Journal of the American College of Cardiology Vol. 48, No. 11, 2006

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.07.053

Early and Late Results of the Modified Fontan Operation for Heterotaxy Syndrome

30 Years of Experience in 142 Patients

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OBJECTIVES We sought to evaluate the early and late results of the modified Fontan operation for patients with heterotaxy syndrome, assess variables traditionally known to correlate with poor outcome, and assess current health status of survivors after the Fontan procedure.

BACKGROUND The natural history of unoperated cardiac lesions in heterotaxy is known to be poor. Therefore, the Fontan operation has been proposed to improve survival.

METHODS Patients with heterotaxy were identified from the Mayo Clinic Fontan database. Hospital and outpatient records were abstracted for preoperative, operative, and postoperative clinical and hemodynamic data. All patients not known to be deceased were sent health status questionnaires.

RESULTS A total of 142 patients with heterotaxy syndrome had a modified Fontan operation. Asplenia was present in 76 patients (54%). Median age at operation was 9 years (range 2 to 35 years). Median follow-up was 4 years (range 0 to 23 years). There were a total of 61 deaths (43%), with 32 (23%) within 30 days of operation or before hospital discharge. The 5-, 10-, and 15-year survival was 64%, 57%, and 53%, respectively. In the modern era (1995 to 2004) early mortality was 10%. Of the 81 survivors, questionnaires were available from 41 (51%). Eighty percent reported having no or mild symptoms. However, 19 (46%) had arrhythmias, 5 (12%) had a thromboembolic event, and 1 (2%) developed protein-losing enteropathy.

CONCLUSIONS Early survival has improved for heterotaxy patients after the Fontan operation; however, late morbidity and mortality remain substantial. Better strategies for long-term treatment of this high-risk group need to be identified. (J Am Coll Cardiol 2006;48:2301–5) © 2006 by the American College of Cardiology Foundation

The natural history of patients with complex cardiac lesion and heterotaxy is poor. The 1-year mortality is >85% for patients with asplenia and >50% for patients with polysplenia (1,2). The modified Fontan operation has been used to improve survival in patients with heterotaxy syndrome and functional single ventricle. Due to complex venous and situs anomalies, the technical aspects of constructing the pathways for a modified Fontan connection are complicated. Frequently, conduits and baffles are necessary to effectively divert caval, hepatic, and pulmonary venous blood flows. Initial reports of the outcome of the modified Fontan operation for heterotaxy syndrome revealed early mortality of 13% to 80% (3–6).

Since these early reports, there have been numerous improvements in surgical and postoperative techniques. We sought to evaluate the early and late results of the modified Fontan operation for patients with heterotaxy syndrome. Variables traditionally known to correlate with poor outcome were assessed. Current health status of survivors was obtained.

METHODS

Patients. A total of 142 patients with heterotaxy syndrome were identified in the Mayo Clinic Fontan database from 1975 through 2004. No patients with heterotaxy syndrome who had a Fontan procedure were excluded. Hospital and outpatient records were abstracted for preoperative, operative, and postoperative clinical and hemodynamic data. Additionally, all patients who were not known to be deceased were sent health status questionnaires. Current addresses and date of death were cross-referenced with Accurint, a locate-and-research database. Patients who did not return their questionnaires after the first mailing received 2 additional mailings and a reminder by telephone. The median age at Fontan procedure was 9 years (range: 2 to 35 years) with 82 (58%) being male. Median follow-up was 4.5 years; the longest was 23 years.

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Manuscript received March 20, 2006; revised manuscript received June 23, 2006, accepted July 3, 2006.

JACC Vol. 48, No. 11, 2006
December 5, 2006:2301–5

Abbreviations and Acronyms
AV = atrioventricular
IVC = inferior vena cava
SVC = superior vena cava

Anatomy. Asplenia was diagnosed in 76 patients (54%) and polysplenia in 66 (46%) (Table 1). Ambiguous abdominal situs was the most frequent type of visceral situs (76%). Levocardia (56%) was slightly more common than dextrocardia (42%). The majority of patients had a common atrioventricular valve (79%). The ventricular morphology was usually unbalanced, with 70% having non-left ventricular morphology. Anomalous pulmonary venous connections were present in 64% of patients. Abnormalities of the systemic venous connections also were common. Bilateral superior vena cavae (SVC) were found in 75 (53%) patients. Interruption of the inferior vena cava (IVC) with azygos or hemiazygos continuation to the SVC was present in 75 patients (54%). The hepatic veins entered the atrium separate from the IVC in 79 cases (57%).

Eras of operation. The 30-year study period was divided into 3 equal chronologic eras based on the date of the Fontan operation. The early era, 1975 through 1984, included 30 patients. The majority of operations were performed during the middle era, 1985 through 1994, with 91 patients. An additional 21 patients had the operation in the most recent era, 1995 through 2004 (Fig. 1). There was no statistically significant difference between eras in age at surgery, gender, or number of previous surgical palliations (Table 2).

Previous palliative procedures. For 22 patients (16%), the Fontan operation was their first surgical procedure. Seventy-nine patients (56%) had 1 previous palliative procedure, 30 (21%) had 2, and 11 (8%) had ≥3 (Table 3).

Fontan connection. The types of Fontan connections that were used are listed in Table 4. Only 6 patients had a fenestration, and all of those were performed in the recent era. Atrioventricular (AV) valve replacement was performed in 8 patients (6%) and repaired in 37 patients (26%) at the time of the Fontan procedure.

Statistical analysis. We used the same independent variables of interest that were used in previous outcome studies of the Fontan operation from the Mayo Clinic (3,4,7–9). Univariate assessment of the association of variables with mortality was performed using chi-square and Wilcoxon rank sum tests. Cumulative survival was estimated using the

Table 1. Anatomy

Anatomy	Asplenia (n = 76)	Polysplenia (n = 66)	Total (n = 142)	Percent
Visceral situs				
Solitus	4	10	14	10
Inversus	6	14	20	14
Ambiguous	66	42	108	76
Cardiac position				
Levocardia	41	39	80	56
Dextrocardia	34	25	59	42
Mesocardia	1	2	3	2
AV valve anatomy				
Common	70	41	111	79
Left atresia	1	7	8	6
Right atresia	1	5	6	4
Normal	4	11	15	11
Ventricular morphology				
Two ventricles of equal size	8	9	17	12
Left dominant	17	9	26	18
Right dominant	37	36	73	51
Indeterminate	14	12	26	18
Pulmonary venous connections				
Normal	20	31	51	36
Total anomalous	45	20	65	46
Partial anomalous	11	14	25	18
IVC connection				
Atrium	49	16	65	46
Azygos/hemiazygos to SVC	26	49	75	54
SVC location				
Right	25	9	34	24
Left	18	14	32	23
Bilateral	33	43	76	53
Hepatic venous connections				
IVC	42	17	59	43
Separate	32	47	79	57

AV = atrioventricular; IVC = inferior vena cava; SVC = superior vena cava.

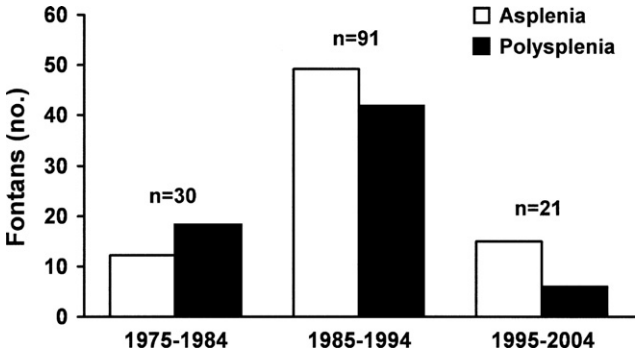

Figure 1. Number of Fontan operations performed at Mayo Clinic for heterotaxy syndrome.

Kaplan-Meier method. Models were constructed with Cox proportional-hazard models using a stepwise elimination of the nonsignificant variables performed using a p value cut point to retain variables <0.05. For all other comparisons, 2-tail p values of ≤0.05 were taken as evidence of findings not attributable to chance.

RESULTS

Early mortality. Overall, 32 patients (23%) died within 30 days after operation or before hospital discharge. Early mortality decreased over time, from 50.0% in the early era to 16.5% in the middle era and 9.5% in the most recent era. Comparing the early era with both the middle ($p < 0.001$) and the recent eras ($p = 0.003$), there has been a significant decrease in early mortality. Comparing the middle era to the recent era, there is a trend toward decreased mortality, but it is not statistically significant ($p = 0.42$). No early deaths occurred in 6 patients who had fenestration as part of the Fontan procedure (all performed in the most recent era).

Univariate predictors of early mortality. The variables that correlated significantly with early mortality were a preoperative cardiothoracic ratio >0.6, elevated systemic ventricular end-diastolic pressure, prolonged bypass time, postoperative mean right atrial pressure >20 mm Hg, and postoperative renal failure (Table 5).

Late mortality. Using a combined approach of chart review and Accurint searches, 29 late deaths were identified, ranging from 97 days to 20 years after operation. The cause of death was known in 19 cases. Five patients died after late reoperation, 4 with asplenia died from sepsis, 4 were sudden and presumed due to an arrhythmia, 3 were attributed to progressive myocardial failure, 1 to pulmonary hemorrhage, 1 to suicide, and 1 to a motor vehicle accident. Clinical or autopsy data could not be obtained for 10 of the 29 patients. However, accurate dates of death were available for all 29 patients.

Actuarial cumulative survival at 5, 10, and 15 years was 64%, 57%, and 53%, respectively. In the early surgical era, early mortality was high (50%) and cumulative long-term survival was poor (33%, 33%, and 30% at 5, 10, and 15 years, respectively). Early- and long-term survival improved in the 2 more recent eras. Combining only the 2 most recent eras, the 5-, 10-, and 15-year survival was 72%, 63%, and 60%, respectively (Fig. 2).

Univariate predictors of late mortality. Only bypass time >120 min and AV valve replacement were predictive of late mortality, with odds ratios of 5.59 and 6.24, respectively ($p < 0.05$).

Current health and functional status. Excluding the 32 early deaths and the 29 late deaths, there were 81 (57%) late survivors available to assess current health and functional status. Follow-up data were obtained for 41 (51%) of these patients by written questionnaire or by return clinic visit during the data acquisition portion of this study. For these 41 patients, the median follow-up interval after the Fontan operation was 15 years (range 1 to 23 years). Of these patients, 80% reported having no or mild symptoms with ordinary physical activity, 18% had moderate symptoms with less than normal physical activity, and 3% had symptoms at rest. Specific signs and symptoms consisted of easy fatigue (49%), palpitations (39%), shortness of breath (32%), persistent cyanosis (24%), and chest pain (20%).

Despite this optimistic self-reported current health status, these 41 patients had numerous medical complications. Nineteen patients (46%) reported a history of an arrhythmia and 9 (22%) required placement of a permanent pacemaker. A thromboembolic event occurred in 5 patients (12%). Protein-losing enteropathy was diagnosed in 1 patient (2%). One patient had cardiac transplantation (lateral tunnel), 1 was currently listed for transplant (right ventricular outflow tract to pulmonary artery), and 1 was being evaluated for transplantation (Kawashima-type connection).

Most (95%) of these 41 patients were taking ≥1 medication. The most frequent medications included angiotension-converting enzyme inhibitors or angiotensin II receptor blockers (73%), digoxin (66%), daily antibiotic prophylaxis (53%), aspirin (54%), warfarin (43%), beta-blocker (24%), and aldactone (18%). Of the patients with asplenia, 81% were taking daily antibiotic prophylaxis.

Most survivors (78%) were employed or attending formal education programs at the time of this review. Of those employed, 50% were working full time. Part-time employ-

Table 2. Demographics Based on Era of Operation

Variable	Overall	1975–1984	1985–1994	1995–2004	p Value
Asplenia	76 (54%)	12 (40.0%)	49 (53.9%)	15 (71.4%)	NS
Gender (male)	82 (58%)	20 (66.7%)	54 (59.3%)	8 (38.1%)	NS
Age, yrs (range)	9 (2–35)	9 (3–19)	10 (2–35)	5 (2–24)	NS
Prior palliative procedures	1 (0–4)	1 (0–3)	1 (0–4)	1 (0–3)	NS

Table 3. Prior Palliative Procedures

Procedure	n
Blalock-Taussig shunt	90 (63%)
Cavopulmonary anastamosis	20 (14%)
Waterston shunt	16 (11%)
Atrial septectomy	13 (9%)
Pulmonary artery band	11 (8%)
Potts shunt	4 (3%)
Total	154

ment was by choice in 28% of those employed, and 22% were limited to part-time employment by their current cardiac status.

DISCUSSION

Before the concept of total right heart bypass to treat tricuspid atresia, patients with heterotaxy and functional single ventricle were only candidates for palliative procedures to either augment or restrict pulmonary blood flow. Even after the description of the Fontan operation, the criteria developed by Choussat et al. (10) essentially excluded patients with heterotaxy syndrome from having a Fontan operation. However, clinicians expanded the indications and in the mid-1970s the Fontan operation was used to treat patients with all forms of complex functional single ventricle, including patients with heterotaxy syndrome. Unfortunately the mortality for patients with heterotaxy who had a Fontan operation was high. Humes et al. (4) reported an early mortality of 43%. In early outcome series after the Fontan operation, heterotaxy frequently was one variable that predicted poor outcome (7).

Investigators in the 1980s recognized that heterotaxy per se may not have been the most critical variable that predicted high mortality. Rather, the more important factors relating to mortality were poor ventricular function, AV valve regurgitation, and complex surgical repair with prolonged bypass time (7). Investigators believed that the Fontan operation could be successful for patients with heterotaxy if the operation was performed before development of ventricular dysfunction and/or significant AV valve insufficiency. Surgical techniques improved over time, permitting shorter duration of cardiopulmonary bypass.

In the present study, several recognized risk factors for early mortality (AV valve repair, decreased ventricular systolic function, and elevated pulmonary arteriolar resistance) were not predictive of outcome. Similar experience has been reported in other recent series (3,8,11,12). This may be due to several factors, such as better patient selection, staged repair, advancement of surgical techniques, and improved postoperative management. Despite these encouraging results, children with functional single ventricle and total anomalous pulmonary venous connections have a 53% mortality at the time of initial palliative operation, and the mortality for the subsequent cavopulmonary anastomosis also is substantial (38%) (13). Therefore, many "high-risk" patients with heterotaxy and functional single ventricle may never reach the age to have a Fontan operation (14,15).

Atrioventricular valve repair or replacement previously has been associated with early mortality (3). Therefore, clinical practice has evolved and led to AV valve repair/replacement before completion of the Fontan connection. In the current cohort, AV valve repair or replacement was not predictive of early mortality, which may be an important factor resulting in improved early mortality.

Table 4. Type of Fontan Connection

Procedure	n
Lateral tunnel	75 (53%)
Direct RA-PA	16 (11%)
Intra-atrial conduit	15 (11%)
Extracardiac conduit	13 (9%)
Atrial appendage to PA	11 (8%)
Kawashima	10 (7%)
RVOT-PA	1 (1%)
25-mm Hancock conduit (RA-PA)	1 (1%)

PA = pulmonary artery; RA-PA = right atrium to pulmonary artery; RVOT-PA = right ventricular outflow tract to pulmonary artery.

Table 5. Variables Associated With Early Mortality

Factors	Univariate p Value	Odds Ratio (CI)
Preoperative		
Cardiothoracic ratio >0.6	<0.05	2.51 (1.01–6.25)
End-diastolic pressure (mm Hg)	<0.05	1.10 (1.01–1.19)
AV valve regurgitation	NS	
Ejection fraction	NS	
Mean PAP >20 mm Hg	NS	
Rpa >4 U m^2	NS	
Operative		
Bypass time (min)	<0.01	1.01 (1.00–1.02)
AV valve repair/replace	NS	
APVC repair	NS	
Postoperative		
Mean RA pressure >20 mm Hg	<0.05	3.92 (1.38–11.1)
Renal failure	<0.0001	39.2 (11.0–138.8)
Chest tube drainage >14 days	NS	

APVC = anomalous pulmonary venous connection; AV = atrioventricular; CI = confidence interval; PAP = pulmonary arterial pressure; RA = right atrium; Rpa = pulmonary arterial resistance.

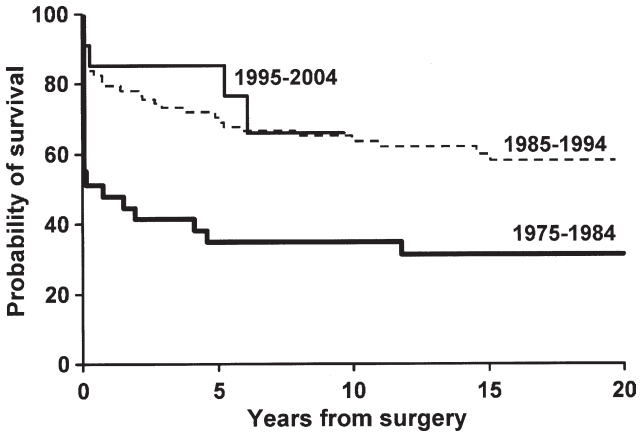

Figure 2. Kaplan-Meier curve depicting the survival after the Fontan procedure for patients with heterotaxy syndrome.

The types of Fontan connection have evolved over the past 30 years. Also, because of the complex anatomy associated with heterotaxy the methods of accomplishing the Fontan connections are quite varied among patients with heterotaxy. This makes it difficult to determine the relationship between the type of Fontan procedure and outcome.

In the recent era (1995 to 2004), early mortality after Fontan decreased to 9.5% but remained greater than the early mortality for patients with double-inlet left ventricle and tricuspid atresia (3% and 2%, respectively) during a similar time period at the Mayo Clinic (8,9). Because early mortality for patients with heterotaxy syndrome remains substantially higher than for patients with other forms of functional single ventricle, one may propose that all patients with heterotaxy syndrome who have a Fontan operation should also have a fenestration performed. Currently, at our center, patients with heterotaxy syndrome have Fontan completion via a fenestrated intra-atrial Gore-Tex tube conduit. The long-term benefits of this technique merit further analysis.

It has been argued that the improvements in the care and outcome of patients with functional single ventricle may not translate into improved results for heterotaxy patients. It was thought that their numerous associated anatomic and physiologic maladies would negate these advances. Although results have not reached the level seen in double-inlet left ventricle or tricuspid atresia, survival for heterotaxy patients has clearly improved. It is also encouraging to note that of the 76 patients with asplenia, only 4 died late of clinical sepsis. We were unable to ascertain antibiotic prophylaxis status in these 4 patients, however, in the surveyed patients with asplenia, 19% were not taking antibiotic prophylaxis, which may be a contributing risk factor.

Rhythm disturbances account for a substantial degree of morbidity and mortality. Arrhythmias were reported in 46% of the patients with heterotaxy compared with 57% of patients with double-inlet left ventricle (8). Because patients with heterotaxy undergo extensive intra-atrial baffling procedures, one might anticipate a higher incidence of arrhythmia than for patients having less extensive atrial surgery. We did not find this to be true. However, the patients with heterotaxy had a shorter follow-up interval (4 vs.12 years) than the patients with double-inlet left ventricle. Longer follow-up may demonstrate that patients with heterotaxy have an even higher risk of sudden death and arrhythmias than patients with less complex forms of functional single ventricle. Thus, a detailed and aggressive approach to surveillance and therapy for arrhythmias is essential.

Survival after the Fontan operation for patients with heterotaxy has improved despite the anatomic complexity of their cardiac disease. Many factors have contributed to the improved survival. In our assessment of long-term survival many of these factors were subtle and evolved simultaneously. This made it difficult in the retrospective statistical analysis to delineate specific factors that affect outcome. It is most likely that improved patient selection, staging of surgical repair, younger age at time of Fontan operation, refinements in surgical techniques, and advancement of postoperative care have all contributed to the improved results.

Conclusions. Over the past 30 years, there has been a significant improvement in the early outcome for patients with heterotaxy syndrome after a modified Fontan operation. However, mortality and morbidity remain substantial. Discovery of innovative treatment methods is essential. Furthermore, meticulous long-term medical management at centers specializing in the care of congenital heart disease is mandatory.

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