A	N/A	10 (4)	16%	N/A	N/A	N/A
Mental health counseling by a social worker, psychologist, or psychiatrist	19 (2)	39%	N/A	N/A	N/A	16 (5)	26%	N/A	N/A	N/A
Medication for mental health problems	13 (1)	26%	N/A	N/A	N/A	8 (5)	13%	N/A	N/A	N/A
Diagnosed with anxiety	6 (5)	13%	N/A	N/A	N/A	10 (5)	16%	N/A	N/A	N/A
Diagnosed with depression	1 (3)	2%	N/A	N/A	N/A	6 (5)	10%	N/A	N/A	N/A
Hearing tested and told it wasn't normal	14 (4)	30%	N/A	N/A	N/A	10 (4)	16%	N/A	N/A	N/A
Wear hearing aids	4 (2)	8%	N/A	N/A	N/A	1 (6)	2%	N/A	N/A	N/A
Low calcium levels ever	10 (17)	29%	N/A	N/A	N/A	12 (15)	24%	N/A	N/A	N/A
Ever calcium supplements or medications to correct your calcium levels	10 (6)	22%	N/A	N/A	N/A	9 (8)	16%	N/A	N/A	N/A
Ever thyroid problems	3 (9)	7%	N/A	N/A	N/A	4 (10)	7%	N/A	N/A	N/A
Ever speech therapy	36 (1)	72%	N/A	N/A	N/A	30 (5)	49%	N/A	N/A	N/A
Recurrent childhood infections requiring medication or admission to hospital	14 (2)	29%	N/A	N/A	N/A	12 (6)	6%	N/A	N/A	N/A
Ever told by a doctor you have any abnormal facial features	13 (4)	28%	N/A	N/A	N/A	11 (10)	20%	N/A	N/A	N/A
Ever diagnosed with DiGeorge syndrome	16 (10)	39%	N/A	N/A	N/A	14 (10)	25%	N/A	N/A	N/A

Table 3.2: Health status now versus 1 year ago from both functional health status questionnaires. The answers from both questionnaires are reported as raw data. CHQ-CF87 – Child Health Questionnaire-Child Form 87. SF-36 – Medical Outcomes Study Short Form-36 Health Survey version 2.

	CHQ-CF87 Change in health (CH) m = 2	SF-36 Reported health transition (HT) m = 1
Much better now than 1 year ago	1/49 (2%)	4/65 (6%)
Somewhat better now than 1 year ago	3/49 (6%)	12/65 (18%)
About the same now as 1 year ago	27/49 (55%)	47/65 (72%)
Somewhat worse now than 1 year ago	8/49 (16%)	1/67 (2%)
Much worse now than 1 year ago	10/49 (20%)	1/65 (2%)

Table 3.3: Questionnaire scores with published norms and Z-scores. CHQ-CF87 – Child Health Questionnaire-Child Form 87. IAA – interrupted aortic arch. SF-36 – Medical Outcomes Study Short Form-36 Health Survey version 2.

CHQ-CF 87 domains	**IAA patients <18y (n = 51) mean±standard deviation, m = missing**	**Published norms n = 232**	**P**	**Z-score**
Global Health (GGH)	77.2±17.2, m = 2	-	---	---
Physical Functioning (PF)	86.6±15.6, m = 1	88.8±14.0	0.3	-0.2
Role/Social Limitations-Emotional (RE)	85.6±20.7, m = 1	85.9±21.0	0.9	-0.02
Role/Social Limitations-Behavioral (RB)	88.0±25.3, m = 2	86.5±21.5	0.7	0.07
Role/Social Limitations-Physical (RP)	92.3±16.7, m = 2	88.3±21.0	0.1	0.2
(Freedom from) Bodily Pain (BP)	87.8±19.3, m = 1	74.4±23.1	<0.0001	0.6
Behavior (BE)	73.0±16.5, m = 1	76.6±14.6	0.1	0.1
Global Behavior (GBE)	71.0±27.6, m = 0	-	---	---
Mental Health (MH)	77.6±15.2, m = 1	72.7±16.0	0.03	0.7
Self Esteem (SE)	79.3±15.6, m = 2	81.8±15.8	0.3	0.3
General Health Perceptions (GH)	64.5±14.8, m = 2	66.4±14.6	0.4	0.3
Family Activities (FA)	80.0±23.8, m = 2	-	---	---
Family Cohesion (FC)	73.9±22.6, m = 3	-	---	---
SF-36 domains	**IAA patients >18y (n = 66) mean±standard deviation, m = missing**	**Published norms males & females ages 18-24**	**P**	**Z-score**
Physical Component Summary (PF/RP/BP/GH)	52.4±7.5, m = 3	53.5±9.2, n = 216	0.3	-0.1
Mental Component Summary(VT/SF/RE/MH)	49.3±12.0, m = 3	46.1±13.26, n = 216	0.04	0.2
Physical Functioning (PF)	50.7±8.0, m = 1	53.2±9.7, n = 216	0.02	-0.3
Role-Physical (RP)	50.9±8.6, m = 1	52.8±9.6, n = 216	0.09	-0.2
(Freedom from) Bodily Pain (BP)	55.9±8.0, m = 1	52.0±10.6, n = 216	0.0002	0.4
General Health (GH)	49.2±10.9, m = 2	49.7±11.8, n = 216	0.7	-0.04
Vitality (VT)	52.6±11.3, m = 2	47.0±11.7, n = 216	0.0002	0.5
Social Functioning (SF)	49.1±10.0, m = 2	49.2±12.3, n = 216	0.9	-0.009
Role-Emotional (RE)	49.0±11.8, m = 2	49.8±12.5, n = 216	0.6	-0.06
Mental Health (MH)	50.7±11.8, m = 2	46.9±13.0, n = 215	0.01	0.3

Table 3.4: Summary of multiple regression analysis for independent factors associated with lower scores on individual domains for the Child Health Questionnaire-Child Form 87 and the Short Form-36 Health Survey.

CHQ-CF87 **Variable**	**Parameter Estimate**	**P**	**Reliability**	**R^2/adjR^2**
Global Health (GGH)				
Questionnaire reports that patient has been told by a doctor that he/she has abnormal facial features	12.11±5.11	0.02	80%	0.17/0.14
Higher total number of "other" procedures	7.06±3.45	0.05	50% by cluster	
Physical Functioning (PF)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	16.20±3.63	<0.0001	83%	0.52/0.48
Questionnaire reports patient taking calcium supplements or medications to correct calcium levels	13.45±5.02	0.01	61%	
Higher total number of medications	5.27±1.35	0.0003	76%	
Questionnaire reports that patient has had low calcium levels	20.65±4.54	>0.0001	62%	
Lower weight at index IAA repair (kilograms) (squared)	5.63±2.00	0.007	59% by cluster	
Role/Social Limitations-Emotional (RE)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	17.20±5.56	0.003	63%	0.16/0.15
Role/Social Limitations-Behavioral (RB)				
Questionnaire reports patient taking medication for mental health problems	21.64±7.47	0.006	75%	0.15/0.13
Role/Social Limitations-Physical (RP)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	13.97±3.91	0.0009	76%	0.47/0.41
Elapsed time on bypass at index repair (minutes) (inverse)	1770.30±663.18	0.01	74% by cluster	
Questionnaire reports patient taking calcium supplements or medications to correct calcium levels	12.15±4.73	0.01	70% by cluster	
Younger at questionnaire completion (years) (inverse)	863.04±293.42	0.005	69% by cluster	
Higher total number of catheter-based interventional procedures	6.63±2.98	0.03	50% by cluster	
(Freedom from) Bodily Pain (BP)				
Questionnaire reports that patient has had speech therapy	22.82±5.70	0.0002	55%	0.33/0.30
Questionnaire reports that patients has a current diagnosis of DiGeorge	25.20±5.80	<0.0001	50%	
Behavior (BE)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	17.39±3.92	<0.0001	51%	0.36/0.33
Patient reports having DNA testing	11.85±4.22	0.007	56% by cluster	
Global Behavior (GBE)				
Questionnaire reports patient taking medication for mental health problems	33.04±7.03	<0.0001	55%	0.40/0.38
Presence of other medical problems	20.36±6.84	0.005	54% by cluster	

Mental Health (MH)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	18.95±2.84	<0.0001	94%	0.70/0.66
Absence of an anomalous right subclavian	9.95±3.00	0.002	68%	
Higher total number of medications	4.76±1.11	<0.0001	63%	
Presence of other medical problems	12.56±2.85	<0.0001	61%	
Questionnaire reports having abnormal hearing test result	12.65±2.99	0.0001	51%	
Higher total number of catheter-based interventional procedures	8.17±2.16	0.0005	57% by cluster	
Self Esteem (SE)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	13.39±3.57	0.0005	56%	0.40/0.37
Questionnaire reports having a diagnosis of a genetic condition	11.79±3.76	0.003	65% by cluster	
Higher total number of “other” procedures	4.90±1.87	0.01	64% by cluster	
General Health Perceptions (GH)				
Questionnaire reports recurrent childhood infections requiring medication or admission to hospital	12.99±4.23	0.004	59%	0.16/0.14
Family Activities (FA)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	31.42±5.12	<0.0001	77%	0.53/0.49
Questionnaire reports having a diagnosis of a genetic condition	18.88±5.14	0.0006	74% by cluster	
Lower weight at index IAA repair (kilograms) (squared)	8.08±2.95	0.009	64% by cluster	
Lower median family income for (USD) neighborhood (inverse)	66.96±20.97	0.003	61% by cluster	
Family Cohesion (FC)				
Presence of bicuspid aortic valve	32.08±6.72	<0.0001	82%	0.38/0.33
Absence of an anomalous right subclavian	17.21±6.55	0.01	61%	
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	17.40±5.64	0.003	52%	
Lower median family income for neighborhood USD) (inverse)	71.35±23.46	0.004	65% by cluster	

SF-36

Variable	Parameter Estimate	P	Reliability	R^2/adjR^2
Physical Component Summary (PCS)				
Higher total number of arch procedures	2.41±0.85	0.007	71% by cluster	0.11/0.10
Mental Component Summary (MCS)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	14.17±2.65	<0.0001	95%	0.47/0.44
Younger age at questionnaire completion (years) (inverse)	879.63±371.25	0.02	60% by cluster	
Shorter time since last procedure (years) (inverse)	94.64±28.65	0.001	52% by cluster	
Physical Functioning (PF)				
Lower median family income for neighborhood (USD) (inverse)	30.81±11.60	0.01	63% by cluster	0.10/0.09
Role-Physical (RP)				
Higher total number of arch procedures	2.93±0.97	0.004	59%	0.17/0.15
Lower median family income for neighborhood (USD) (inverse)	25.52±12.00	0.04	61% by cluster	
(Freedom from) Bodily Pain (BP)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	8.57±1.69	<0.0001	87%	0.52/0.49
Presence of uncomplicated IAA	5.15±1.87	0.008	78%	
Questionnaire reports that patient has had low calcium levels	5.13±1.93	0.01	54%	
Higher total number of procedures of any type	1.73±0.41	<0.0001	63% by cluster	
General Health (GH)				
Questionnaire reports recurrent childhood infections requiring medication or admission to hospital (present)	10.45±3.14	0.002	50%	0.21/0.18
Higher total number of arch procedures	3.07±1.20	0.01	59% by cluster	
Vitality (VT)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	14.72±2.71	<0.0001	94%	0.32/0.31
Social Functioning (SF)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	11.96±2.02	<0.0001	87%	0.55/0.51
Presence of uncomplicated IAA	5.18±2.27	0.03	68%	
Higher total number of left ventricular outflow tract procedures	2.53±1.05	0.02	55% by cluster	
Lower weight at index IAA repair (kilograms) (inverse)	57.93±16.38	0.0008	56% by cluster	
Shorter time since last procedure (years) (inverse)	-114.58±22.75	<0.0001	60% by cluster	
Role-Emotional (RE)				
Questionnaire reports patient has had a behavioral problem in school	9.04±3.41	0.01	58%	0.32/0.29
Higher total number of medications	3.17±0.86	0.0005	52%	
Higher total number of arch procedures	4.41±1.22	0.0006	80% by cluster	
Mental Health (MH)				
Questionnaire reports that patient has had mental health counseling by a social worker, psychologist or psychiatrist	15.87±2.75	<0.0001	95%	0.34/0.33

Chapter 4

4 Transition to adult congenital heart disease care after repair of interrupted aortic arch

4.1 Abstract

Objectives: Improved survival after pediatric congenital heart surgery has led to the need for successful transition to adult care. Therefore, the Congenital Heart Surgeons' Society (CHSS) sought to determine patterns and factors associated with the time-related transition to adult care of young adults with repaired interrupted aortic arch. This cohort was selected for this study as these patients require ongoing follow-up and a high proportion within the cohort are ≥ age 18 years.

Methods: At the time of this study, the CHSS interrupted aortic arch inception cohort had 158 living patients repaired in infancy who are now ≥ age 18 years. During annual follow-up, patients received a CHSS developed questionnaire on transition to adult care. Transition was also defined as the first incidence of care (visit or intervention) with a physician providing care to adults focused on heart issues, or an investigation or procedure at an adult facility. Multiphase parametric modeling of the hazard function with interval censoring was used to determine the rate of time-related transition to adult care. Bootstrap bagging was used to determine factors associated with time-related transition. Qualitative evaluation of questionnaire responses was completed.

Results: There were 75 respondents. Time-related transition to adult care occurred in 10% of patients by age 18 years, 23% by age 20 years, and 32% by age 21 years. Canadian residence was found to be significantly associated with improved time-related transition (estimate ± standard deviation = 2.33±0.65, p=0.003, reliability=80%). Patients reported varying levels of knowledge regarding their heart condition, with the majority of patients (45%) only reporting some knowledge (the second lowest category on a 5 choice scale), and 9% reporting no

knowledge. We also found that parent(s)/guardian(s) were highly involved in the care of these patients with 71% (52/73, missing=2) attending patient appointments. Finally, the majority of patients still received their primary cardiac care from a pediatric cardiologist (73%=53/73, missing=2). Of those who had received any adult care, the majority of patients were referred non-urgently, and included 8/9 of the Canadian patients who responded.

Conclusions: While transition can be accomplished effectively within many clinical models (such as those with universal coverage, transition programs, or well-developed adult congenital heart disease care programs), the earlier and more complete time-related transition in Canada warrants further investigation. Studies to assess barriers and incentives to transition in North America focused on health care system factors such as patient health care coverage, and the effect of programs to increase transition should be made a priority.

4.2 Background

Since the advent of cardiac surgery, there has been a growing population of patients with CHD who now survive into adulthood due to advances in medical and surgical therapy. It is now estimated that approximately 85% of neonates with CHD currently survive beyond 18 years of age[149, 150]. The current estimate is that there are approximately 100,000 adults with CHD in Canada, and 1,000,000 in the U.S.[152, 153]. However, despite this increase in survival, complete cure in patients with more complex CHD is rare, as they often have late complications and require further therapy for residual or recurrent lesions[154]. Current guidelines recommend that just over half of ACHD patients should be seen every 12 to 24 months at regional ACHD centres due to the possibility of further complications[152, 158-161]. These visits should include a detailed history and examination with standardized diagnostic studies (and more extensive investigations, if required), routine examination for new or progressive disease, and patient and primary care physician education[158]. This has led to increased importance being placed on the transition of care for patients moving from the pediatric to adult life stage, in order to prevent them from being lost to follow-up. Transition is defined as the "purposeful and planned movement of adolescents and young adults with chronic physical and medical conditions from child-centred to adult-oriented health care systems"[155]. Despite this, up to 70% of patients are lost to follow-up or have lapses in their care when they leave pediatric cardiology[156, 157]. As a result, the CHSS sought to determine patterns and factors associated with the transition to adult care of patients with repaired IAA.

4.3 Methods

Data Collection

The inclusion criteria for the IAA cohort were all patients with IAA admitted to a CHSS institution within 30 days of birth (see Appendix 4.1 for the institutions involved). The cohort

was enrolled between 1987 and 1997 from 23 centres across Canada, the U.S., and Brazil. Follow-up for the IAA cohort occurred from September 1, 2009 to August 31, 2010. A total of 472 patients were enrolled. The 25 patients who did not undergo index repair were excluded, leaving 447 patients. There were 278 living patients in this cohort at the time of follow-up, out of 447 patients who had undergone index surgery, and 158 were ≥ age 18 years. Institutional and patient participation was voluntary and confidential. The patients provided informed consent, and approval was obtained according to local CHSS institutional requirements. Ethics approval for the CHSS Data Center was obtained annually from the Research Ethics Board of the Sick Kids Hospital, Toronto, Ontario, Canada.

A combined prospective inception cohort and cross-sectional study design (questionnaire administration) was used. Since inception, annual follow-up has been conducted by the CHSS Data Center. A questionnaire regarding patient status, including details about admissions, investigations, and procedures performed that year, are mailed to the patients' families. Families who did not immediately respond were also contacted by phone or email.

Transition questionnaire

In addition, during the annual follow-up, patients received a CHSS developed questionnaire on transition to adult care (See Appendix 4.2 for the questionnaire with responses) in addition to their regular follow-up form and our standard data collection. The transition questionnaire was developed by the CHSS as a qualitative assessment tool. This questionnaire was created by first determining the factors important to the transition from the literature, followed by the development of the questions with a focus on content, wording, and placing the questions in a meaningful order and format. This was then followed by testing within the CHSS Data Center, with feedback, and final revision. The questionnaire was conceptualized to assist us in collecting details regarding the following domains: current care, first ACHD care or adult care experience, psychosocial factors, and parental involvement in care. The data collected using this questionnaire was not scored, but was evaluated qualitatively. Other data used that were not

obtained from the questionnaire were abstracted from copies of medical records submitted to the CHSS Data Center that had been collected since enrollment or through other questionnaires.

Statistical methods

Data are expressed as a frequency, median with range, or mean with standard deviation, alongside the number of missing values. Multiphase parametric modeling of the hazard function with interval censoring was used to determine the proportion of patients undergoing time-related transition to adult care[188]. Transition to adult care was defined as a self-report of a first occurrence of care as an adult at a non-pediatric institution, or by a non-pediatric physician. Patients chose answers that described a time range for how long ago they received this care, and interval censoring was then used to determine the time-related transition to adult care. The factors associated with transition were sought using multivariable assessment of these parametric models. Only variables with less than 40% missing data, and those associated with more than 5 events were included to minimize the risk of model overdetermination. For continuous variables, different mathematic transformations were tested for optimal calibration of the relationship to risk. Bootstrap bagging (1000 models) with clustering of the variables (variables and clusters with reliability greater than approximately 50% were considered sufficiently reliable for inclusion in the final multivariable model) was used to determine factors associated with time-related transition to adult care. P=0.01 was used in the automated analysis as variable entry criteria. Missing value indicator variables were entered into the final multivariable models, as appropriate. Using our entire database from this cohort, we explored features related to: demographics, morphology, index repair, subsequent procedures, country of residence, and institution. The variables used for the risk analysis can be seen in Table 4.1, and the data regarding 22q11DS were obtained from the questionnaire in Appendix 3.2. All analyses were performed using Statistical Analysis Systems software, version 9.2 (SAS Institute, Inc, Cary NC).

4.4 Results

Responders

As stated above, there were 75 respondents out of 158 living patients (47%), from 23 centres in the U.S. (65 patients – 87%), Canada (9 patients – 12%), and Brazil (1 patient – 1%). Their ages ranged between 18 and 24 years (mean 20±2 years, median 20 years) at the time the questionnaire was completed,, and there was no difference in age by country (p=0.1) when the U.S. and Canada were compared.

Non-responders

Characteristics of the responders and non-responders are shown in Table 4.1. Of the 82 non-responders, 56 of the IAA patients were patients who could only be contacted by their home institution. This type of consent was required in the past by many institutional research ethics boards in order to allow their patients to participate. As a result, we were obligated to have the home institution contact these patients on our behalf. Therefore most of these patients did not receive a questionnaire, as we did not have adequate support for this initiative at each institution. The only difference found between responders and non-responders in the IAA cohort was that the total number of procedures was found to be significantly higher in the responders (p=0.04) (See Table 4.1).

Questionnaire responses and patterns of care

Patients reported the following levels of knowledge about their heart condition: 7/75 (9%) no knowledge; 34/75 (45%) some knowledge; 12/75 (16%) moderate knowledge; 16/75 (21%) good knowledge; 6/75 (8%) and thorough knowledge.

The proportion of patients who reported that their parent(s)/guardian(s) still take them to all of their appointments related to their heart was 79% (59/75), with 5% (4/75) reporting that this occurred sometimes. Of those patients who reported that their parent(s)/guardian(s) still take them to their appointments, 71% (52/73) said they attend the appointment, with 7% (5/73) reporting that they attend the appointment sometimes. Of note, 82% (61/74) of patients said they have never attended an appointment related to their heart without their parent(s)/guardian(s). Only 1 patient reported living with a spouse, and 1 reported living with a partner, as such it is still likely that the majority of patients attend appointments with their parents.

We found that of the patients who responded, 73% (53/73) still received their primary cardiac care from a pediatric cardiologist, and 65% (43/66) have never had any form of adult cardiac care. Of the 21/66 (32%) patients who reported that they had some form of adult care, 12 (57%) reported referral from their pediatric hospital. Of these 12, 5 (42%) were from Canada. Of these same 21 patients, 18 (86%) were referred on a non-emergent basis. Of these 18, 8 (44%) were from Canada, out of a total of 9 Canadian patients in the study.

With regard to frequency of care, we found the following: Of those patients still seeing a pediatric cardiologist, the highest proportion (42%=31/74) were seen within the last 6 months, with an additional 18% (13/74) having seen their pediatric cardiologist within the last 7-12 months, and another 18% (13/74) having seen their pediatric cardiologist 13-24 months ago. While 72% (53/74) reported that they were still seeing their pediatric cardiologist, of those not seeing a pediatric cardiologist (28%=21/74), the highest proportion (38%=8/21), had an appointment for their heart 7-12 months ago. Patients also reported that when they were doing well, 47% (35/75) were seen every 7-12 months about their heart condition, and 28% (21/75) were seen every 13-24 months about their heart condition.

The changing denominator in the above results is due to missing responses.

Time-related transition to adult care and associated factors

Multiphase parametric modeling found that the overall time-related transition to adult care occurred in 10% of patients by age 18 years, 23% by age 20 years, and 32% by age 21 years (Figure 4.1, A). The results of our risk analysis using bootstrap bagging and clustering of the variables found that the only factor associated with time-related transition to adult care was Canadian residence (estimate ± standard deviation = 2.33±0.65, p=0.003, reliability=80%) (Figure 4.1, B). Figure 4.1-B demonstrates that 84% of Canadian patients transitioned to adult care by age 21 years, in comparison to only 23% of U.S. patients. From this cohort, a total of 20 patients transitioned (and provided us with information regarding the timing), of which 8 patients were from Canada and 12 were from the U.S. The number of patients who had never seen an adult care physician regarding their heart or who had never had a heart related procedure or investigation at an adult facility was 43 (65%).

4.5 Discussion

Summary of main findings

Patients reported varying levels of knowledge regarding their heart condition, with the majority of patients only reporting some knowledge (the second lowest category on a 5 choice scale), and surprisingly almost 10% reporting no knowledge despite being over the age of 18. We also found that parent(s)/guardian(s) were highly involved in the care of these patients with approximately 70% attending appointments. Finally, the majority of patients still received their primary cardiac care from a pediatric cardiologist, and of those who had received any adult care, roughly half of the patients who received it from Canada were referred non-urgently, accounting for 8/9 Canadian responders. Surprisingly, we found that only 32% of patients had transitioned to adult care by age 21, and that the only variable associated with the time-related transition to adult care was Canadian residence. Notably, 65% of patients never had any form of adult cardiac care despite being over the age of 18 years.

Transition patterns from other studies

A publication by Dore and colleagues of 104 patients demonstrated that referral to an adult centre was primarily made by pediatric cardiologists (56%), medical cardiologists (26%), and general practitioners (11%)[169]. This study also showed that the average age at referral was 28+/-11 years (range 16-72, median 24 years), and the time from the last cardiology visit varied greatly with a range of 1 month-25 years (median 3 years). It was noted that 29 patients had no follow-up for more than 5 years, and of these, 14 had no follow-up for more than 10 years. Six patients were referred due to complications related to their cardiac problems. A study by Reid et al. based at the Sick Kids Hospital demonstrated that only 47% of CHD patients underwent a successful transition to adult care[170]. This research was conducted in 2000, and the patients were aged 19-21.This paper demonstrated that 27% of patients did not have any appointments for cardiac care after the age of 18. It also demonstrated that the factors associated with successful transfer in the entire cohort were more pediatric cardiac surgeries, older age at last visit to the Sick Kids Hospital, and documented recommendations in the chart for follow-up at a CACH centre. When only those patients completing questionnaires were analyzed, the factors found to be associated with successful transfer were documented recommendations and patient belief that ACHD care should occur at a CACH centre, comorbid conditions, lack of substance use, using dental antibiotic prophylaxis, and attending cardiac appointments without parental or sibling accompaniment.

Parental involvement and patient knowledge

In our study, we found a high level of parental involvement at patient appointments, despite the fact that these patients are now young adults. There is very little literature on the effect of parental involvement on a patient's care. While parental involvement can have a profound influence on a patient's ability to manage their care, a study by Clarizia et al. demonstrated that increased parental involvement has been found to leave children unsure of their diagnosis, and unable to communicate directly with their health care providers[171]. This study also found these parents often did not encourage independence, even in tasks that were age-appropriate[171]. Similarly, Reid et al. found that attending cardiac appointments without parents or siblings also

correlated with successful transition to adult care (OR: 6.59; 95% CI: 1.61-27.00)[170]. This was compounded by patients' lack of knowledge regarding their own health.

When IAA patients were asked what their knowledge level was regarding their heart condition, varying levels of patient self-reported knowledge regarding their condition was found. The majority of patients reported a poor level of knowledge regarding their condition, with 45% reporting they had some knowledge of their condition, and 9% reporting they had no knowledge of their condition. Increased patient knowledge could profoundly influence their ability to manage their care.

Clarizia et al. also found that patients with more knowledge had a better understanding about transition to adult care (100% vs. 7%, $p<0.01$), and were more likely to directly communicate with their health care providers that those patients who were less knowledgeable or had no knowledge (88% vs. 33% $p=0.03$)[171]. It is of prime importance that patients with CHD be informed that they need life-long follow-up and are at increased risk for complications due to residual lesions and sequelae. It has long been noted that adults with CHD have a low level of knowledge regarding their heart condition. In a study of 104 patients by Dore et al., the clinical diagnosis was completely unknown by 36/104 (35%) patients, only 79% had knowledge of antibiotic prophylaxis, and 66% of women have ever discussed the risks of pregnancy with their doctor[169]. Preparing young patients to transition to adult care is important to having successful transition[155, 173, 174], and central to this is the awareness of the roles of the patient, the parent, and the health care provider[170, 171, 173-179]. Patients must be taught about their diagnosis, management, and general and disease-specific preventative measures[170, 174, 176]. In addition, patient skills must be built to ensure they can manage their care, and understand the importance of continued care for their disease although they may feel well. Confidence was found to be improved through having knowledge about their heart condition, and gave patients the ability to manage their health care independently from their parents[171]. Reid and colleagues found that patients who had undergone more pediatric cardiac surgeries, and who had more comorbid conditions had a higher rate of transition, which one could speculate may be related to having more knowledge of their condition[170]. Scal et al. found that those patients with more complex needs were more likely to

have addressed the importance of transition, which may also relate to having increased knowledge[172]. Increasing the structure, number, and importance of transition programs may in part help improve transition.

Health system infrastructure

One of the main issues that may be causing the lack of transition, especially in the U.S. is a lack of appropriate care facilities with ACHD trained caregivers. In countries such as Canada, the United Kingdom, the Netherlands, and Switzerland, clinics focused on care for ACHD patients have been longstanding[180]. Fifteen ACHD centres exist in Canada (CACH Network), of which 5 are multi-disciplinary centres of excellence to varying degrees, and serve a wide catchment[181]. Although there are some exceptions, most patients ≥ 18 years are required to be seen at an adult facility in Canada's government funded universal health care system. In the U.S., there is a diverse practice (with patients being seen by both pediatric and adult care practitioners, at pediatric and adult sites), and the age of transition varies greatly because of the differences in available health care coverage. It has been recommended that transition to ACHD care occur at age 18, or by the end of high school[182, 183]. Held in 2000, the goals from the 32nd Bethesda Conference included having 30-50 regional centres of excellence across the U.S. However, despite recommendations, no adequate plan exists to train the staff required to take care of these patients at centres such as those recommended[184, 185]. More formal training programs are required to train the personnel in cardiology, sonography, and adult congenital cardiology to staff existing and future centres of ACHD care.

In our study we found that the time-related transition to adult care was increased in the Canadian population. It should be noted that 8/9 of the Canadian patients who transitioned were from a single institution. Although these are small numbers, the system of care at that particular institution may account for the differences seen between countries. This institution is also recognized as having an established transition program. Of note, all programs in Canada are able to refer to the CACH Network. We can speculate that the higher rate of transition in Canada compared to the U.S. found in our study is likely due to multiple causes related to: the lack of an

established care network in the U.S.; the presence of universal health care in Canada for all patients at all ages; and possibly the increased presence of transition programs to an established care network in Canada.

Ideal care

Although the term "ideal care" may be a grand concept, we feel that there are several essential features which would improve the rate of transition to adult care. Foster et al. described 6 features of successful transfer which we believe are essential: 1) a policy related to timing of transfer; 2) a preparation/education program for the patient beginning in adolescence; 3) a coordinated transfer process; 4) an interested and well equipped adult facility; 5) administrative assistance; and 6) the involvement of primary care[182].

We feel patients should be educated through transition programs regarding their own lesion, their surgeries, and what residual lesions they have that may require ongoing or future follow-up. The Good 2 Go transition program at the Sick Kids Hospital in Toronto, which is not just cardiac-specific, provides many of the items described in the above paragraph[210]. The program also provides patients with a MyHealth Passport which is a pocket sized card created in conjunction with a health care provider, which can be carried at all times and details the patient's medical conditions, medications, allergies, procedures, and treatments[210]. This program takes into account the ideas that transition is a process with a set timelines, and teaches children to be self-advocates who are self-efficacious[210]. With regard to "ideal care", for the cardiac program, transfer is targeted to those 16 years of age and older. In addition, patients and their future care providers (e.g. general practitioners, cardiologists, and surgeons) should be provided with comprehensive notes on their previous care, including operative and catheterization reports, and reports of prior investigations and admissions, all of which should be transferred in an organized fashion.

We feel it is essential that a transition program include counseling on topics such as education, career, endocarditis prophylaxis, insurance, sexuality and reproduction, cardiovascular risk factors, physical activity, and follow-up specific to each patient's lesion[211]. Patients with ACHD should also have access to physicians and a multi-disciplinary team of the highest quality who have formal education in the field, including cardiologists, surgeons, and echocardiographers[181]. This is especially important when determining where these adult patients undergo procedures, whether at a children's or adult care facility, and whether in a primary or tertiary care facility[212]. Indeed much of this has been elaborated in the recommendations of the 32nd Bethesda Conference, which detailed how ACHD services could be ideally delivered in the U.S.[152, 182, 184, 185, 213].

Study limitations

The present study had several important limitations.

There are several possible sources of selection bias in this study. Initial enrollment at participating institutions was voluntary, allowing for the possibility of selection bias, as we are unaware of the number of patients at any given institution who had the diagnosis (the denominator) and their baseline characteristics. Our response rate was also impacted by the fact that we were obligated to have the home institution contact a proportion of patients on our behalf. The fact that there was a proportion of patients whom we could not contact, that each home institution was required to contact due to research ethics boards regulations at certain institutions, contributed to a poor response rate because most of these patients did not receive a questionnaire. This may have also led to selection bias, if the patients at each institution had different underlying characteristics. It can be speculated that the difference in the total number of procedures found between responders and non-responders was due to our lack of information regarding any further procedures the non-responders had, as they did not provide us with this information. Responders may also be different than non-responders as they needed to survive the duration of time until the study, leading us to the hypothesis that they may healthier than non-

responders, therefore introducing selection bias into our results as both groups were inherently different with regard to their health status.

Although the enrollment period (1987-1997) afforded impressive long-term follow-up, it represents an ‘‘early era’’ in the techniques for the repair that these patients underwent. Outcomes have significantly improved in the more recent era (discussed in Chapter 2), and it is hard to predict the effect of improved outcomes on transition to adult care.

One of the limitations of our study was that we did not have the exact date of transition available. Therefore, we obtained a self-reported date range from patients regarding transition. This information was obtained directly from patients in a retrospective fashion through the transition questionnaire. It would have been preferable to determine the date of transition in a prospective fashion, so that the exact date could have been recorded. As a result, we were required to use interval censoring rather than a more accurate method that utilized the exact date. It should also be noted that we used the age when adult care was first established as the age at transition, however, we are uncertain whether this therapeutic relationship was maintained. In a prospective setting, transition to adult or ACHD care could have been better ascertained.

Transition was also defined as the first incidence of care (visit or intervention) with a physician providing care to adults focused on heart issues, or an investigation or procedure at an adult facility. This definition was used as various models of care occur in the U.S. and Canada, at both pediatric and adult hospitals, by adult cardiologists and pediatric cardiologists, when patients transition to adult care. We were also concerned whether patients could understand the subtle differences in the various types of physicians who provide care for them (e.g. heart doctor for adults vs. heart doctor who sees adult patients who had a heart condition/heart surgery as a child).

Finally, the use of the transition questionnaire that we developed was a limitation as it was unvalidated, although we used it in a purely qualitative fashion.

For a complete discussion of study limitations, please see Chapter 5 (pages 116).

4.6 Conclusions

Health care system factors may be facilitating the earlier and more complete transition to adult care in Canada. While transition to adult care is evolving and can be accomplished effectively within many clinical models, such as those with transition programs, the high proportion of time-related transition to adult care in Canada highlights a model warranting further investigation. Studies to assess barriers and incentives to transition in North America focused on patient health care coverage (government as a universal single payer versus individual patient insurance), the effect of programs to increase transition, and the effect of widely accessible care networks should be made a priority. This will help ensure that patients with rare diseases, such as IAA, receive continuity of care across transition.

From the patterns and factors we have found associated with transition to adult care, it is clear that a systematic formalized approach is required to successfully transition patients to ACHD care. This is especially important as these patients will often face acquired hypertension, coronary artery disease, and numerous other issues such as those pertaining to pregnancy/family planning, education and career, which may compound their congenital diagnosis or be best served by dedicated ACHD care centres and practitioners. Patients are rarely "cured" of their problem, and this common misconception must be avoided to ensure patients receive the best care possible as adults.

4.7 Tables for chapter 4

Table 4.1: Responders vs. non-responders for the interrupted aortic arch cohort. Arch – aortic arch. IAA – interrupted aortic arch. LVOT – left ventricular outflow tract. USD – United States dollars. VSD – ventricular septal defect.

Variable	Transition, n = 75 Number (missing)	Value	Transition non-responders, n = 82 Number (missing)	Value	p-value
Patient demographic information					
Male	41 (0)	55%	46 (0)	56%	0.9
DiGeorge syndrome	13 (0)	17%	11 (0)	13%	0.5
Other cardiac anomalies	13 (0)	17%	15 (0)	18%	0.9
Other medical problems	27 (0)	36%	20 (0)	24%	0.1
Patient data at time of questionnaire completion					
Age (years)	75 (0)	20±2, 20 (18-24)	82 (0)	20±2, 20 (18-24)	0.4
Total medications being taken	63 (12)	1±1, 0 (0-9)	2 (80)	1±0, 1 (1-1)	0.4
Median neighborhood family income from last census adjusted for inflation (USD)	61 (14)	70278±27611, 64111 (16633-140766)	2 (80)	71575±35755, 71575 (46292-96857)	0.9
Patient morphologic information					
Type A IAA	26 (0)	35%	29 (0)	35%	0.9
Type B IAA	49 (0)	65%	53 (0)	65%	0.9
Isolated VSD	59 (0)	79%	62 (0)	76%	0.6
Large VSD size	51 (0)	68%	63 (0)	77%	0.2
Presence of an anomalous right subclavian	17 (0)	23%	21 (0)	26%	0.7
Presence of a bicuspid aortic valve	30 (0)	40%	32 (0)	39%	0.9

Characteristics of index repair					
Weight at index IAA repair (kilograms)	67 (8)	3.3±0.8, 3.2 (2.0-8.0)	71 (11)	3.3±0.9, 3.2 (1.2-7.0)	0.7
Thoracotomy	27 (0)	36%	33 (0)	40%	0.6
Direct arch repair	43 (0)	57%	49 (0)	60%	0.8
Arch repair using patch	16 (0)	21%	20 (0)	24%	0.6
Goretex interposition graft	12 (0)	16%	9 (0)	11%	0.4
Arch repair using homograft pulmonary artery	7 (0)	9%	7 (0)	9%	0.9
Cardiopulmonary bypass used	50 (0)	67%	51 (0)	62%	0.6
Elapsed time on bypass at index repair (minutes)*	44 (31)	48.8±65.7, 0.0 (0.0-225.0)	53 (29)	49.2±68.0, 0.0 (0.0-306.0)	0.9
Total circulatory arrest used	50 (0)	67%	51 (0)	62%	0.6
Total circulatory arrest time at index repair (minutes)	48 (27)	29.2±33.8, 0.0 (0.0-109.0)	57 (25)	22.0±27.1, 0.0 (0.0-88.0)	0.4
Procedural sequence and timing					
Total number of surgical procedures	75 (0)	2.0±1.0, 2.0 (1.0-4.0)	82 (0)	1.7±0.9, 2.0 (1.0-5.0)	0.1
Total number of interventional catheter-based procedures	75 (0)	0.6±1.3, 0.0 (0.0-8.0)	82 (0)	0.3±0.9, 0.0 (0.0-6.0)	0.6
Total number of other procedures	75 (0)	0.7±1.3, 0.0 (0.0-9.0)	82 (0)	0.5±1.1, 0.0 (0.0-9.0)	0.2
Total number of arch procedures	75 (0)	1.5±1.0, 1.0 (1.0-7.0)	82 (0)	1.5±0.7, 1.0 (1.0-4.0)	0.9
Total number of LVOT procedures	75 (0)	0.4±0.8, 0.0 (0.0-3.0)	82 (0)	0.2±0.6, 0.0 (0.0-3.0)	0.2
Total number of procedures	75 (0)	2.6±1.7, 2.0 (1.0-11.0)	82 (0)	2.1±1.4, 2.0 (1.0-11.0)	0.04
Time since last procedure (years)	75 (0)	15.5±5.3, 18.1 (3.0-23.2)	82 (0)	18.3±3.8, 19.0 (6.3-23.3)	
Time since last surgical procedure (years)	75 (0)	16.5±4.8, 18.8 (5.9-23.2)	82 (0)	18.8±3.4, 19.3 (7.3-23.6)	
Redo procedures					
Redo with total circulatory arrest	14 (0)	19%	16 (0)	20%	0.9
Any total circulatory arrest	58 (0)	77%	63 (0)	77%	0.9

22q11 data					
Patient has had genetic of DNA testing	33 (7)	49%	0 (81)	0%	1.0
Patient has been diagnosed with a genetic condition	23 (8)	34%	1 (80)	50%	1.0
Patient has a current diagnosis of DiGeorge	18 (9)	27%	1 (80)	50%	0.5
Patient has had a learning difficulty in school	48 (2)	66%	2 (80)	100%	0.5
Patient has had a behavioral problem in school	13 (2)	18%	1 (80)	50%	0.3
Patient has had mental health counseling by a social worker, psychologist or psychiatrist	24 (3)	33%	1 (80)	50%	1.0
Patient has taken medication for mental health problems	14 (3)	19%	0 (80)	0%	1.0
Patient has been diagnosed with anxiety	14 (3)	19%	0 (80)	0%	1.0
Patient has been diagnosed with depression	6 (4)	8%	1 (80)	50%	0.2
Patient has had an abnormal hearing test	15 (2)	21%	0 (80)	0%	1.0
Patient wears hearing aids	2 (4)	3%	0 (80)	0%	1.0
Patient has had low calcium levels	13 (13)	21%	0 (80)	0%	1.0
Patient had been given calcium supplements or medication to correct calcium levels	12 (6)	17%	0 (80)	0%	1.0
Patient has had a thyroid problem	5 (8)	7%	0 (81)	0%	1.0
Patient has had speech therapy	39 (3)	54%	0 (81)	0%	0.5
Patient had recurrent childhood infections requiring medication or admission to hospital	14 (4)	20%	0 (80)	0%	1.0
Patient has been told by a doctor that he/she has abnormal facial features	15 (8)	22%	0 (80)	0%	1.0

4.8 Figures for chapter 4

Figure 4.1: Time-related transition to adult care for patients in the interrupted aortic arch cohort. All patients start at age 16 which is when transition is thought to begin. A, Shows the overall time-related transition to adult care for all patients, where n = 75. The upper (open circles) and lower (dots) data points are shown, as this graph is produced from interval censored data. B, Shows the overall time-related transition to adult care when Canadian and U.S. patients are stratified. Note that the single Brazilian patient is excluded for simplicity. *Solid lines* represent parametric point estimates; *dashed lines* enclose 70% confidence intervals; *circles with error bars* represent nonparametric estimates. U.S. – United States.

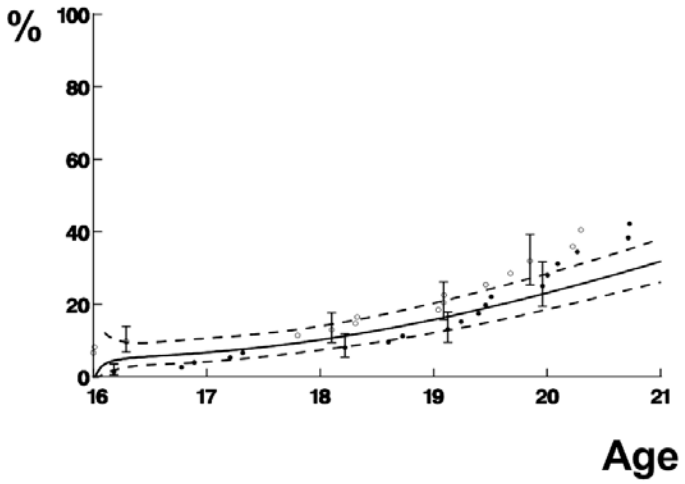


Figure A.

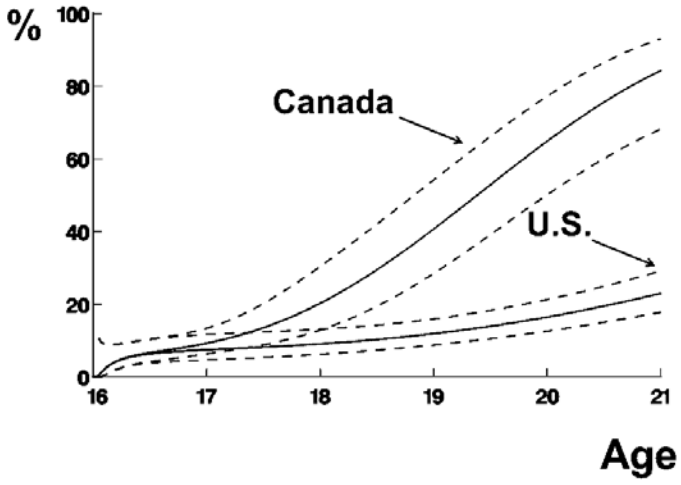


Figure B.

Chapter 5

5 Conclusions

5.1 Summary of research

The overarching theme of this dissertation is that, multi-institutional prospective inception cohort studies of rare lesions, can be used to conduct long-term outcomes analyses pertaining to subsequent procedures after the primary repair, FHS, and transition to adult care. The three studies presented in this manuscript are linked not only because the same cohort was used for the analyses, but because they also represent the diversity of outcomes that can be studied using prospective inception cohorts in order to improve the care of our patients through a multi-dimensional approach.

In Chapter 2, the novel statistical techniques of nested competing risks and modulated renewal were used to determine the likelihood of repeated subsequent procedures on the aortic arch and LVOT, and the factors that were associated with repeated subsequent procedures in our cohort of patients with IAA. Although it is known that patients undergoing IAA repair are at persistent risk of subsequent procedures and mortality, this paper presented the probabilities that accompany these events. We found that with every subsequent arch procedure, the acute probability of further procedures decreased, suggesting that perhaps that with every further procedure the chance of a solution to the problem increased (i.e., not developing any further arch problems). In contrast, the chronic risk of problems related to the LVOT increased with every subsequent procedure, suggesting that with every further procedure the chance of a solution decreases (i.e. developing further LVOT problems). We also demonstrated that complex interrelationships exist among these subsequent procedures by using time-varying covariates, such that the choice of surgical or catheter-based procedures can impact whether or not a procedure is definitive, and

that subsequent procedures adversely affected mortality. Most importantly, we demonstrated an overall theme that IAA is a chronic disorder and not a structural anomaly definitively treated in the newborn period. This assembly of analytic techniques has created a new interpretation of the impact of IAA on a patient, the patient's family, and clinicians: IAA is a chronic disorder with lifelong implications.

In Chapter 3, widely applied generic FHS questionnaires were utilized in order to assess the self-reported FHS of patients with IAA. These results were then compared to normative data, and factors associated with lower scores in each domain of the CHQ-CF87 in adolescents, and the SF-36 in adults, were determined. This study found that morbidities related to 22q11DS, psychosocial issues, and recurrent medical problems affect the self-reported FHS of IAA survivors, and dominate in comparison to factors related to cardiac history (i.e. morphologic and procedural variables). Nonetheless, both adolescents and adult survivors generally perceive themselves to have the same or higher FHS than their peers – a seemingly paradoxical association that may reflect several well-described phenomena (i.e., response shift, disability paradox, sense of coherence). The models that we produced have goodness of fit generally higher than those presented in the literature in other cohorts of patients with CHD, suggesting that we have been able to accurately elucidate factors that adversely affect FHS[148]. Determination of these factors has provided us with targets for improving the care of patients with IAA. Therefore, evaluation and surveillance strategies aimed at definitive surgical treatment, improved mental health, and the treatment of issues related to 22q11DS should be important components of comprehensive cardiac care in both adolescence and adulthood. These findings should reassure us that despite the chronic nature of IAA, these patients generally have FHS that they feel is comparable to their peers. Ongoing assessment of FHS in this cohort will be required to detect deteriorations related to increasing medical complexity, changes that result from further interventions, and stress associated with mature adult roles.

In Chapter 4, an evaluation of the adult survivors within our cohort of patients with IAA was presented with the aim of assessing (for the first time) transition to adult care in this population with chronic disease using time-related analysis techniques. While analyzing the factors

associated with transition to adult care in IAA patients, we determined that there was earlier and more complete transition to adult care in Canada, and that this may also strongly be influenced by institutional programs related to transition. From the patterns we found associated with transition to adult care, it is clear that a systematic formalized approach is helpful to successfully transition patients to ACHD care. The self-reported low levels of patient knowledge and high level of parental/guardian involvement demonstrated in our study, have the potential to improve through transition programs focused on patient education. While transition to ACHD care is evolving and can be accomplished effectively within many clinical models, such as those with transition programs, the high proportion of transition to adult care in Canada highlights a model warranting further investigation. More specifically, areas of further investigation should include funding sources (government as a universal single payer versus other forms) and care networks. This will help ensure that patients with rare diseases, such as IAA, receive continuity of care across transition.

5.2 Limitations

There are a number of potential general and study-specific limitations that warrant discussion.

General limitations

The first set of limitations result from these studies being based on a prospective observational inception cohort design, with annual follow-up and cross-sectional questionnaire administration. It should be noted that causal relationships cannot be demonstrated using this methodology, but would require a randomized control trial which would not have been an appropriate methodology.

As IAA is a rare lesion, a cohort of patients was assembled from 32 institutions in the U.S., Canada, and Brazil. While this allowed the CHSS to obtain an adequate number of patients to

include in the study, this methodology is not without its inherent flaws. Firstly, the patients involved in this study were primarily recruited from tertiary care centres involved with the CHSS. While patients with IAA are generally treated at tertiary care centres, the fact that these centres were involved with the CHSS may have had an impact on the study. This is because the 100 members of the CHSS are a select group of surgeons who require sponsorship to become a member, prior to allowing enrollment of their patients into this cohort. This membership is partially based on research productivity and duration of time in practice. Consequently, there is selection bias inherent in the cohort, as these patients were from a select group of centres, operated on by a select group of surgeons involved in research. This has the potential to affect the care that they have received. Although we can hypothesize that the treatment at these tertiary centers was "better" and as a consequence, these patients did better, it should be noted that the majority of patients with IAA would have required referral to a tertiary care centre (minimizing bias).

Secondly, all patients with IAA who presented to any of the 32 institutions participating in this cohort within 30 days of birth, between 1987 and 1997, were approached for enrollment for this cohort. However, the design of this study prevents us from knowing the true number of patients with IAA who could have been enrolled (i.e. the number of patients who met enrollment criteria). The design of this cohort limits us only to those centres who agree to participate, to those patients who agreed to participate at each centre, and we are therefore uncertain whether all patients meeting the enrollment criteria were enrolled, possibly resulting in selection bias. Unfortunately, we do not have any data regarding the number of patients who refused participation. Due to the possibility of this selection bias, we are unsure whether those patients who were enrolled are different from those who were not enrolled, as we do not have any baseline information regarding unenrolled patients. We also had a significant percentage of patients enrolled in this study whom the CHSS Data Center were not allowed to contact, but whom the institutions were required to follow, as per the regulations of their research ethics boards. While we included these patients in our denominator, as we felt this would be most accurate, our response rate was lowered as a result of this. It should be noted that in many studies, patients who cannot be contacted are not included in the denominator in order to boost response rates. Because we had very little data provided to us by these institutions about these

patients, with almost no annual follow-up, selection bias could have resulted from the fact that these patients from these few centres were different based on underlying characteristics, institutional differences or preferences prevalent in their care. Questionnaire responders may also be different than non-responders as they needed to survive the duration of time until the study, leading us to the hypothesis that they may healthier than non-responders, therefore introducing selection bias into our results as both groups may be inherently different with regard to their health status.). Finally, it should be noted that while follow-up was only considered complete if patients returned their annual questionnaire, that most recent follow-up date was obtained for every patient (Social Security Death Master File search, home institution/relatives contacted, etc.).

Another disadvantage of long-term follow-up studies is era effect, which is the tradeoff for the long duration of follow-up in these studies. Era effect denotes the fact that changes in medical and surgical therapy have occurred throughout the duration of the study follow-up period. While the enrollment period (1987-1997) afforded impressive long-term follow-up, it represented an "early era" in the techniques of the index repair. Outcomes have significantly improved in the more recent era. For example, Morales and colleagues, examining a cohort undergoing repair between 1995 and 2005, reported 100% freedom from a subsequent arch procedure at 5 years[191]. However, it is also generally recognized that single institution results are better than multi-institution outcomes[191]. Having an understanding of the era in which adults with CHD were managed is imperative, because these patients will always have been managed at some time in the past. From the study by Morales, it will be interesting to determine how the hazard for subsequent arch and LVOT procedures develops beyond a decade of follow-up. In addition, examining the FHS of patients within a more contemporary cohort may give us a better impression of whether medical management can improve FHS, although the variables examined which were related to this were not found to have a significant impact on FHS. As FHS gains importance, it will be interesting to see whether patients treated in the current era will have different FHS profiles than our cohort, and it will be important to clarify this. In addition, because the field of pediatric cardiac surgery is relatively new and the majority of programs are also relatively young, it is hard to predict the effect of this on transition to adult care, and this will need further examination.

While it is possible that there were changes in management during the enrollment period and thereafter, we were unable to clearly elicit these due to the large number of patients and centres involved in our study. It should be noted, that with regards to the CHD, there are no formal guidelines, and practice is often surgeon or institution specific. As a result of this, although techniques can change over time, widespread adoption of a given practice is never uniform. However, our large multi-institutional cohort, did provide us with the ability to capture this practice variation.

The next limitation pertains to the fact that the questions for the analyses were not all determined a priori to the study design, as such information which could have otherwise been collected, was not available. For example, data related to age and level of education of parents, ethnicity, and socioeconomic status were not available. If the questions were defined a priori, the CHSS Data Center would have been able to make an effort to obtain these data. Also, the indications for procedures were not recorded (solely the occurrence of procedure was recorded), and this important piece of information was unobtainable. While the CHSS Data Center are aware of the value of this information, because congenital heart surgery is a young field with multiple rare lesions, there are very limited guidelines, and much of the surgical decision making is based on surgeon and institutional preference in collaboration with cardiology. Therefore, although this can be viewed as a limitation, it would be next to impossible to predict what drove decision making in individual patients.

Finally, a large number of variables were tested in all studies, which can increase the risk of spurious results associated with multiple comparisons. In order to minimize the risk of this, we only included variables which had a bootstrap or a bootstrap cluster reliability greater than 50%, and which obtained significance in the final model in all studies. In order to minimize the number of variables tested and to create simplicity in explaining variables, we did not test for interactions.

Study-specific limitations

Subsequent procedures study

This study had two important study-specific limitations. First, because this was an observational inception study, we were unable to serially and consistently measure the morphologic characteristics (e.g., LVOT diameter) that might have helped to explain the associations among subsequent procedures observed. Second, this study focused on an analysis of subsequent procedures rather than on variables measuring the evolving pathologic features and pathophysiology (which might have helped explain the pattern of subsequent procedures). As with the morphologic data, the latter would require a prospective study designed with the intent to measure these variables.

Functional health status study

There are several study-specific limitations associated with this study. The first was that the response rate was suboptimal. Due to various logistical issues, it was difficult to establish contact with a large population of patients primarily dispersed across Canada and the U.S., and this may have contributed to an undetected response bias. As stated in chapter 3, 56 of these patients needed to be contacted directly by the institution, and there was also a proportion of patients with whom we had not been in contact with for more than 10 years. Although we detected very few differences between responders and non-responders when all variables were compared, non-responders may differ in other non-measured ways that may impact FHS that we were unable to capture. Although it is difficult to predict which way the non-responders may have affected our results, it can be hypothesized that non-responders have poorer socioeconomic status, more mental health issues and therefore have poorer FHS based on the variables we elucidated as being associated with lower FHS scores. On the other hand, one method that the CHSS uses to find patients is contacting the institution at which the patient is followed. It could consequently be theorized that those who were lost to follow-up were lost because they had fewer medical

problems and had not been seen recently, and therefore may have had better FHS in relation to the fact that they had fewer recent procedures.

There were also several issues related to our use of questionnaires. By selecting questionnaires that were not disease-specific, disease-specific measures may have been overlooked, which would have been important to our assessment of FHS in this population. However, the reason these questionnaires were selected was because both the CHQ-CF87 and SF-36 are widely validated questionnaires and allowed for comparison with normative data. Another, major drawback of the questionnaires is that there is no established consensus on how large a difference in domain score must be in order to achieve clinical significance (MCID), as opposed to statistical significance alone. While MCID is an important idea, there are several remaining conceptual and empirical problems which remain, that pertain to whether the same values differ if used for single time points versus over time[131]. There are also remaining questions regarding whether these differences can be applied equally to improvement and deterioration, or to all disease groups, and what method should be used to determine MCID[131]. However, it is established that MCID values for groups is different from that for individual scores[214], and that the MCIDs for groups are usually smaller than that for individuals, partially because the size of group mean differences do not affect the precision of a measurement (they affect the standard error), and also because one cannot assume that all individuals will be affected in the same direction[131]. While the manual for the SF-36 does provide MCIDs with values given above and below specific ranges in certain cases, many of them have qualifications[131]. The MCIDs provided were also created based on the assumption that the baseline score for the group being evaluated is lower than the average for the general population, which does not appear to be the case for our population (Table 5.1)[131]. No data regarding MCID values for the CHQ-CF87 could be found.

The use of the 22q11DS questionnaire which we developed was a limitation as it was an unvalidated questionnaire, which we used in a purely qualitative fashion. Ideally, we would have been able to have all patients genetically tested for a diagnosis of 22q11DS and their physical and psychosocial features verifies, but this was not possible with regard to our study design.

Patients provided self-reported information regarding the various potential features of 22q11DS, although we were unable to confirm whether they had a genetic diagnosis. However, we felt that this was sufficient as it is the phenotypic expression that affects FHS, not simply having the genotype. Ideally, we would have had corroborating information from a health care practitioner regarding these features and their treatment.

As the CHQ-CF87 and SF-36 questionnaires are self-report questionnaires, those patients who were so cognitively impaired that they were unable to complete the questionnaire were excluded, and unrepresented within our study. Both the CHQ-CF87 and SF-36 are self-report questionnaires, and as such, if patients were unable to complete these alone, results could not be included (i.e. were not valid). However, it is undeniable that these patients contribute to the picture of FHS in patients with IAA, and their exclusion was a limitation of our study which chose to focus on the self-reported perspective of patients, which is thought to be the most important perspective by some, as opposed to that of parents or guardians. In addition, while it can be speculated that these patients may have poorer FHS in certain domains, this may not be true in all domains (e.g. (freedom from) Bodily Pain, and Family Cohesion). Questionnaires were also excluded if parents helped patients complete the questionnaire, or completed it inadvertently.

Finally, another limitation is that no tool is appropriate for use in both the adolescent and adult population. Common generic questionnaires are often age group specific and deal with age specific issues. The questions within them are also formulated so that patients within the age group can easily comprehend them. Consequently, direct comparisons cannot be made between the results of the 2 questionnaires. Both questionnaires have different domains, and even when similar domains are compared, the number and content of the items (i.e., questions) that comprise each domain are often not equivalent. While we did attempt to combine similar domains statistically, when we evaluated whether being in one age group or the other was statistically significant, it often was, and thus we abandoned this approach. As a result, we are left with the concern that using different questionnaires may have led us to different answers. This is a concern that can only be resolved when a single questionnaire appropriate to both age

groups is developed, or when the entire study population falls within a range whereby they can be assessed with one questionnaire. As we have compared our results to the normative data suggested; however, there may be significant differences between our population of patients and the normative data related to multiple demographic, socioeconomic, and cultural factors which we could not determine. We only had access to the published means and standard deviations for the normative data, and not the values for every patient. This only allowed us to compare the data against a hypothetical mean.

Transition to adult care study

The present study had several important limitations. One of the limitations of our study was that the exact date of transition could not be determined and was self-reported. As a result, we obtained a date range from patients regarding when they saw a physician for adults, which required our study to use of interval censoring as opposed to a method which utilized the exact date. This information was obtained directly from patients in a retrospective fashion through the transition questionnaire. It would have been preferable to determine the date of transition in a prospective fashion, so that the exact date could have been recorded. It should also be noted that we used the age when adult care was first established as the age at transition; however, we are uncertain whether this therapeutic relationship was maintained. In a prospective setting, transition to adult or ACHD care could have been better ascertained.

Transition was also defined as the first incidence of care (visit or intervention) with a physician providing care to adults focused on heart issues, or an investigation or procedure at an adult facility. This definition was used as various models of care occur in the U.S. and Canada, at both pediatric and adult hospitals, by adult cardiologists and pediatric cardiologists, when patients transition to adult care. However, certain pediatric physicians follow their patients for life, and these patients may have not been included in those patients who are classified as having transitioned. We were also concerned whether patients could understand the subtle differences in the various types of physicians who provide care for them (e.g. heart doctor for adults vs. heart doctor who sees adult patients who had a heart condition/heart surgery as a child).

Finally, the use of the transition questionnaire that we developed was a limitation as it was an unvalidated questionnaire, which we used in a purely qualitative fashion.

5.3 Implications of research

While the unifying theme of this thesis was to demonstrate the utility of multi-institutional prospective inception cohort studies in rare lesions, the results of the three studies presented in this dissertation have both general and study-specific implications which can be applied directly to the care of patients.

General implications

First, we have demonstrated the successful use of multi-institutional prospective inception cohort databases to study numerous outcomes. While we have already specified the limitations present within this thesis in the preceding section, the methodology and data that we have used also has tremendous advantages. The data and methods used have allowed us to evaluate a rare lesion, in a relatively cost-effective manner that may not have been otherwise possible.

A second implication of this study, which has been demonstrated using not only the IAA cohort but also other cohorts studied by the CHSS, is that multi-institutional cooperation is vital to evaluate long-term outcomes in rare lesions. Rare lesions requiring surgical treatment are problematic, because no individual surgeon or physician can obtain adequate experience with any single lesion. The model used at the CHSS Data Center focuses on individual lesions, and by enrolling patients from multiple centres, this allows the entire range of pathologies within any diagnosis, and the various treatment pathways to be represented. This observational research method should be further translated to other specialties with rare congenital lesions. With the increase in survivors of congenital disease, and a subsequent shift in research interest from mortality to long-term functional outcomes.

Study-specific implications

Subsequent procedures

There are numerous implications from our study related to subsequent procedures in patients with IAA. For the first time, the extent of subsequent procedures was demonstrated, with patients in our cohort having up to 11 subsequent procedures. The first implication from this finding is that patients with IAA require a lifetime of follow-up and surveillance for recurrent issues, so the infrastructure required for this type of care must be put into place. As we demonstrated, many patients are currently lost to follow-up (CHSS Data Center and home institution unable to contact patient), and the possible dangers of this should not be underestimated when the importance of lifetime health care is explained to patients and their families. In addition, these patients require appropriate referral to centres with the ACHD care expertise; a resource that is currently lacking for numerous reasons in many areas across the world[158, 168, 181].

As related to the chronicity of recurrence for aortic arch and LVOT procedures, our research demonstrates that while aortic arch issues recur in the acute phase, LVOT procedures recur during the chronic phase. As a result, follow-up should be tailored to mirror this pattern, with patients who have had aortic arch procedures undergoing increased evaluation early, while those who have had LVOT procedures undergo increased surveillance in the late phase. We also demonstrated that catheter-based procedures were less likely to be definitive, and this will perhaps change the likelihood that practitioners opt for surgical therapy, as opposed to catheter-based therapy, which appears to be a temporary solution.

Ultimately, the chronic nature of IAA must be understood by all those involved. Patients, families, and practitioners providing care for this group of patients should first and foremost be made aware that the index repair will likely not be the last intervention required by a patient. They should also be made aware of the chronicity of recurrence, the likelihood of needing a further subsequent intervention based on modality of repair chosen, and that they require a

specialized infrastructure, which must be available and sought after, to manage their condition along with the growing number of survivors with the same lesion.

Functional health status

There are two interesting implications from our study on FHS in patients with IAA. The first implication is that IAA patients have self-reported FHS that is generally the same or better than their normal counterparts. Although our response rate could allow for differences that may change this trend, as discussed previously the finding of same or better scores has been reported in other studies of FHS. If our finding is accurate, it reminds those physicians and the public who may wonder why we push so hard to save these patients, that these patients may ultimately have self-perceived FHS perhaps better than our own.

Second, the primary groups of variables that we determined to be adversely associated with FHS in adolescents and adults should be targeted as areas, which if treated or managed, can improve FHS in this population. The main groups of variables which we found associated with lower FHS in the CHQ-CF87 were those related to mental health status, the presence of a genetic condition or testing for a genetic condition, and those undergoing a higher number of “other” or catheter-based interventional procedures. The groups of variables associated with lower SF-36 scores also included those related to mental health status and total number of procedures, in addition to recurrent childhood infections requiring medication or admission, low calcium levels, behavioral problems, and shorter time since last procedure. Although it is not possible to affect whether or not a patient has a genetic anomaly, treatment of morbidities associated with 22q11DS should be targeted to issues such as mental health and behavioral problems, immunodeficient conditions, hearing and speech problems, and low calcium levels. Another focus for improving FHS could be aimed at reducing the total number of procedures. Surgical strategies or interventional therapies aimed at decreasing the number of interventions required, or those providing a definitive or more durable repair should be an area of focus. Therefore, evaluation and surveillance strategies aimed at definitive surgical treatment, improved mental health, and the

treatment of issues related to 22q11DS should be an important program component of cardiac care in both adolescence and adulthood.

Transition to adult care

The primary finding from the IAA cohort in the transition study was that increased transition to adult care was associated with country of residence. It was not found to be associated with factors related to the demographic or morphologic variables, cumulative numbers of procedures, or time since last surgical procedure or procedure of any kind. In addition, previous CHQ-CF87 scores in the TGA analysis were not associated with transition. Although country of residence was found to be an associated factor, the majority of patients were from one institution (7/8). It is therefore difficult to decipher whether it is the country of residence that was an associated factor, or whether this was simply a surrogate for the institution. The institutional practices at this Canadian institution, which has a targeted transition program, should be more closely investigated. Alternatively, the other programs should be further investigated to determine whether patients who do not meet the criteria set out in our study of transition receive any other forms of follow-up, allowing patients to receive appropriate care. In addition, further evaluation of the health care system factors which may be different in both the U.S. and Canada should be completed.

From our study, we can see that while the transition rates to adult care are less than optimal, that patient knowledge, the role of parental involvement, and the need for improved infrastructure are important. Although the term “ideal care” may be a grand concept, the data suggests that there are several essential features that would improve the rate of transition to ACHD care. Foster et al. described 6 features of successful transfer that we believe are essential: a policy related to timing of transfer, a preparation/education program for the patient beginning in adolescence, a coordinated transfer process, an interested and well equipped adult facility, administrative assistance, and the involvement of primary care[182]. Patients should be educated regarding their lesion, surgeries, medications, and any residual lesions they have that may require ongoing or future follow-up. In addition, patients and their care providers (e.g. general practitioners,

cardiologists, and surgeons) should be provided with comprehensive notes on all previous care including operative and catheterization reports, complications, and anticipated therapies which should be transferred in an organized fashion. We believe it is essential that a transition program should include counseling on topics such as education, career, endocarditis prophylaxis, insurance, sexuality and reproduction, cardiovascular risk factors, physical activity, and follow-up specific to each patient's lesion[211]. Patients with ACHD should also have access to physicians and a multi-disciplinary team of the highest quality who have formal education in the field, including cardiologists, surgeons, and echocardiographers[181]. This is especially important when determining where these adult patients undergo procedures, whether at a children's or adult hospital, or tertiary care facility[212]. Indeed much of this has been elaborated in the recommendations of the 32nd Bethesda Conference held in 2000, which detailed how ACHD services could be ideally delivered in the U.S.[152, 182, 184, 185, 213].

From the patterns and factors we have found associated with transition to adult care, it is clear that a systematic, formalized approach is required to successfully transition patients to ACHD care. This is especially important as they will often face acquired hypertension, coronary artery disease, and other cardiovascular issues, which may compound their congenital diagnosis. Patients are rarely "cured" of their problem, and this common misconception must be avoided to ensure patients receive appropriate management as adults. This will help ensure that as these patients age they receive the best care possible.

5.4 Future directions for research

The limitations and implications presented in this chapter have highlighted several important directions for future study in patients with IAA.

Our study on subsequent procedures found most importantly that IAA is a chronic disease and that patients often undergo numerous procedures, thus highlighting the need for studies to determine which repairs are the most definitive. Future studies of this topic could be conducted in three areas. The first area is definitive repairs. One method to help determine which repairs are most definitive, would be to examine the comparative durability of repairs for specific lesions at various levels of the LVOT and the aortic arch. Although this would require a large number of patients and the cooperation of numerous institutions, randomized control trials comparing different repairs, or studies looking at the risk of subsequent procedures in groups of patients who underwent a given strategy would allow us to once determine which repairs have the least risk of further intervention. If successful, this would allow patients to undergo fewer procedures, and ultimately decrease mortality, which increases with each subsequent procedure, as demonstrated in this thesis. The primary restriction in performing randomized control trials is that they are highly unfeasible for numerous reasons which include difficulty recruiting adequate numbers of patients, surgeon or patient preference for a given procedure, inability to blind appropriately, and follow-up issues including inadequate resources for the duration of required follow-up[215]. The second area is repetition of our study with detailed patient data (anatomical and hemodynamic) due to a priori determination of the questions being posed. Our study of subsequent procedures would have benefitted from inclusion of detailed anatomical and hemodynamic measurements which we did not have, in order to assess how these features increased or decreased the risk of a subsequent procedure. As a result, a prospective study in which there was primary and standardized longitudinal data collection, including anatomical and hemodynamic measurements not captured in our study, could be carried out in order to predict the likelihood of subsequent events based on native and changing patient characteristics. Finally, it would be valuable to carry out a similar analysis on a contemporary cohort, of patients with IAA, to determine whether our results regarding subsequent procedures would remain the same in the face of current medical and surgical treatment. Determination of the hazard for subsequent procedures beyond a decade in a contemporary cohort should be analyzed. Although generally results don't change as fast as expected, verification of this is an important next step. While a study of the comparative durability of various techniques would require a randomized controlled trial or studies with extremely large numbers of patients, with its inherent difficulties in a surgical context, the latter two could be undertaken in a carefully designed contemporary inception cohort study.

There are four clear areas for future research that have been elucidated from our work on FHS in patients with IAA. One of the limitations of our work was that patients above and below the age of 18 could not be directly compared due to the use of two different FHS questionnaires, although the age of 18 is an arbitrary cut point. As such, our research has shown the need for a tool that can be used across a wide age range, and it has demonstrated the need for a tool that can be used across the time period when patients are transitioning from adolescence to adulthood. This is especially important as patients do not all develop at the same rate, and cognitive and mental function may not be similar in patients above and below the age of 18. The development and validation of an appropriate tool, or the validation of an existing tool for use in this context is required. Our current study on FHS also demonstrated that factors related to repeated procedures, mental health, and genetic issues, had an adverse association with the FHS of patients with IAA. The effect of targeted strategies to ameliorate these factors should be assessed by repeated assessment of FHS before and after intervention. More specifically, FHS should be assessed before and after subsequent procedures, before and after interventions to improve mental health, and before and after therapies to improve the conditions associated with 22q11DS. These assessments of FHS could help determine which therapies are most effective at improving FHS in areas that are known to adversely affect it. The third area of study should be targeted at repeated assessments of FHS in order to determine the particular events and stresses causing deteriorations or variations in FHS, in comparison to day to day variability. As there is currently limited assessment of FHS in patients with CHD in the literature, this would provide another area where factors adversely affecting FHS could be targeted and improved. Finally, a natural progression of our work would be to assess this population using a disease-specific tool, which would provide further insights into the role of disease in these patients.

The area that could perhaps be most easily targeted to benefit patients is transition to ACHD care, and our study helped delineate several areas for future study. While many groups have outlined structured transition plans and the components necessary within transition programs, one target for further evaluation should be the rates of transition in settings where these programs are and are not implemented. Another area of study relates to the fact that there are numerous

clinical models in both Canada and the U.S. Transition rates should be assessed for the different clinical models in Canada and especially within the U.S., where there is much more variation, to determine which models allow for the highest transition to ACHD care. A more careful assessment would allow identification of those models with the best rates of transition, so that similar programs could be adopted by those with lower rates of transition. Rates of transition should also be assessed to determine which models provide the highest rates in relation to target age of transition, target age at start of transition, the effect of targeted discussions regarding future care, and written timelines and roles for stakeholders (patients, parent(s)/guardian(s), general practitioners). While the ideas presented in this paragraph are predicated on the assumption that transition is beneficial to patients, and although it is likely that transition is better than no follow up at all, studies should assess the difference in care received and clinical outcomes between those who are transitioned to adult care, and those who remain under the care of their pediatric physicians. Future research should also address the barriers and incentives to transition, and even the causes of lapsed care, with a focus on the effect of patient health care coverage in the U.S. These studies would also ideally be completed in order to allow comparison of targeted strategies to increase transition in settings with and without the intervention to determine the effects on rates of transition to adult care.

These proposed studies highlight the areas that require future evaluation in patients with IAA. The results of these studies once complete, in combination with the results presented within this thesis, will help provide a comprehensive and cohesive approach to the care of patients with IAA.

5.5 Conclusions

In conclusion, this dissertation has demonstrated the effective use of multi-institutional prospective inception cohort studies to examine rare lesions by evaluating their long-term outcomes in multiple dimensions. This dissertation has followed the progress of IAA patients

from the time of their index repair, to looking at their FHS in adolescence and adulthood, and their transition to adult care.

Using novel statistical techniques, we demonstrated the chronic nature of IAA whereby patients often require multiple procedures after their index repair. We elucidated the chronicity of recurrence and the factors associated with subsequent arch and LVOT procedures after the index repair, and most importantly we determined the effect of the type of procedure and its timing on subsequent procedures. We then provided the first evaluation of FHS in patients with IAA, and demonstrated that these patients had FHS scores that were surprisingly the same or better than their peers despite the chronic nature of their illness. We found that the factors most commonly associated with lowering scores were those features suggestive of 22q11DS, the presence of self-reported behavioral/mental health problems, and a higher number of procedures. Depending on the FHS domain, factors explained from 10% up to 70% of score variability; values higher than those previously reported. Finally, as suspected, we demonstrated that the transition of these patients to adult care was poor, and that the primary factor associated with transition was related to country of residence, which may have acted as a surrogate for a program with an established transition program with highly accessible ACHD care. We also found that these patients had a surprisingly poor level of knowledge regarding their condition, that their parents remained heavily involved in their care despite the fact that they were now young adults, and that the majority were still cared for by pediatric cardiologists despite rather than having transitioned to adult care.

These inter-related studies have provided us with new insights to add to the body of knowledge regarding IAA. These studies have also helped us to identify ways to improve the lives of patients living with IAA by targeting the findings of our studies as not only new avenues for research, but as areas where immediate actions can be taken for immediate results. We have also identified the need for research to identify definitive therapies, to repeatedly assess FHS and understand the events that cause it to fluctuate, and to better understand the barriers and incentives to transition to ACHD care. Although IAA is currently a chronic disease requiring a lifetime of care, we hope that through the work done in this dissertation, and through future

work, that it will one day be seamlessly treated and managed, giving these patients a life equal to those without this disease.

5.6 Tables for chapter 5

Table 5.1: Minimal clinically important differences for the component summary scores and domains of the Short Form-36 Health Survey.

SF-36 Component summary or domain	Minimal clinically important difference
Physical component summary (PCS)	2-3
Mental component summary (MCS)	3
Physical functioning (PF)	2 for scores below 40 3 for scores at or above 40
Role-physical (RP)	2
(Freedom from) Bodily pain (BP)	2 for scores below 40 3 for scores at or above 40
General Health (GH)	2 for scores below 40 3 for scores at or above 40
Vitality (VT)	2 for scores below 40 3 for scores at or above 40
Social functioning (SF)	3
Role-emotional (RE)	4
Mental health (MH)	3

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Appendices

Appendix 2.1: Participating Congenital Heart Surgeons' Society institutions.

Institution name
United States
University of Alabama at Birmingham, Birmingham, Alabama
The Children's Hospital, Denver, Colorado
Miami Children's Hospital, Miami, Florida
University of Miami, Miami, Florida
All Children's Hospital, St. Petersburg, Florida
Loma Linda University Medical Center, Loma Linda, California
Children's Hospital of Los Angeles, Los Angeles, California
University of California, Los Angeles, School of Medicine, Center for Health Science, Los Angeles, California
Children's Hospital and Health Center, San Diego, California
University of California, San Francisco, California
Children's Memorial Hospital, Chicago, Illinois
University of Chicago, Chicago, Illinois
University of Iowa Hospitals and Clinics, Iowa City, Iowa
The Children's Hospital, Boston, Massachusetts
Mott Hospital, Ann Arbor, Michigan
Children's Hospital of Michigan, Detroit, Michigan
Mayo Clinic, Rochester, Minneapolis
University of Nebraska, Nebraska, Nevada
Children's Hospital of Buffalo, Buffalo, New York
Columbia Presbyterian, New York, New York
Duke University Medical Center, Durham, North Carolina
Children's Hospital Medical Center, Cincinnati, Ohio
Milton S. Hershey Medical Center, Hershey, Pennsylvania
The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
St. Christopher's Hospital for Children, Philadelphia, Pennsylvania
Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Medical University of South Carolina, Charleston, South Carolina
Primary Children's Hospital, Salt Lake City, Utah
Canada
British Columbia Children's Hospital, Vancouver, British Columbia
Sick Kids Hospital, Toronto, Ontario
Montreal Children's Hospital, Montreal, Quebec
International
Heart Institute, Sao Paulo, Brazil

Appendix 2.2: Statistical methods.

Flow charts were created to track patients through multiple consecutive procedures to death or the last follow-up visit.

Nested competing risks

Competing risks analyses were used to examine the rates of transition from an initial state (hazard function) to the mutually exclusive time-related events of various procedure types or death without that procedure type. This was used to determine the proportion of patients reaching these events or states at any given time after the initial state.

Competing risks analyses were performed in a similar manner for each of the following mutually exclusive, competing outcomes: 1) from the index IAA repair to either death or a first subsequent arch procedure; 2) from a first subsequent arch procedure to either death or a second subsequent arch procedure; 3) from the index IAA repair to either death or a first subsequent LVOT procedure (still at risk or no longer at risk of subsequent LVOT procedures); and 4) from a first subsequent LVOT procedure to either death or a second subsequent LVOT procedure. Patients considered no longer at risk of LVOT procedures, underwent repairs such as the Damus-Kaye-Stansel or heart transplantation, and were censored at that time. This was also done within the modulated renewal context (see below). For each competing risks analysis, non–risk-adjusted nonparametric estimates for time-related freedom from death or the specified procedure type were plotted using the Kaplan-Meier method. The underlying hazard function was modeled parametrically, determining multiple phases of risk, as previously described[188]. All graphs were truncated when approximately 10% of patients remained at risk.

Modulated renewal

Repeated arch and LVOT procedures were analyzed as time-related repeating events with the unit of study being the patient and not the procedure (arch or LVOT). Nelson's cumulative event method provided nonparametric estimates, and a multiphase hazard method provided the parametric estimates[188, 216]. Because the temporal pattern of risk for each additional subsequent event was similar, we used the modulated renewal process method[217]. For this, the patients experiencing a first event were restarted at a new time zero and tracked to a second event, and so forth, for each successive event[217].

Risk analysis

We used multiple imputation using the Markov Chain Monte Carlo technique to impute the missing values[218]. We used fivefold multiple imputation using the Statistical Analysis Systems procedure PROC MI, version 9.2 (SAS Institute, Inc, Cary, NC). In multivariable hazard modeling, for each imputed complete data set, we have estimated the regression coefficients and their variance-covariance matrix. Then, using the method of Rubin, we combined the estimates from the 5 models[218]. This was performed using the SAS procedure PROC MIANALYZE, version 9.2 (SAS Institute, Inc, Cary, NC). The relevant missing value indicator variables were created and included in multivariable analyses to adjust for possible bias introduced by missing data.

The demographic, morphologic, and procedural factors associated with each outcome were sought through multivariable analysis of these parametric models. Only variables with less than 40% of data missing, and those associated with more than 5 events were included, to minimize the risk of model overdetermination. For continuous variables, different mathematic transformations were tested for optimal calibration of the relationship to risk (note, for the interval from the index procedure to the most recent procedure this was calculated as 1/(variable þ 1), as the intervals were 0 in some cases), and the significance of various interaction terms was explored. Nine as time-varying covariates were created to adjust for the effects of other

procedures in our risk analyses. These variables included the length of the interval from the index procedure to the most recent procedure of a given type (arch, LVOT, ‘‘other’’), specification of the most recent procedure (arch, LVOT, ‘‘other’’), and the number of cumulative procedures of each type (arch, LVOT, ‘‘other’’; see the example patient described, which demonstrates how these variables were created). To ensure adjustment for these as time-varying covariates, these variables were always included in the bootstrap modeling used to assess for variable entry reliability. For the arch model, all time-varying intervals and specification of the most recent procedure type (LVOT or ‘‘other’’) were always included in the multivariable modeling. For the LVOT model, no as time-varying covariates were included because the number of events was less, and the initial attempts at model building with these variables included showed they were not significant. For the mortality model, all as time-varying covariates were always included in the modeling, except for the most recent procedure as an arch procedure. An initial bootstrap was performed without mandating inclusion of any specific variable into the modeling to determine which transformation of the interval variables should always be included in the subsequent final model building. Bootstrap bagging was then performed, again with these as time-varying covariates always included, and clustering of the variables was used to further guide the final variable selection and to assess the reliability of the variable inclusion into the final multivariable models. Missing value indicator variables were entered into the final multivariable models, as appropriate.

The risk factors for subsequent arch and LVOT procedures were initially identified by bootstrap bagging variable selection using 500 resampled data sets[219]. P = .01 was used in the automated analysis as variable entry criteria. From the output, variables or clusters of variables appearing in 50% or more of the bootstrap sample analyses were considered sufficiently reliable for inclusion in the final multivariable model building.

Factors Associated With Mortality

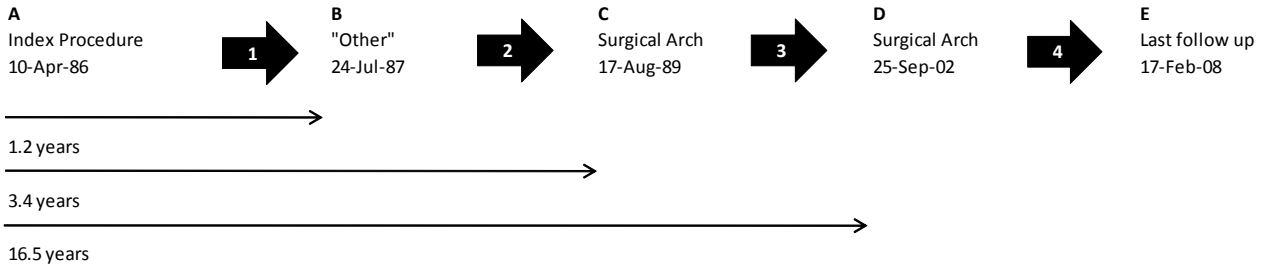
The factors associated with mortality were explored within the same modulated renewal context as repeated procedures by handling the event of death as a competing risk[220]. This allowed us to

include occurrences of preceding procedural events and their timing, number, type, and interaction as potential associated factors for death. Non-proportionality of risk was accommodated using the multiphase hazard method[188].

Example Patient

The following example patient demonstrates a sample sequence of events for an IAA patient. This patient underwent 3 subsequent procedures after the index procedure. Each procedure was given 1 record in the data set, resulting in 4 records, and the as time-varying covariate variables change for each record. The first set of 3 variables denoted the most recent procedure type (pr_aar, pr_lvot, pr_oth). The next set of 3 variables denoted the cumulate number of each type of procedure (cum_aar, cum_lvot, cum_oth). The final set of 3 variables denoted the interval from the index procedure to the most recent procedure of that type in years (iv_aar, iv_lvot, iv_oth). As this example is followed through the 4 procedures, the adjustment in the as time-varying covariates can be seen.

Example Patient



		pr_aar	pr_lvot	pr_oth	cum_aar	cum_lvot	cum_oth	iv_aar	iv_lvot	iv_oth
Record 1	A to before B	1	0	0	1	0	0	0	0	0
Record 2	B to before C	0	0	1	1	0	1	0	0	1.2
Record 3	C to before D	1	0	0	2	0	1	3.4	0	1.2
Record 4	D to before E	1	0	0	3	0	1	16.5	0	1.2

Variable Names	**Definition**
pr_aar	Most recent procedure is an arch procedure
pr_lvot	Most recent procedure is an LVOT procedure
pr_oth	Most recent procedure is an "other" procedure
cum_aar	Cumulative number of arch procedures
cum_lvot	Cumulative number of LVOT procedures
cum_oth	Cumulative number of "other" procedures
iv_aar	Time interval from the index procedure to the most recent arch procedure (years)
iv_lvot	Time interval from the index procedure to the most recent LVOT procedure (years)
iv_oth	Time interval from the index procedure to the most recent "other" procedure (years)

Appendix 2.3: Type of subsequent aortic arch, left ventricular outflow tract, and "other" procedures stratified by the subsequent procedure number. ASD – atrial septal defect. LVOT – left ventricular outflow tract. PA – pulmonary artery. PFO – patent foramen ovale. RVOT – right ventricular outflow tract. VSD – ventricular septal defect.

A. Type of aortic arch procedure	**1st**	**2nd**	**3rd**	**4th**	**≥5**	**TOTAL**
Balloon dilation of aortic arch	54	8	2	1	2	**67**
Patch augmentation of aortic arch	38	12	3			**53**
End to end anastomosis	5		1			**6**
Aorto-aortic bypass	10	1				**11**
Replace aorto-aortic bypass	5	4				**9**
Aortic interposition graft	7	5				**12**
TOTAL	**119**	**30**	**6**	**1**	**2**	**158**

B. Type of LVOT procedure	1st	2nd	3rd	4th	≥5	TOTAL
Balloon dilation of aortic valve	12	2				14
Balloon dilation of aortic and subaortic region	3		1			4
Balloon dilation of subaortic region	1					1
Fibromuscular resection	34	6	4			44
Fibromuscular resection, aortic valvuloplasty	2	1				3
Aortic valvuloplasty	2	1				3
Konno procedure	6	9	1			16
Modified Konno, aortic valvuloplasty		1				1
Ross/Konno procedure	2		1			3
Left ventricle to aorta conduit	1					1
Rastelli procedure	3					3
Truncal valvuloplasty	1					1
Damus-Kaye-Stansel procedure	2					2
Mechanical aortic valve replacement		2		1		3
Aortic annular enlargement, mechanical valve replacement, fibromuscular resection			1			1
TOTAL	**69**	**22**	**8**	**1**	**0**	**100**

C. Type of surgical "other" procedure	1st	2nd	3rd	4th	≥5	TOTAL
Heart transplant	1	2				
Arterial switch, ASD/PFO, VSD closure	2					
Double switch		1				
Atrial switch, deband PA, VSD closure	1					
Atrial switch, Rastelli	1					
Rastelli procedure	4					
Damus-Kaye-Stansel		1				
Glenn procedure	6					
Adjust modified Glenn		1				
Hemi-fontan	4					
Hemi-fontan, deband PA, atrial septectomy	1					
Fontan	2	6	1		1	
Pulmonary conduit	1					
Pulmonary conduit, VSD closure	1					
Right ventricular outflow tract patch, muscle bundle resection, deband PA	1					
Pulmonary conduit reoperation ± ASD/PFO closure ± PA procedure ± repair RVOT pseudoaneurysm	4	2			2	
ASD/PFO closure	3					
VSD + ASD closure	17	2	1			
VSD closure + ASD closure, deband PA, PA procedure	31	2				
VSD closure ± PA procedure ± ligation of innominate artery	2	2				
VSD + ASD closure, left ventricle to right atrial patch	1					
Aortopexy		1				
Patch one or both Pas	1	1	1			
Patch repair of both PAs, pacemaker		1				
PA band or revision of PA band	5					

C. Type of surgical "other" procedure (continued)	1st	2nd	3rd	4th	≥5	TOTAL
Deband PA, patch main PA	1					
Systemic to PA shunt	2					
Systemic to PA shunt revision or replacement		1	1			
Aortopulmonary window repair	4					
Release bronchial compression	2	1				
Right ventricular outflow tract patch					1	
Tricuspid valve repair		1				
Tricuspid valve repair, PFO, VSD closure	1					
Ligation of main pulmonary artery					1	
Remove thrombus in right atrium		1				
Replace VSD patch	1					
Other	3					
TOTAL	**103**	**25**	**5**	**0**	**5**	**138**

D. Type of catheter-based "other" procedure	1st	2nd	3rd	4th	≥5	TOTAL
Balloon conduit and/or pulmonary artery(ies)	8	5	2	3		**18**
Balloon aorta-left pulmonary artery shunt	1					**1**
Balloon superior vena cava			1			**1**
Balloon and stent conduit and/or pulmonary artery (ies)	8	4	1	2	4	**19**
Balloon pulmonary artery and stent innominate artery		1				**1**
Balloon and stent innominate artery	1					**1**
Coil occlusion of collateral		2	1	1	3	**7**
Balloon of pulmonary artery and coil occlusion of collateral	1					**1**
Balloon and blade septostomy of atrial septum	1					**1**
Endocardial biopsy post-transplant	1	2	1			**4**
TOTAL	**21**	**14**	**6**	**6**	**7**	**54**

Appendix 2.4: Final multivariable model for subsequent aortic arch procedures, left ventricular outflow tract procedures, and mortality after index procedure. LVOT – left ventricular outflow tract. VSD – ventricular septal defect. PTFE – polytetrafluoroethylene. IAA – interrupted aortic arch. PA – pulmonary artery. *Variables without reliability estimates were always included in models as time-varying covariate adjustment factors.

VARIABLES	Estimate ± Standard Error	p-value	Reliability*
SUBSEQUENT AORTIC ARCH PROCEDURES			
EARLY PHASE			
Time interval from index procedure to the most recent arch procedure (years) (inverse transformation)	13±4.1	0.002	
Most recent procedure is an LVOT procedure	-2.8±1.1	0.02	
Time interval from index procedure to the most recent LVOT procedure (years)	0.82±0.25	0.001	
Most recent procedure is an "other" procedure	-5.1±1.4	0.0002	
Time interval from index procedure to the most recent "other" procedure (years)	0.69±0.25	0.006	
Presence of aortopulmonary window	0.77±0.36	0.03	54%
Age at the time of index procedure (years) (inverse transformation)	0.22±0.07	0.001	66%
Index procedure included a concomitant LVOT procedure	3.1±1.2	0.01	52%
Left subclavian artery used to repair aortic arch during index procedure	1.4±0.45	0.002	70%
VSD closed during index procedure	-0.61±0.25	0.01	54%
Most recent procedure is a surgical arch procedure	-2.8±0.87	0.002	65%
LATE PHASE			
Time interval from index procedure to the most recent arch procedure (years) (inverse transformation)	2.5±0.70	0.0003	
Most recent procedure is an LVOT procedure	-1.7±0.63	0.008	
Time interval from index repair to the most recent LVOT procedure (years) (inverse transformation)	-3.3±0.77	<0.0001	
Most recent procedure is an "other" procedure	1.4±0.44	0.0009	
Time interval from index repair to the most recent "other" procedure (years) (inverse transformation)	2.3±0.69	0.001	
Presence of truncus arteriosus	2.0±0.44	<0.0001	67%
Date of birth – study enrollment start date (years) (natural log transformation)	-0.51±0.13	<0.0001	72%
PTFE interposition graft used to repair aortic arch during index procedure	1.8±0.31	<0.0001	93%
Cumulative number of arch procedures	0.97±0.19	<0.0001	77%

SUBSEQUENT LEFT VENTRICULAR OUTFLOW TRACT PROCEDURES			
EARLY PHASE			
Presence of an anomalous right subclavian artery	0.88±0.34	0.01	76%
Homograft pulmonary artery used to repair aortic arch during index procedure	1.1±0.34	0.0008	51%
Most recent procedure is the index procedure	0.86±0.40	0.03	50%
LATE PHASE			
VSD of small or medium size	1.2±0.39	0.002	70%
PTFE interposition graft used to repair aortic arch during index procedure	0.98±0.43	0.02	60%
MORTALITY			
EARLY PHASE			
Cumulative number of arch procedures	1.5±0.27	<0.0001	
Time interval from index procedure to the most recent arch procedure (years) (natural log transformation)	-1.3±0.58	0.03	
Most recent procedure is a LVOT procedure	0.48±0.48	0.3	
Cumulative number of LVOT procedures	0.34±0.43	0.4	
Time interval from index procedure to the most recent LVOT procedure (years)	0.28±0.11	0.01	
Most recent procedure is an “other” procedure	-0.22±0.44	0.6	
Cumulative number of “other” procedures	1.1±0.23	<0.0001	
Time interval from index procedure to the most recent “other” procedure (years)	-0.59±0.26	0.02	
VARIABLES RELATED TO MORPHOLOGY			
Male	-0.47±0.16	0.004	69%
Presence of truncus arteriosus	1.20±0.22	<0.0001	80%
Date of birth – study enrollment start date (years)	-0.19±0.03	<0.0001	65%
VSD of small or medium size	0.46±0.21	0.03	62%
Hypoplastic left heart – Class I	-0.72±0.19	0.0001	57%
VARIABLES RELATED TO INDEX IAA REPAIR			
Weight at index procedure (kilograms) (inverse transformation)	2.3±0.84	0.006	72%
Index procedure done via thoracotomy	-1.4±0.33	<0.0001	50%
Pulmonary artery banding procedure done at index procedure	1.1±0.31	0.0003	54%
Systemic to PA arterial shunt created during index procedure	0.73±0.24	0.002	79%
VARIABLES RELATED TO PROCEDURES AFTER THE INDEX IAA REPAIR			
Subsequent VSD closure	1.2±0.35	0.0009	67%
Subsequent procedure with total circulatory arrest	1.4±0.33	<0.0001	82%
Subsequent aortic procedure with patch augmentation	-1.4±0.56	0.01	62%

Appendix 3.1: Participating Congenital Heart Surgeons' Society institutions.

Institution name
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University of Alabama at Birmingham, Birmingham, Alabama
The Children's Hospital, Denver, Colorado
Miami Children's Hospital, Miami, Florida
University of Miami, Miami, Florida
All Children's Hospital, St. Petersburg, Florida
Loma Linda University Medical Center, Loma Linda, California
Children's Hospital of Los Angeles, Los Angeles, California
University of California, Los Angeles, School of Medicine, Center for Health Science, Los Angeles, California
Children's Hospital and Health Center, San Diego, California
University of California, San Francisco, California
Children's Memorial Hospital, Chicago, Illinois
University of Chicago, Chicago, Illinois
University of Iowa Hospitals and Clinics, Iowa City, Iowa
The Children's Hospital, Boston, Massachusetts
Mott Hospital, Ann Arbor, Michigan
Children's Hospital of Michigan, Detroit, Michigan
University of Nebraska, Nebraska, Nevada
Children's Hospital of Buffalo, Buffalo, New York
Columbia Presbyterian, New York, New York
Duke University Medical Center, Durham, North Carolina
Children's Hospital Medical Center, Cincinnati, Ohio
Milton S. Hershey Medical Center, Hershey, Pennsylvania
The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Medical University of South Carolina, Charleston, South Carolina
Primary Children's Hospital, Salt Lake City, Utah
Canada
Sick Kids Hospital, Toronto, Ontario
Montreal Children's Hospital, Montreal, Quebec
International
Heart Institute, Sao Paulo, Brazil

Appendix 3.2: 22q11 Deletion Syndrome questionnaire and raw responses. n = 141.

Genetic conditions

1) Have you ever had any genetic or DNA testing? Please check one only.

Yes	72=52%
No	52=38%
Do not know	14=10%
Missing	3=2%

2) If you have had genetic or DNA testing, why did you have this genetic testing done? Please check one only.

I have not had genetic or DNA testing	36/52=85%
Possible problem	48/70=69%
Routine Testing	2/70=3%
Do not know	5/70=7%
Other	15/70=21%
Missing	2/72=7%

If other (please specify)	15
To confirm genetic defect	2
?DiGeorge	3
?22q11	1
? Velocardiofacial Syndrome (VCFS)	1
Voluntary	1
Other	7

3) Have you ever been diagnosed with any genetic conditions? Please check one only.

Yes	48=36%
No	77=57%
Do not know	10=7%
Missing	6=4%

4) If the answer to question 3 is yes, what condition have you been diagnosed with?

22q11	8/43=19%
DiGeorge	22/43=51%
VCFS	7/43=16%
DiGeorge/VCFS	1/43=2%
Heart related condition	2/43=5%
Truncus arteriosus	1/43=2%
Other	2/43=5%
Missing	5/48=10%

Learning, Behavior, and Mental Health

5) Have you ever had difficulties with learning in school (e.g. did you need special assistance)? Please check one only.

Yes	99=71%
No	40=29%
Do not know	0=0%
Missing	2=1%

6) If the answer to question 5 is yes, what type of learning problems have you had?

Special education	16/75=21%
Subject/language/speech difficulties/ Cognitive/comprehension/ Development/processing/learning	45/75=60%
Concentration/ADD/ADHD	9/75=12%
ADHD with either special education or Learning issue	2/75=3%
Other	3/75=4%
Missing	24/99=24%

7) Have you ever had any behavioral problems in school (e.g. suspension)? Please check one only.

Yes	27=19%
No	111=80%
Do not know	1=1%
Missing	2=1%

8) If the answer to question 7 is yes, what behavioral problems have you had?

Detention/Suspension	4/21=19%
Anger/frustration/talking back or in class Losing control/hitting/inappropriate Behavior	7/21=33%
Social skills	2/21=10%
Trouble focusing	1/21=5%
Autism/not sitting in seat/not obeying/OCD	1/21=5%
Apathy	1/21=5%
Self-injury/hitting/threatening/cursing	1/21=5%
DiGeorge/anxiety	1/21=5%
Panic attacks/autism	1/21=5%
ADHD/Graves disease	1/21=5%
Nothing serious	1/21=5%
Missing	6/27=22%

9) Have you ever had any mental health counseling by a social worker, psychologist, or psychiatrist? Please check one only.

Yes	50=36%
No	88=63%
Do not know	2=1%
Missing	1=1%

10) If the answer to question 9 is yes, why did you have counseling?

Mood/fear/anxiety/depression/suicidal	8/33=24%
Psychiatric	1/33=3%
Family/divorce/abuse	4/33=12%
Behavior/anger	4/33=12%
Social skills	1/33=3%
ADHD	1/33=3%
Autism	2/33=6%
Combination of social/ADD/ADHD	1/33=3%
Combination ADD/depression/social	1/33=3%
Combination behavior/agitation/ Aggression/OCD	1/33=3%
Patient's request	1/33=3%
Parent's request	1/33=3%
Psychiatric related	2/33=6%
Unable to determine patient's given answer	1/33=3%
Other	5/33=15%
Don't know	1/33=3%
Missing	17/50=34%

11) Have you ever taken medication for mental health problems? Please check one only.

Yes	29=21%
No	110=79%
Do not know	0=0%
Missing	2=1%

12) Have you ever been diagnosed with anxiety? Please check one only.

Yes	20=14%
No	115=82%
Do not know	5=4%
Missing	1=1%

13) Have you ever been diagnosed with depression? Please check one only.

Yes	8=6%
No	128=92%
Do not know	3=2%
Missing	2=1%

14) Have you ever been diagnosed with schizophrenia? Please check one only.

Yes	2=1%
No	134=96%
Do not know	3=2%
Missing	2=1%

Other Medical Problems

Hearing

15) Have you ever had your hearing tested and been told it wasn't normal? Please check one only.

Yes	31=22%
No	104=75%
Do not know	4=3%
Missing	2=1%

16) If the answer to question 15 is yes, why was your hearing abnormal?

Anatomical defect	5/17=29%
Hearing loss/deafness	7/17=41%
Fluid in ears	2/17=12%
Fluid in ears/auditory processing disorder	1/17=6%
Chronic ear infections	1/17=6%
Don't know	1/17=6%
Missing	14/31=45%

17) Do you wear hearing aids? Please check one only.

Yes	6=4%
No	129=96%
Missing	6=4%

Calcium

18) Have you ever had low calcium levels? Please check one only.

Yes	27=20%
No	85=61%
Do not know	27=19%
Missing	2=1%

19) If the answer to question 18 is yes, why did you have low calcium levels?

As infant/child	4/14=29%
DiGeorge/?DiGeorge	3/14=21%
Hypoparathyroidism	4/14=29%
?Genetic	1/14=7%
After heart surgery	1/14=7%
During pregnancy	1/14=7%
Missing	13/27=48%

20) Has a doctor ever given you calcium supplements or medication to correct your calcium levels? Please check one only.

Yes	27=20%
No	104=76%
Do not know	6=4%
Missing	4=3%

Thyroid

21) Have you ever had any problems with your thyroid? Please check one only.

Yes	12=9%
No	112=82%
Do not know	13=9%
Missing	4=3%

22) If the answer to question 21 is yes, what problem did you have?

Hypothyroidism	4/7=57%
Thyroid removal	1/7=14%
At birth	1/7=14%
Underdeveloped at birth	1/7=14%
Missing	5/12=42%

Other

23) Have you ever had any speech therapy at any time in your life? Please check one only.

Yes	87=63%
No	51=37%
Do not know	1=1%
Missing	2=1%

24) If the answer to question 23 is yes, why did you have speech therapy?

Articulation/pronunciation	19/51=37%
Delayed speech	6/51=12%
Cognitive issues	6/51=12%
Anatomical issues	6/51=12%
Cleft palate	5/51=10%
Any combination of above	6/51=12%
Feeding issues	1/51=2%
DiGeorge syndrome	1/51=2%
Unclear from patient answer	1/51=2%
Missing	36/87=41%

25) Did you have recurrent childhood infections requiring medication or admission to hospital? Please check one only.

Yes	30=22%
No	106=77%
Do not know	1=1%
Missing	4=3%

26) Have you ever been told by a doctor that you have any abnormal facial features? Please check one only.

Yes	32=23%
No	99=72%
Do not know	6=4%
Missing	4=3%

Appendix 4.1: Participating Congenital Heart Surgeons' Society institutions.

Institution name
United States
Miami Children's Hospital, Miami, Florida
All Children's Hospital, St. Petersburg, Florida
Loma Linda University Medical Center, Loma Linda, California
Children's Hospital of Los Angeles, Los Angeles, California University of California, Los Angeles, School of Medicine, Center for Health Science, Los Angeles, California
Children's Hospital and Health Center, San Diego, California
University of California, San Francisco, California
Children's Memorial Hospital, Chicago, Illinois
University of Chicago, Chicago, Illinois
University of Iowa Hospitals and Clinics, Iowa City, Iowa
The Children's Hospital, Boston, Massachusetts
Mott Hospital, Ann Arbor, Michigan
Children's Hospital of Michigan, Detroit, Michigan
University of Nebraska, Nebraska, Nevada
Columbia Presbyterian, New York, New York
Children's Hospital Medical Center, Cincinnati, Ohio
Milton S. Hershey Medical Center, Hershey, Pennsylvania
The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania
Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania
Primary Children's Hospital, Salt Lake City, Utah
Canada
Sick Kids Hospital, Toronto, Ontario
Montreal Children's Hospital, Montreal, Quebec
International
Heart Institute, Sao Paulo, Brazil

Appendix 4.2: Transition questionnaire with raw responses. n = 75. There are 42 patients <20 years of age. There are 33 patients ≥ 33 years of age.

Level of Care Currently being Received

1) **How many months ago was the last time you saw a heart doctor for children (pediatric cardiologist)? Please check one only.**

	Total	**Under 20**	**≥20**
0-6 months ago	31=42%	21=51%	10=30%
7-12 months ago	13=18%	9=22%	4=12%
13-24 months ago	13=18%	7=17%	6=18%
25-48 months ago	2=3%	1=2%	1=3%
More than 48 months ago	12=16%	1=2%	11=33%
Do not know	3=4%	2=4%	1=3%
Other (please specify):	0=0%	0=0%	0=0%
Missing	1=1%	1=2%	0=0%

2) **Is a heart doctor for children (pediatric cardiologist) still the primary doctor responsible for care of your heart condition? Please check one only.**

	Total	**Under 20**	**≥20**
Yes	53=73%	36=90%	17=52%
No	19=26%	3=8%	16=48%
Other (please specify):	1=1%	1=2%	0=0%
Not sure because the doctor changes	1		
Missing	2=3%	2=5%	0=0%

3) **How many months ago was your last appointment that focused on your heart condition, with any type of doctor? Please check one only.**

	Total	**Under 20**	**≥20**
Still seeing heart doctor for children	53=72%	36=88%	17=52%
0-6 months ago	4=5%	2=5%	2=6%
7-12 months ago	8=10%	1=2%	7=21%
13-24 months ago	6=8%	1=2%	5=15%
25-48 months ago	1=1%	0=0%	1=3%
More than 48 months ago	0=0%	0=0%	0=0%
Do not know	2=3%	1=2%	1=3%
Other (please specify):	0=0%	0=0%	0=0%
Missing	1=1%	1=2%	0=0%

4) What type of doctor did you see at your last appointment related to your heart condition? Please check one only.

	Total	Under 20	≥20
Still seeing heart doctor for children	53=75%	36=88 %	17=57%
Walk-in Clinic Doctor	0=0%	0=0%	0=0%
General practitioner/Family doctor	3=4%	1=2%	2=7%
Emergency room doctor	1=1%	1=2%	0=0%
Heart doctor for adults	6=8%	0=0%	6=20%
Heart doctor who sees adults who had a heart condition/heart surgery as a child	4=6%	0=0%	4=13%
Heart surgeon for children	4=6%	3=7%	1=3%
Heart surgeon for adults	0=0%	0=0%	0=0%
Do not know	0=0%	0=0%	0=0%
Other (please specify):	0=0%	0=0%	0=0%
Missing	4=5%	1=2%	3=9%

5) Where did you see the doctor who saw you at your last appointment that focused on your heart condition? Please check one only.

	Total	Under 20	≥20
Walk-in Clinic	2=3%	2=5%	0=0%
Emergency room at a children's hospital	1=1%	1=2%	0=0%
Emergency room at an adult hospital	0=0%	0=0%	0=0%
Office of a general practitioner/family doctor	2 =3%	1=2%	1=3%
Office of a specialist outside of a hospital	10=13%	7=16%	3=9%
Children's Hospital	33=44%	22=51%	11=34%
Adult Hospital	15=20%	2=5%	13=39%
Adult/Children's Hospital	10=13%	6=14%	4=13%
Do not know	1=1%	0=0%	1=3%
Other (please specify):	1=1%	1=2%	0=0%
Hospital outreach clinic	1		
Missing	0=0%	0=0%	0=0%

6) At your last appointment that focused on your heart condition,

a. did you have a physical examination? Please check one only.

	Total	Under 20	≥20
Yes	46=63%	30=70%	16=52%
No	23=32%	11=26%	12=39%
Do not know	4=6%	1=2%	3=10%
Missing	2=3%	0=0%	2=6%

b. did you have an Electrocardiogram (ecg)? Please check one only.

	Total	Under 20	≥20
Yes	58=77%	33=79%	25=76%
No	12=16%	6=14%	6=18%
Do not know	5=7%	3=7%	2=6%
Missing	0=0%	0=0%	0=0%

c. did you have an Echocardiogram (echo)? Please check one only.

	Total	Under 20	≥20
Yes	59=79%	36=86%	23=70%
No	13=17%	5=12%	8=24%
Do not know	3=4%	1=2%	2=6%
Missing	0=0%	0=0%	0=0%

d. did you have an Exercise test (bicycle or treadmill)? Please check one only.

	Total	Under 20	≥20
Yes	11=15%	7=17%	4=12%
No	62=83%	33=79%	29=88%
Do not know	2=3%	2=5%	0=0%
Missing	0=0%	0=0%	0=0%

e. did you have a Perfusion Scan of the heart? Please check one only.

	Total	Under 20	≥20
Yes	6=8%	4=10%	2=6%
No	57=77%	31=76%	26=79%
Do not know	11=15%	6=15%	5=15%
Missing	1=1%	1=2%	0=0%

f. did you have a CT Scan (Computed Tomography Scan) of the heart? Please check one only.

	Total	Under 20	≥20
Yes	7=10%	4=10%	3=9%
No	57=78%	32=78%	25=78%
Do not know	9=12%	5=12%	4=13%
Missing	2=3%	1=2%	1=3%

g. did you have an MRI (Magnetic Resonance Imaging Scan) of the heart? Please check one only.

	Total	Under 20	≥20
Yes	19=25%	13=31%	6=18%
No	51=68%	28=67%	23=70%
Do not know	5=7%	1=2%	4=12%
Missing	0=0%	0=0%	0=0%

h. did you have any other tests? If yes, please specify.

	Total	Under 20	≥20
X-ray	2	1	1
Pacemaker interrogation	1	1	0
Holter monitor for 24 hours	1	0	1
Blood tests	2	0	2
Pacemaker – Test to determine blood clots	1	0	1

7) How often are you generally seen for your heart condition when you are doing well? Please check one only.

	Total	Under 20	≥20
Every 0-6 months	8=11%	6=14%	2=6%
Every 7-12 months	35=47%	19=45%	16=48%
Every 13-24 months	21=28%	10=24%	11=33%
Every 25-48 months	9=12%	6=14%	3=9%
Less often than every 48 months	1=1%	0=0%	1=3%
Do not know	1=1%	1=2%	0=0%
Other (please specify):	0=0%	0=0%	0=0%
Missing	0=0%	0=0%	0=0%

First Appointment

8) Have you ever seen a heart doctor for adults (adult cardiologist) or a heart doctor who sees adult patients who had a heart condition/heart surgery as a child (adult congenital cardiologist),
<u>OR</u>
had a heart related procedure (test, heart catheterization or heart surgery) at an adult hospital?

	Total	**Under 20**	**≥20**
Yes	21=32%	7=19%	14=48%
No	43=65%	29=78%	14=48%
Do not know	2=3%	1=3%	1=3%
Other (please specify):	0=0%	0=0%	0=0%
Missing	9=12%	5=12%	4=12%

9) If your answer to Question 8 was 'Yes', when was the first time this happened?

	Total	**Under 20**	**≥20**
My answer to Question 8 was 'No', 'Do not know', or 'Other'	45=69%	30=83%	15=52%
0-6 months ago	3=5%	2=6%	1=3%
7-12 months ago	8=12%	2=6%	6=21%
13-24 months ago	3=5%	1=3%	2=7%
25-48 months ago	1=2%	1=3%	0=0%
More than 48 months ago	5=8%	0=0%	5=17%
Do not know	0=0%	0=0%	0=0%
Other (please specify):	0=0%	0=0%	0=0%
Missing	10=13%	6=14%	4=12%

10) If your answer to Question 8 was 'Yes', were you sent for this appointment/procedure before or after your 18th birthday? Please check one only.

	Total	**Under 20**	**≥20**
My answer to question 8 was 'No', 'Do not know', or 'Other'	45=69%	30=83%	15=52%
Before 18th birthday	4=6%	2=6%	2=7%
After 18th birthday	16=25%	4=11%	12=41%
Do not know	0=0%	0=0%	0=0%
Other (please specify):	0=0%	0=0%	0=0%
Missing	10=13%	6=14%	4=12%

11) Where was this appointment/procedure? Please note for this question, we request you to check ALL that apply.

	Total	Under 20	≥20
My answer to Q8 was no	45=69%	30=81%	15=54%
Have not had a medical appointment since the age of 18	1=2%	1=3%4	0=0%
Walk-in Clinic	0=0%	0=0%	0=0%
Emergency room at a children's hospital	0=0%	0=0%	0=0%
Emergency room at an adult hospital	0=0%	0=0%	0=0%
Office of a general practitioner/family doctor	0=0%	0=0%	0=0%
Office of a specialist outside of a hospital	0=0%	0=0%	0=0%
Children's Hospital	2=3%	1=3%	1=4%
Adult Hospital	10=15%	2=5%	8=29%
Adult/Children's Hospital	5=8%	2=5%	3=11%
Do not know	2=3%	1=3%	1=4%
Other (please specify):	0=0%	0=0%	0=0%
Missing	10=13%	5=12%	5=15%

12) Was this appointment/procedure arranged by the hospital you were seen at as a child? Please check one only.

	Total	Under 20	≥20
My answer to Q8 was no	45=68%	30-81%	15=52%
Have not had a medical appointment since the age of 18	1=2%	1=3%	0=0%
Yes	12=18%	4=11%	8=28%
No	4=6%	2=5%	2=7%
Do not know	4=6%	0=0%	4=14 %
Other (please specify):	0=0%	0=0%	0=0%
Missing	9=12%	5=12%	4=12%

13) Was this an urgently arranged appointment/procedure or part of your routine follow-up? Please check one only.

	Total	Under 20	≥20
My answer to Q8 was no	45=68%	30=81%	15=52%
Have not had a medical appointment since the age of 18	1=2%	1=3%	0=0%
Urgently arranged appointment	2=3%	2=5%	0=0%
Part of routine follow-up	18=27%	4=11%	14=48%
Do not know	0=0%	0=0%	0=0%
Other (please specify):	0=0%	0=0%	0=0%
Missing	9=12%	5=12%	4=12%

14) Approximately when was your first routine heart related appointment after your 18th birthday? Please check one only.

	Total	Under 20	≥20
Have not had a medical appointment since the age of 18	14=19%	11=27%	3=9%
0-6 months after your 18th birthday	36=49%	19=46%	17=52%
7-12 months after your 18th birthday	6=8%	2=5%	4=12%
More than 12 months after your 18th birthday	5=7%	0=0%	5=15%
Do not know	8=11%	4=10%	4=12%
Other (please specify):	5=7%	5=12%	0=0%
Still seeing pediatric cardiologist will transition in January 2011	1	1	0
Still seeing pediatric cardiologist	3	3	0
Being set up by Toronto General, will call with appointment	1	1	0
Missing	1=1%	1=2%	0=0%

15) Was there a change in location/hospital made to your follow-up when you became 18? Please check one only.

	Total	Under 20	≥20
Yes	13=18%	4=10%	9=27%
No	52=70%	32=78%	20=61%
Do not know	7=9%	3=7%	4=13%
Other (please specify):	2=3%	2=5%	0=0%
It changed at 19	1	1	0
No appointment since the age of 18	1	1	0
Missing	1=1%	1=2%	0=0%

16) Was there a change in doctor made to your follow-up when you became 18? Please check one only.

	Total	Under 20	≥20
Yes	17=23%	5=13%	12=56%
No	52=71%	32=80%	20=63%
Do not know	4=5%	3=8%	1=3%
Other (please specify):	0=0%	0=0%	0=0%
Missing	2=3%	2=5%	0=0%

17) Have you had a booked medical appointment regarding your heart since the age of 18 with any of the following types of doctors? Please note for this question, we request you to check ALL that apply.

	Total	Under 20	≥20
Have not had a medical appointment since the age of 18	12	8	4
General practitioner/family doctor	14	6	8
Heart doctor for children	31	22	9
Heart doctor for adults	10	2	8
Heart doctor who sees adults who had a heart condition/heart surgery as a child	6	1	5
Heart surgeon for children	5	4	1
Heart surgeon for adults	1	1	0
Do not know	1	0	1
Pediatric Cardiologist who sees Adults	2	0	2
Other (please specify):	0	0	0

14 patients selected 2 items
2 patients selected 3 items

Ideal Care

18) How often do you think you should be seen by a doctor about your heart condition? Please check one only.

	Total	Under 20	≥20
Every 0-6 months	10=15%	7=19%	3=10%
Every 7-12 months	31=47%	18=50%	13=43%
Every 13-24 months	19=29%	7=19%	12=40%
Every 25-48 months	5=8%	4=11%	1=3%
Less often than every 48 months	1=2%	0=0%	1=3%
Do not know	0=0%	0=0%	0=0%
Other (please specify):	0=0%	0=0%	0=0%
Missing	9=12%	6=14%	3=9%

Individual Factors

19) Which of the following are you? Please check one only.

	Total	Under 20	≥20
Single	73=97%	41=98%	32=97%
Common-law	1=1%	1=2%	0=0%
Married	1=1%	0=0%	1=3%
Separated	0=0%	0=0%	0=0%
Divorced	0=0%	0=0%	0=0%
Other (please specify):	0=0%	0=0%	0=0%
Missing	0=0%	0=0%	0=0%

20) Who do you live with? Please note for this question, we request you to check ALL that apply.

	Total	Under 20	≥20
Parents	60	35	25
Spouse	1	0	1
Partner	1	1	0
Friend	1	0	1
College/university residence	8	2	6
With family member or family friend	2	2	0
On own	2	0	2
Other (please specify):	6	3	3
Grandparents	2	2	0
Group home	4	1	3

3 patients selected 2 items
1 patient selected 3 items

21) What is your current educational status? Please check one only.

	Total	Under 20	≥20
Part time student	9=12%	4=9%	5=15%
Full time student	41=55%	30=71%	11=33%
No longer attending school	16=21%	3=7%	13=39%
Planning to go back to school	8=11%	5=12%	3=9%
Other (please specify):	1=1%	0=0%	1=3%
Special education	1		
Missing	0=0%	0=0%	0=0%

22) What is your current employment status? Please check one only.

	Total	Under 20	≥20
Working part time	19=25%	9=21%	10=30%
Working full time	6=8%	0=0%	6=18%
Not currently employed	30=40%	20=47%	10=30%
Not currently employed, but looking for work	4=5%	2=5%	2=6%
Unable to work due to medical reasons	12=16%	8=19%	4=12%
Homemaker	0=0%	0=0%	0=0%
Other (please specify):	4=5%	3=7%	1=3%
Summer, full time	1	0	1
During the summer	1	1	0
Self-employed	1	1	0
Work co-op with school life	1	1	0
Missing	0=0%	0=0%	0=0%

23) To what educational level have you completed? Please check one only.

	Total	Under 20	≥20
No formal schooling	1=1%	1=2%	0=0%
Between grade1-8	1=1%	0=0%	1=3%
Between grades 9-11	14=19%	11=27%	3=10%
High school graduate	29=41%	18=44%	11=37%
Trade or technical school	1=1%	1=2%	0=0%
Some community college	11=15%	4=10%	7=23%
Community college graduate	2=3%	0=0%	2=7%
Some university	5=7%	1=2%	4=13%
University graduate	0=0%	0=0%	0=0%
Other (please specify):	7=10%	5=12%	2=7%
Some technical school	1	1	0
DSE class	1	0	1
Grade 12	4	4	0
Special needs program in high school No grade level	1	0	1
Missing	4=5%	1=2%	3=9%

24) Do your parent(s)/guardian(s) still take you to your appointments related to your heart? Please check one only.

	Total	Under 20	≥20
Yes	59=79%	37=88%	22=67%
No	12=16%	5=12%	7=21%
Sometimes	4=5%	0=0%	4=12%
Other (please specify):	0=0%	0=0%	0=0%
Missing	0=0%	0=0%	0=0%

25) If your parent(s)/guardian(s) do not take you to any of your appointments related to your heart, do you go your appointments by yourself? Please check one only.

	Total	Under 20	≥20
My parent(s)/guardian(s) still take me to all of my appointments	59=84%	37=95%	22=71%
Yes	8=11%	2=5%	6=20%
No	2=3%	0=0%	2=6%
Other (please specify):	1=2%	0=0%	1=3%
Group home takes him to most appointments	1	0	1
Missing	5=7%	3=7%	2=6%

26) If your parent(s)/guardian(s) take you to all or some of your appointments related to your heart, do they wait in the waiting room? Please check one only.

	Total	Under 20	≥20
My parent(s)/guardian(s) do not take me to any of my appointments	12=16%	5=13%	7=21%
Yes	23=32%	12=30%	11=33%
No	29=40%	17=43%	12=36%
Sometimes	8=11%	5=13%	3=9%
Other (please specify):	1=1%	1=2%	0=0%
To keep abreast my status, they speak to doctor once my visit is completed	1	1	
Missing	2=3%	2=5%	0=0%

27) If your parent(s)/guardian(s) take you to all or some of your appointments related to your heart, do they come inside and see the doctor with you? Please check one only.

	Total	Under 20	≥20
My parent(s)/guardian(s) do not take me to any of my appointments	12=16%	5=13%	7=21%
Yes	52=71%	30=75%	22=67%
No	3=4%	2=5%	1=3%
Sometimes	5=7%	2=5%	3=9%
Other (please specify)	1=1%	1=3%	0=0%
Yes. Once I have finished with Dr.	1	1	0
Missing	2=3%	2=3%	0=0%

28) If your parent(s)/guardian(s) take you to all or some of your appointments related to your heart, do they do most of the talking at your appointment? Please check one only.

	Total	Under 20	≥20
My parent(s)/guardian(s) do not take me to any of my appointments	12=17%	5=13%	7=22%
Yes	28=39%	18=46%	10=31%
No	10=14%	4=10%	6=19%
Sometimes	20=28%	12=31%	8=25%
Other (please specify)	1=1%	0=0%	1=3%
Unspecified	1	0	1
Missing	4=5%	3=7%	1=3%

29) Have you ever attended an appointment related to your heart without your parent(s)/guardian(s)? Please check one only.

	Total	Under 20	≥20
Yes	13=18%	5=12%	8=25%
No	61=82%	36=88%	25=76%
Other (please specify)	0=0%	0=0%	0=0%
Missing	1=1%	1=2%	0=0%

30) How many months has it been since your parent(s) or guardian(s) have attended an appointment related to your heart and came inside to see the doctor with you? Please check one only.

	Total	Under 20	≥20
My parent(s)/guardian(s) still take me to all of my appointments	59=81%	37=93%	22=67%
0-6 months ago	3=4%	1=3%	2=6%
7-12 months ago	1=1%	1=3%	0=0%
13-24 months ago	4=5%	1=3%	3=9%
25-48 months ago	2=3%	0=0%	2=6%
More than 48 months ago	3=4%	0=0%	3=9%
Do not know	1=1%	0=0%	1=3%
Other (please specify):	0=0%	0=0%	0=0%
Missing	2=3%	2=5%	0=0%

31) What do you think your level of knowledge is about your heart condition? Please check one only.

	Total	Under 20	≥20
No Knowledge	7=9%	5=12%	2=6%
Some Knowledge	34=45%	19=45%	15=45%
Moderate Knowledge	12=16%	4=10%	8=24%
Good Knowledge	16=21%	11=26%	5=15%
Thorough knowledge	6=8%	3=7%	3=9%
Missing	0=0%	0=0%	0=0%

32) How much is your heart condition impacting the quality of your life? Please check one only.

	Total	Under 20	≥20
No impact	30=40%	13=31%	17=52%
Mild impact	19=25%	10=24%	9=27%
Some impact	11=15%	9=21%	2=6%
Moderate impact	9=12%	5=12%	4=12%
Severe impact	6=8%	5=12%	1=3%
Missing	0=0%	0=0%	0=0%

33) How much is your heart condition impacting your overall health? Please check one only.

	Total	Under 20	≥20
No impact	34=45%	19=45%	15=45%
Mild impact	20=27%	11=26%	9=27%
Some impact	10=13%	5=12%	5=15%
Moderate impact	5=7%	2=5%	3=9%
Severe impact	6=8%	5=12%	1=3%
Missing	0=0%	0=0%	0=0%

34) How much is your heart condition impacting your ability to be physically active? Please check one only.

	Total	Under 20	≥20
No impact	25=33%	13=31%	12=36%
Mild impact	21=28%	12=29%	9=27%
Some impact	12=16%	8=19%	4=12%
Moderate impact	8=11%	3=7%	5=15%
Severe impact	9=12%	6=14%	3=9%
Missing	0=0%	0=0%	0=0%

35) Are you currently having any of the following symptoms?

a. Chest pain at rest. Please check one only.

	Total	Under 20	≥20
Yes	4=6%	2=5%	2=6%
No	64=89%	36=90%	28=88%
Do not know	1=1%	0=0%	1=3%
Other (please specify):	3=4%	2=5%	1=3%
Sometimes	2	1	1
Mild but rarely happens could collapse to sometimes	1	1	0
Missing	3=4%	2=5%	1=3%

b. Chest pain with activity. Please check one only.

	Total	Under 20	≥20
Yes	4=6%	2=5%	2=6%
No	56=78%	29=73%	27=84%
Do not know	3=4%	2=5%	1=3%
Other (please specify):	9=13%	7=18%	2=6%
Sometimes	8	6	2
Mild could collapse or leave as unspecified	1	1	0
Missing	3=4%	2=5%	1=3%

c. Shortness of breath at rest. Please check one only.

	Total	Under 20	≥20
Yes	4=6%	3=8%	1=3%
No	67=94%	36=92%	31=97%
Do not know	0=0%	0=0%	0=0%
Other (please specify):	0=0%	0=0%	0=0%
Missing	4=5%	3=7%	1=3%

d. Shortness of breath with activity. Please check one only.

	Total	Under 20	≥20
Yes	25=35%	14=35%	11=34%
No	41=57%	23=58%	18=56%
Do not know	0=0%	0=0%	0=0%
Other (please specify):	6=8%	3=8%	3=9%
Sometimes	5	3	2
Mildly	1	0	1
Missing	3=4%	2=5%	1=3%

e. Palpitations/heart racing. Please check one only.

	Total	Under 20	≥20
Yes	13=18%	8=20%	5=16%
No	51=71%	30=75%	21=66%
Do not know	6=8%	1=3%	5=16%
Other (please specify):	2=3%	1=3%	1=3%
Sometimes	2	1	1
Missing	3=4%	2=5%	1=3%

f. Swelling of your feet or ankles. Please check one only.

	Total	Under 20	≥20
Yes	5=7%	2=5%	3=9%
No	64=89%	38=95%	26=81%
Do not know	2=3%	0=0%	2=6%
Other (please specify)	1=1%	0=0%	1=3%
Sometimes	1	0	1
Missing	3=4%	2=5%	1=3%

36) Please list any activity or exercise recommendations that your doctor has given you?

	Total	Under 20	≥20
No exercise restrictions	6=32%	3=21%	3=60%
Lifting restrictions	2=14%	2=14%	0=0%
No contact/impact sports	3=16%	2=14%	1=20%
Recommend cardiovascular activities	4=29%	4=29%	0=0%
Very little recommendations to exercise	1=5%	1=7%	0=0%
To maintain some form of physical activity	1=5%	1=7%	0=0%
Let her stop or rest when she feels the need	1=5%	0=0%	1=20%
For gym-activity as tolerated. ITP most major problem	1=5%	1=7%	0=0%
Missing	56=75%	28=67%	28=84%

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Table 1.2: A summary of Table 7.1 'Composition and Interpretation of the Lowest and Highest Scores for the SF-36v2 Health Survey Component Summary Measures and Health Domain Scales'. Reproduced with permission from User's Manual for the SF-36v2® Health Survey (2nd ed.) © 2007, page 76, OptumInsight, Lincoln, RI[131]. SF-36v2® is a registered trademark of the Medical Outcomes Trust and is used under license. The SF-36v2® Health Survey is copyrighted © 1992, 1996, 2000, by Medical Outcomes Trust and QualityMetric Incorporated.

Figure 1.1: Celoria and Patton classification of interrupted aortic arch. Reprinted from the American heart journal, Vol. number 58, Celoria GC and Patton RB, Congenital absence of the aortic arch, Page 409, Copyright 1959, with permission from Elsevier[11].

Figure 1.2: A schematic representation of the aorta and pulmonary artery originating from a fetal heart. Reprinted from the American heart journal, Vol. number 58, Celoria GC and Patton RB, Congenital absence of the aortic arch, Page 411, Copyright 1959, with permission from Elsevier[11].

Figure 1.3: Direct repair of interrupted aortic arch. Content is reproduced from Brown JW et al., Outcomes in patients with interrupted aortic arch and associated anomalies: a 20-year experience, European journal of cardio-thoracic surgery, 2006, Volume 29, Issue 5, page 668, by permission of Oxford University Press/European Association for Cardio-thoracic Surgery[21].

Figure 1.4: Left common carotid artery turn down repair of type B interrupted aortic arch. Content is reproduced from Brown JW et al., Outcomes in patients with interrupted aortic arch and associated anomalies: a 20-year experience, European journal of cardio-thoracic surgery, 2006, Volume 29, Issue 5, page 668, by permission of Oxford University Press/European Association for Cardio-thoracic Surgery[21].

Chapter 2: Persistent risk of subsequent procedures and mortality after interrupted aortic arch repair. Content with modifications reprinted from the Journal of thoracic and cardiovascular surgery, 140, Jegatheeswaran A et al., Persistent risk of subsequent procedures and mortality in patients after interrupted aortic arch repair: A Congenital Heart Surgeons' Society study, Copyright 2010, with permission from Elsevier/American Association for Thoracic Surgery.