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Morbidity in Children and Adolescents Following Surgical Correction of Interrupted Aortic Arch

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Abstract

Background—Previous studies of outcome following operative correction of interrupted aortic arch (IAA) focus on mortality and rates of re-intervention. We sought to investigate the clinical status of children and adolescents following surgery for interrupted aortic arch (IAA).

Methods—A cross-sectional study of subjects with IAA between the ages of 8-18 years was performed with subject undergoing concurrent genetic testing, electrocardiogram, cardiac magnetic resonance imaging, cardiopulmonary exercise testing, and assessment of health status and health-related quality of life as well as concurrent retrospective cohort study reviewing their post-operative utilization of medical care including operative and trans-catheter reintervention, non-cardiac operations, and hospitalizations.

Results—21 subjects with IAA with median age of 9 years were studied. Re-intervention rates were 38% on the left ventricular outflow tract, 33% for the aortic arch, and 24% for both. Rates of re-intervention were highest in the first year of life and decreased in subsequent years. Left ventricular ejection fraction was preserved (72±6%). Maximal oxygen consumption, maximal work, and forced vital capacity were both significantly diminished from age and gender norms (p<0.0001). Health status and quality of life were both severely diminished.

Conclusion—Subjects with IAA demonstrate a significant burden of operative and trans-catheter intervention and large magnitude deficits in exercise performance, health status, and health related quality of life.

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Keywords

Congenital Heart Disease; Cardiac MRI; Cardiopulmonary exercise testing; Quality of life

INTRODUCTION

Interrupted aortic arch (IAA) is defined by the absence of anatomic continuity within the aortic arch. It is rare, accounting for 0.7% of congenital heart disease[1]. Operative correction for IAA can be accomplished through either a staged approach or a single operation. For both strategies, risks of mortality and re-intervention have been described[2-6]. To date, other aspects of the clinical status of subjects who survive surgery have received less attention, other than a single study that demonstrated worse neurodevelopmental outcomes in IAA patients at 2 years of age[7]. In this study, we sought to provide a cross-sectional multi-dimensional characterization of clinical status in this population in school-age and adolescent survivors after operative correction as well as retrospective data regarding their rates of re-intervention and utilization of health care resources.

MATERIALS AND METHODS

Study Population

The study protocol was approved by the Institutional Review Board of The Children's Hospital of Philadelphia. Subjects, aged 8 to 18 years, who had undergone bi-ventricular operative correction of IAA were identified from research and clinical databases and contacted for enrollment. Exclusion criteria included subsequent heart transplant, presence of additional major intra-cardiac anomalies (e.g. transposition of the great arteries), and if they were not fluent in English and could not complete study questionnaires. Subjects underwent comprehensive evaluation at The Children's Hospital of Philadelphia, including review of medical records and interviews with family members to detail cardiac and non-cardiac operative history, and previous inpatient admissions. They also underwent protocol-guided electrocardiogram (ECG), cardiac MRI (CMR), and cardiopulmonary exercise test (CPET) within 3 months of each other. Instruments to assess health status, Child Health Questionnaire-Parent Form 50 (CHQ50), and health-related quality of life, Pediatric Cardiac Quality of Life Inventory (PCQLI), were administered during study visits. Anatomic classification of IAA was performed according to published descriptions[8, 9].

Data Collection

Study procedures were performed as follows. Analysis of 22q11.2 microdeletion was performed in all subjects using fluorescence in situ hybridization[10] or multiplex ligand-dependent probe amplification[11]. Electrocardiograms (ECG) were performed on MAC 5000 machine (General Electric, USA) using a standard clinical protocol, with interpretation by one member of the study team (RT). Outcomes of interest included predominant rhythm, ectopy, heart block, and bundle branch block. Cardiac Magnetic Resonance Imaging (CMR) studies and Cardiopulmonary

Exercise Testing (CPET) were performed as previously described[12]. The primary outcomes of interest were left ventricular ejection fraction (EF) and cardiac index (CI). Primary outcomes for CPET included oxygen consumption at maximum exertion (VO2max) and work rate. Anaerobic threshold was measured by the V-slope method[13]. Oxygen consumption at maximum exertion (VO2max) and at the anaerobic threshold (AT) were

normalized to percent expected for age, gender and weight[14]. A maximal effort CPET was defined by a respiratory exchange ratio (RER) of ≥ 1.10[12, 15].

During study visits, subjects and their parents were invited to complete the PCQLI. Parents of subjects were invited to complete the CHQ50. Health status, assessed by the CHQ50, characterizes the level of wellness versus illness in individual subjects, which encompasses the impact of physiologic impairment and control of illness. It has been validated in children across a range of chronic conditions[16]. Health related quality of life, assessed by the PCQLI, quantifies the effect of a specific disease on an individual's ability to function and derive satisfaction from their life across multiple contexts. It was developed for and validated in children with congenital heart disease[17, 18]. For CHQ50 the primary outcomes were “transformed physical” and “transformed psychosocial”[16]. Sub-domains were reported as secondary outcomes. For PCQLI the primary outcome was Total Score, as reported by both subject and parents and compared to values of children with “mild CHD” and “severe CHD”[17, 18].

Statistical Analysis

Descriptive statistics for continuous variables were calculated. Analysis was performed in two parts. First, risk for hospitalization, re-intervention, and non-cardiac operation were assessed from chart review and patient interviews. Since subjects were of different ages (and therefore had unequal duration of follow-up), risks for events of interest were represented as event rates calculated in person-years (number of events divided by the sum of follow-up time for study subjects). Uniformity of event rates was assessed using histograms with eras defined based on visual inspection. Event rates were then expressed for the entire follow-up period and by era. Comparisons were made using chi-squared test. Second, the current state of subjects was described with CPET, CMR, EKG, functional assessment, and quality of life measures. Student's two tailed t-tests were used to compare the study population to expected values. Primary outcome measures for each domain were identified prior to analysis. No other adjustments were performed for multiple comparisons. All analyses were performed using Intercooled STATA 9.2 (College Station TX, USA).

RESULTS

Study Population

A total of 93 individuals were identified as potential subjects, of which 23 were deceased and 14 were ineligible because of complicated cardiac anatomy, older age, heart transplant, and failure to complete operative correction. Of the remaining 56 individuals, 21 (38%) agreed to participate (16 declined and 22 could not be contacted). Additional information regarding subjects who were not enrolled was not available. Subjects had a median age of 9 years (range 8-18 years) at enrollment in the study (Table 1). The overwhelming majority (90%) of subjects had type B IAA, while the remainder had type A IAA. The majority (67%) had documented 22q11.2 deletion, of which all had type B IAA.

Hospitalizations and Procedures Following Operative Correction

All subjects underwent a single-operative correction at 7.3±3.7 days of life (median: 7 days, range: 3-15 days). A Yasui procedure was performed in 2/21 subjects. The remaining 90% (19/21) underwent primary IAA repair. Of those undergoing primary correction, 1/19 had their initial operation at an outside institution, the details of which were not discernible from available records. Of the remaining 18 subjects, 13 (72%) had homograft patch augmentation of the aortic arch performed, with 5 (28%) undergoing arch anastomosis without patch augmentation. Subjects were hospitalized (for all causes including cardiac and

non-cardiac procedures) at a rate of 4.4 per 10 person-years (Table 2). Incidence was highest in the first year of life, decreasing between 1-8 years and 8-18 years ($p<0.001$, $p<0.002$).

Post-operative cardiac catheterizations were performed at a rate of 1.2 per 10 patient years, of which 0.43 per 10 person-years involved trans-catheter interventions (Table 2). Incidence of cardiac catheterizations was highest in the first year of life and decreased between 1-8 years and 8-18 years ($p=0.001$, $p=0.03$). Incidence of catheter-based interventions was also highest in the first year of life relative to ages 1-8, but the incidence between ages 1-8 was not different than ages 8-18 ($p=0.3$). Catheterizations were performed in 67% (14/21) of subjects with 29% (6/21) undergoing more than 2 catheterizations. Ten subjects (48%) underwent an interventional catheterization procedure with no subjects undergoing more than 1 (Table 3). Seven of these procedures (70%) were angioplasty of re-coarctation (33% of the total cohort). The other interventions were: 1) balloon aortic valvuloplasty, 2) device closure of ASD, and 3) balloon angioplasty of conduit stenosis (n=1 each).

Operative re-intervention rate was 0.8 operations per 10 person-years over the entire follow-up period (Table 2). The rate was higher in the first year of life than between ages 1-8 ($p=0.006$). The rate did not differ between ages 1-8 and ages 8-18 ($p=0.3$). At enrollment, 48% of subjects had undergone a second cardiac operation; 24% had one additional operation, 14% had two additional, and 10% had three or more. The most common subsequent cardiac operation was for left ventricular outflow tract obstruction (Table 3). Conduit replacement operations were performed twice during the study period (one each for conduits placed during Yasui and Ross-Konno procedures). No re-operations for recurrent coarctation were performed.

Including both catheter-based and operative interventions, risk of re-intervention for LVOT obstruction was 38% and for recurrent aortic arch obstruction was 33%; 24% of subjects underwent re-intervention for both LVOT obstruction and aortic arch obstruction.

Non-cardiac operations occurred at a rate of 2.3 per 10 person-years. Rates of non-cardiac operations were not different between <1 year, ages 1-8, and ages 8-18 (Table 2).

Current Health Status

ECG were available in 20/21 (95%) of subjects. One subject (5%) demonstrated complete heart block. Bundle branch block was present in 70% of subjects with 13 (65%) demonstrating right bundle branch block and 1 (5%) demonstrating bi-fascicular block. No ectopy or other dysrhythmia were noted on study ECG. Two subjects underwent pacemaker placement, one for “breath-holding spells with episodes of sinus arrest” and one for “second degree AV block.”

CMR measurements were available in 14 subjects (67%) (Table 4), demonstrating preserved left ventricular (LV) ejection fraction (71.7±5.8%) and normal LV cardiac index 3.5±0.6 L/min/sqm. CPET were performed in 95% of subjects (20/21). Percent predicted forced vital capacity (70.5±15% $p<0.0001$, 95% CI 63.5-77.5%), VO2max (68±18% $p<0.0001$, 95% CI: 59.1-76.7%), and maximal work rate (76±22% $p<0.0001$, 95% CI: 63.3-88.7%) were all substantially reduced. Maximal tests were available in 58% of subjects, in whom VO2max was still reduced (70.0±21.9% expected 95% CI: 55.7-84.4%, $p<0.0009$). Oxygen consumption at anaerobic threshold was also reduced at 74±21% (n=8, $p=0.01$, 95% CI: 56.4-91.6%).

CHQ50 were completed by 95% of the subjects. Deficits in Transformed Physical (45.1±13.9, $p=0.021$, 95% CI: 38.5-51.6) and Transformed Psychosocial (43.1±11.9, $p<0.0001$, 95% CI: 37.5-48.7) scores were demonstrated. Reduced scores were also apparent

in several sub-scales: general health (p<0.0001), change in health (p=0.008), physical functioning (p=0.01), behavioral (p=0.03), "self-esteem" (p=0.01), parental impact-emotional (p<0.0001), parental impact-time (p=0.003), family activities (p=0.02), and family cohesion (p=0.03). Though not statistically significant, physical, bodily pain, behavior, mental health, parental impact-time, and family activities were all less than normal values. "Family cohesion" was the only sub-domain with a point estimate greater than published norms, though this was not statistically significant.

Health related quality of life was assessed using the PCQLI in 13 (62%) of the study subjects and 20 (95%) of subjects' parents. The subject Total score (57.5±18.8, 95% CI: 46.1-68.9) was significantly worse than in those with mild CHD (80.7±14.4, p <0.0001) and subjects with Fontan circulation, representing children with complex heart disease (68.7±16.2 p=0.0179). For parent-reported values, the study population Total score (55.9±13.5, 95% CI: 49.6-62.2) was also lower than that for those with mild CHD (84.3±13.6, p<0.0001) and those following Fontan operations (67.7±16.2, p=0.0019).

DISCUSSION

This study combines cross-sectional data on the current status of 21 school-age and adolescent children, who underwent single-stage surgical correction for IAA in infancy, with retrospective cohort data about health care utilization. Subjects with IAA underwent frequent hospitalizations, split between cardiac re-interventions, non-cardiac operations, and other hospitalizations. Rates of hospitalization and cardiac re-intervention were highest in the first year of life, decreasing in subsequent years. There was significantly diminished CPET performance with preserved resting LV function. Health status and quality of life were diminished severely. These findings are consistent with substantial disability.

Previous research on IAA focused on early mortality and re-intervention rate, demonstrating variable perioperative mortality[2, 4-6], with most recent reporting mortality of 3.6% at 2 years[7] and 39% at 21 years[6]. We report data on survivors and cannot comment on how mortality in our cohort compares with previous studies. Operative re-intervention rates have been assessed[3, 4, 6] with 29% of surviving patients undergoing re-intervention on their aortic arch by 15 years (with mortality prior to arch re-intervention of 32%), and 18% required LVOT interventions over 15 years of follow-up (with mortality prior to LVOT re-intervention of 33%)[6]. Our re-intervention rates on LVOT (33%), the aortic arch (38%), or both (24%) were similar.

In addition to cardiac interventions, utilization of medical care was quantified by rate of hospitalizations and non-cardiac operations, which was quite high, with a hospitalization rate of 4.4 per ten person-years, a 44% annual risk of hospitalization. The rate of hospitalizations was also highest in the first year of life.

CPET performance is often used as a surrogate for the ability to participate in age-appropriate activity. Our cohort demonstrated reduced VO2max and maximum work rate, suggesting limitation in peak exercise performance. Recognizing that all CPET measurements are effort-dependent and that only 58% of subjects achieved a maximal aerobic effort, we performed a subgroup analysis in those subjects who completed a maximal test, with consistently reduced mVO2. Submaximal exercise performance (represented by oxygen consumption at anaerobic threshold) was also diminished. Additionally, FVC was significantly reduced, reflecting restrictive lung physiology (with normal FEV1/FVC). To our knowledge restrictive lung diseae has not been previously reported in subjects with IAA or 22q11.2 microdeletion. It is not possible from our data to determine the etiology of this restrictive lung physiology. Overall, these deficits in

provocative exercise testing are consistent with significantly diminished physical function and clear morbidity, despite preserved left ventricular systolic function.

Questionnaire based assessment of health status and health-related quality of life have not been previously applied, to our knowledge, to children with IAA. Deficits in health status and health related quality of life were observed, with uniform deficits in both, despite a small study sample. The magnitude of these deficits was substantial, as they were greater than those seen in large samples of children with severe heart disease, which previously had served as the benchmark for low quality of life following cardiac operation[17]. Overall, these results suggest that health status and quality of life are severely compromised in children following operative correction of IAA.

There are several limitations to this study. The study population is composed of individuals who survived into childhood and were willing to participate in the study. As such it is not population-based and subject to selection bias. Volunteer and selection bias, however, would result in optimistic results, further emphasizing the morbidity in this population. In several domains hypothesis testing was performed for multiple variables. Primary endpoints were identified, and, no additional measures were taken to compensate for multiple comparisons. Cross-sectional data are limited in their ability to demonstrate causality, and, to test specific hypotheses, further studies are necessary. The study cohort underwent operations between 1988-1999 and are representative of that era. This may limit the generalizability to the current era, but this represents the only attempt to our knowledge to characterize the health of children with IAA who reach school age and adolescence. As such it is the best available estimate of the prognosis of children treated in the current era, and we hope will serve as a baseline against which future cohorts can be compared. Our study design provides a cross-sectional view of the health of this cohort, and thus it has limited ability to identify the etiologies of the deficits we describe. Further study is necessary to determine if there are modifiable risk factors that contribute to the described deficits in exercise performance, health status, and quality of life.

Another potential limitation of the study is that the majority of the subjects have 22q11.2 deletion, which may compromise the generalizability of the study to IAA subjects without 22q11.2 deletion syndrome. While recognizing that our study was not powered to discriminate differences between 22q11.2del and non-deleted subjects, we did not detect differences between these subgroups either, suggesting that even those without 22q11.2 deletion syndrome are at risk for significant morbidity.

In presenting multiple aspects of clinical status, these data characterize the overall health of children with IAA. As operative mortality continues to improve, prognosis should be measured not only by mortality and rate of cardiac re-intervention, but also by patient ability to participate in age-appropriate activities, the burden of medical care on families, and quality of life. This is especially true when fetal diagnosis provides the opportunity to communicate this information. This cohort of subjects with IAA demonstrates surprisingly marked morbidity across multiple domains, which we hope will provide updated expectations, guide counseling and planning for families with children with IAA, and offer opportunities to consider novel interventions to improve on the observed outcomes.

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Table 1

Patient characteristics

Age (years)	11.6 ± 3.6 (median: 9 range: 8.3-18.2)
Gender	
Female	62% (13)
Male	38% (8)
Race	
White	81% (17)
African American	19% (4)
Presenting anatomy:	
IAA Type A	10% (2)
IAA Type B	90% (19)
22q11.2 deletion	67% (14)
Weight (kg)	36.6 ± 19.2
Height (cm)	139.8 ± 18.2
BMI	17.9 ± 4.0
	7.3 ± 3.7
Age at complete repair (days)	median: 7 (range: 3-15)
Surgical approach	
Single stage operation	100% (21)
Surgical repair	
[a]VSD patch and arch reconstruction	86% (18)
[b]VSD patch, arch reconstruction, and LVOT augmentation	5% (1)
Yasui Procedure	10% (2)

Abbreviations: BMI: Body Mass Index, IAA: interrupted aortic arch, LVOT: left ventricular outflow tract, VSD: ventricular spetal defect.

Data are expressed as mean (± SD), median (range), or as number (percentage).

[a]Ventricular septal defect closure indicating that relief of outflow tract obstruction was not necessary.

[b]LVOT augmentation includes any procedure that includes patch augmentation of the LVOT

Table 2

Rates of hospitalization, operation, and cardiac catheterization following initial operation

	<1 year	1-8 years	8-18 years	p^a	p^b
Hospitalizations	26.2	5.6	2.7	<0.001	0.002
Non-cardiac operations[c]	3.3	2.2	1.5	0.173	0.160
Cardiac operations	28.6	6.8	4.7	0.006	0.3
Cardiac catheterizations	4.8	1.2	0.3	0.001	0.03
Interventional cardiac catheterizations	1.9	0.3	0.2	0.01	0.3

All event rates are expressed as events per 10 person-years

[a] p-value is for the comparison between event rates <1 year and 1-8 years.

[b] p-value is for the comparison between event rates 1-8 year and 8-18 years.

[c] Noncardiac operations included: myringostomy tubes (n=20), tonsiloidectomy and adenoidectomy (n=6), palate procedure (n=6), dental surgery (n=6), Nissen fundoplication (n=3)

Table 3

Cardiovascular interventions following primary operative correction

Cardiac events	
Subsequent operations	Median: 0 (range: 0-5)
0	52% (11)
1	24% (5)
2	14% (3)
3 or more	10% (2)
Specific operations	
LVOT augmentation[a]	10 operations in 7 patients (33%)
Aortic arch re-operation	0 (0%)
Ross-Konno	3 (14%)
Aortic valve replacement	1 (5%)
Conduit replacement	2 (10%)
Pacemaker	2 (10%)
Other[b]	6 (29%)
Catheterization	
Total catheterizations	
0	33% (7)
1	38% (8)
≥2	29% (6)
Interventional catheterizations	
0	52% (11)
1	48% (10)
≥2	0% (0)
Specific Interventions: (n=10)	
Angioplasty aortic arch	70% (7)
Conduit procedure	10% (1)
ASD device closure	10% (1)
Balloon valvuloplasty aortic valve	10% (1)

Abbreviations: ASD: atrial septal defect and LVOT: left ventricular outflow tract

[a]Surgical palliation of LVOT obstruction included supravalvar, valvar, subvalvar stenosis, exclusive of a Ross-Konno and/or aortic valve replacement.

[b]Other operations included repair pacemaker revision (n=2), along with right ventricular outflow tract aneurysm resection, and device closure of patent foramen ovale (all n=1).

Table 4

Cardiovascular status

Cardiac Magnetic Resonance Imaging (n=14)		***p*[a]**
Indexed LV EDV (ml/sqm)	64.6 ± 8.0	
Indexed LV SV (ml/sqm)	18.6 ± 5.4	
LV ejection fraction (%)	71.7 ± 5.8	
LV Cardiac Index (L/min/m^2)	3.5 ± 0.6	
Indexed LV Mass (g/sqm)	47.7 ± 14.1	
Cardiopulmonary Exercise Test (n=20)		
Maximal effort % (n)[b]	58% (11)	
Forced vital capacity (L)	1.8 ± 0.7	
Predicted forced vital capacity (%)	70.5 ± 15	<0.0001
FEV1/FVC (n=16)	0.87 ± 0.09	
Maximum heart rate (n=19)	171.1 ± 22.4	
mVO2 (ml/kg/min)	27.0 ± 7.3	
Percent predicted mVO2 (n=19)	67.9 ± 18.2	<0.0001
Oxygen consumption at AT (ml/kg/min) (n=8)	17.3 ± 3.7	
Percent predicted AT (n=8)	74 ± 21	0.01
Maximum work (watts/kg) (n=14)	2.3 ± 0.6	
Percent predicted max work (n=14)	76 ± 22	<0.0001
Indexed O2 pulse (mlO2/beat/sqm)	5.0 ± 1.4	
Respiratory quotient	1.13 (0.8-1.32)	

Abbreviations: AT: anaerobic threshold, EDV: end-diastolic volume, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, LV: left ventricle, mVOW: oxygen consumption at maximal exertion, SV: stroke volume

Data are expressed as mean (± SD), or number (percentage), median (range), or percentage (number).

[a] *p* values are for comparison to age-defined norms (Student's two tailed t-test)

[b] Maximal effort is defined as respiratory exchange ratio ≥1.1 at peak exercise.