Published in final edited form as:
Congenit Heart Dis. 2013 January ; 8(1): 32–39. doi:10.1111/j.1747-0803.2012.00692.x.

Comparison of Fontan Survivors with and without Pacemakers: A Report from the Pediatric Heart Network Fontan Cross Sectional Study

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Abstract

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The authors have no conflicts of interest to disclose.

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Objective—Although many Fontan patients undergo pacemaker placement, there are few studies characterizing this population. Our purpose was to compare clinical characteristics, functional status and measures of ventricular performance in Fontan patients with and without a pacemaker.

Patients and Design—The NHLBI funded Pediatric Heart Network (PHN) Fontan Cross Sectional Study characterized 546 Fontan survivors. Clinical characteristics, medical history and study outcomes (Child Health Questionnaire (CHQ), echocardiographic evaluation of ventricular function, and exercise testing) were compared between subjects with and without pacemakers.

Results—Of 71 subjects with pacemakers (13%), 43/71 (61%) were in a paced rhythm at the time of study enrollment (age 11.9±3.4 years). Pacemaker subjects were older at study enrollment, more likely to have single left ventricles, and taking more medications. There were no differences in age at Fontan or Fontan type between the pacemaker and no pacemaker groups. There were no differences in exercise performance between groups. CHQ physical summary scores were lower in the pacemaker subjects (39.7±14.3 vs. 46.1±11.2, p = 0.001). Ventricular ejection fraction z-score was also lower (−1.4±1.9 vs. −0.8±2.0, p = 0.05) in pacemaker subjects.

Conclusions—In our cohort of Fontan survivors, those with a pacemaker have poorer functional status and evidence of decreased ventricular systolic function compared to Fontan survivors without a pacemaker.

Keywords

Fontan procedure; pacemaker; functional status; ventricular function

Introduction

Although the Fontan procedure has provided palliation for patients with single ventricle physiology since its introduction nearly 40 years ago[1] and survival has improved dramatically[2], this group of patients remains at high risk for medical morbidities. A number of patients develop rhythm abnormalities including bradyarrhythmias, such as sick sinus syndrome, and/or atrial tachyarrhythmias, such as intra-atrial reentrant tachycardia, following the Fontan procedure, and undergo pacemaker placement. There are a number of single center reports suggesting pacemaker placement is safe in this population, and leads to improvement in a variety of medical conditions [3–7]. However, there are few reports outlining the clinical characteristics and functional status of Fontan patients with a pacemaker compared to those without a pacemaker.

The Pediatric Heart Network's (PHN) Fontan Cross-Sectional Study assessed medical history and clinical outcomes in a large population of Fontan survivors at 7 pediatric cardiology centers in North America. Using this dataset we sought to profile Fontan survivors with a pacemaker, and compare clinical characteristics and outcome measures, including functional status and echocardiographic indices of ventricular function, between Fontan subjects with a pacemaker and those without a pacemaker.

Methods

The Fontan Cross-Sectional Study was conducted by the PHN and funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health. The primary aim of this cross-sectional study was to explore associations between laboratory evaluation of ventricular performance and functional health status. The design of the Fontan Cross-Sectional Study has previously been described in detail [8]. Briefly, Fontan survivors between 6 and 18 years of age followed at the 7 PHN clinical centers were screened for potential eligibility. Potentially eligible subjects and families were then contacted and were eligible for participation if they were willing to undergo an echocardiogram, complete a functional

health status questionnaire, and have blood drawn for serum B-type natriuretic peptide (BNP) level. Exclusion criteria included a medical or psychiatric disorder that would prevent successful study testing, participation in another clinical study that would prevent successful completion of study testing, lack of fluency in English or Spanish by the patient's caregivers (languages of the consent forms), and pregnancy or planned pregnancy prior to completion of study testing. Institutional review or ethics board approval was obtained at each institution. Written informed consent was obtained from a parent or guardian of each study subject.

Study testing, including an echocardiogram, an electrocardiogram, exercise testing, cardiac magnetic resonance imaging (MRI), resting serum BNP concentration, health status questionnaires, and medial record review were completed within 3 months of study enrollment. Standardized data collection forms were used to abstract data from the medical records. Data collected included specific anatomic cardiac diagnosis, age at enrollment, age at Fontan, type of Fontan, age, gender, race and ethnicity. In addition, other pre- and post-Fontan medical history variables were obtained, including medications at the time of study enrollment. The presence or absence of a pacemaker and timing of pacemaker placement in each subject were determined from medical record review. The cardiac rhythm was determined using a resting electrocardiogram obtained prior to exercise testing performed as part of the Fontan Cross-Sectional Study.

Outcome variables included functional health status assessed using the Child Health Questionnaire (CHQ) parent report, which provides ten domain scores as well as physical functioning and psychosocial functioning summary scores to assess the well-being of children 5 to 18 years of age [9,10]. The CHQ user's manual provides normative data from 379 health children, and differences in mean summary score values of 5 to 10 points represent true disease effects[9].

Echocardiographic evaluation of ventricular structure and function (end-diastolic and end-systolic volumes, ejection fraction), cardiopulmonary exercise testing, and measurement of serum BNP concentration were also performed. The analysis of echocardiograms and serum BNP concentrations were performed at core laboratories. Subjects with pacemakers did not undergo cardiac MRI.

Core laboratory evaluation of the echocardiograms included analysis of the functional single ventricle in an apical (ventricular long axis) imaging plane and in a parasternal short axis imaging plane as previously described [11]. Briefly, the endocardial border of the functional single ventricle was traced at end-diastole and end-systole, and volumes were calculated using a modified biplane Simpson's method.

Subjects without pacemakers were compared to subjects with a pacemaker. Statistical analyses were performed using SAS software version 9.2 (SAS Institute, Cary, NC) and the R system version 2.8.1 (R Foundation for Statistical Computing, Vienna, Austria). Data are summarized using frequencies, medians, and means with standard deviations as appropriate. Fisher's exact test of equality across groups was used when comparing the distributions of categorical variables by group. Wilcoxon rank sum tests (which are robust to nonnormality) and Student's t-tests were used for comparison of the distribution of continuous variables. Covariate-adjusted comparisons were obtained by multiple regression analyses.

Results

The medical records of 1078 Fontan survivors at the 7 PHN centers were screened for potential eligibility. Of these, 644 were eligible for participation, and 546 consented to participate (consent rate 85%). The mean time interval from Fontan procedure to study

enrollment was 8.5 years [12]. At the time of enrollment, 71/546 (13%) subjects had a pacemaker. The proportion of Fontan survivors with pacemakers at each site ranged from 4% to 34%. Demographic and clinical characteristics for the two groups are shown in Table 1. The date of pacemaker placement was available in 70 subjects. The age at pacemaker placement was 7.1±4.6 years (range 1.6 to 17.5 years). Time from Fontan procedure to pacemaker placement was 3.3±4.1 years (range 0 days to 12.8 years). Eleven of the 71 pacemaker subjects (15%) underwent pacemaker placement prior to or at the time of most recent Fontan procedure. Reasons for pacemaker placement listed in the medical records included bradycardia (n=26), implantation concurrent with most recent Fontan (n=18), intra-atrial reentrant tachycardia (n=8), sinus node dysfunction (n=7), ventricular tachycardia (n=5), low cardiac output (n=4), junctional rhythm (n=1), complete heart block (n=1), and unknown (n=1). Of the 71 subjects with a pacemaker, 43 (61%) were paced at the time of study enrollment based on their resting ECG. As previously reported, pacing modes determined from the resting electrocardiogram in the paced subjects were AAI in 69% and DDD in 31% [13]. Pacemaker subjects were older, more likely to have a diagnosis of double inlet left ventricle, more likely to have L-looped ventricles, and more likely to have single ventricles of left ventricular (LV) morphology than were subjects with no pacemaker. After adjusting for age, the type of Fontan procedure did not differ between subjects with a pacemaker and those without a pacemaker in our cohort (p=0.17).

Post-Fontan Medical History

Post-Fontan medical history variables are shown in Table 2. Subjects with pacemakers had undergone more additional surgical procedures, excluding pacemaker placement, than Fontan subjects without a pacemaker. Subjects with a pacemaker were more likely to have a history of arrhythmia than subjects without a pacemaker.

Pacemaker subjects were more likely to have a history of thrombosis than the no pacemaker subjects after adjusting for age at enrollment. Thrombosis occurred prior to pacemaker placement in 5/12 pacemaker subjects with a history of thrombosis.

Protein losing enteropathy and a history of new onset of ventricular dysfunction, defined as ventricular dysfunction any time since hospital discharge following the Fontan procedure, were marginally more common in the pacemaker subjects after adjusting for age at enrollment. New onset ventricular dysfunction occurred prior to pacemaker placement in 8/14 pacemaker subjects with this history. Of these 8 subjects, ventricular ejection fraction could be calculated in 6 at the time of the study echocardiogram, and only 2 had ejection fraction z-scores <−2.0.

Medication Usage

Medication usage is shown in Table 3. After adjusting for clinical site and age at enrollment, subjects with pacemakers were taking a greater number of medications at the time of study enrollment. Only antiarrhythmic use was not more common in the pacemaker subjects.

Outcome measures

Mean CHQ physical functioning summary score was lower in the pacemaker subjects compared to those with no pacemaker (39.7±14.3 vs. 46.1±11.2, p=0.001, Table 4). The mean physical functioning summary scores for both groups were lower than the mean value in a population of normal children (53.0±8.8, p<0.001 for both comparisons)[9]. The role/social limitations domain z-score was lower when pacemaker subjects were compared to the no pacemaker group (−0.9±1.8 vs. −0.3±1.3, p=0.02). The general health perceptions domain z-score was lower in the pacemaker subjects than the no pacemaker subjects

(−1.1±1.0 vs. −0.7±1.0, p<0.001). There were no differences in the mean CHQ psychosocial functioning summary score between the subjects with and without a pacemaker.

The echocardiographic findings are also shown in Table 4. Mean ventricular end-diastolic volume z-scores were not different between the groups. The ventricular ejection fraction and ejection fraction z-scores were marginally lower in the pacemaker subjects when compared to the no pacemaker group (p=0.05). There were no differences in the severity of either semilunar or atrioventricular valve regurgitation between groups.

There were no differences between groups for any of the exercise variables, and no differences in serum BNP concentration were found (Table 4).

Discussion

In the large cohort of Fontan survivors participating in the PHN Fontan Cross-Sectional Study we found that the patients with a pacemaker were more likely to have had other medical morbidities, including thrombosis and new onset of ventricular dysfunction following the Fontan procedure. As a group, Fontan survivors with a pacemaker had lower functional health status, based on the CHQ physical functioning summary scores, and lower echocardiographic indices of ventricular systolic function compared to those Fontan survivors without a pacemaker. While we were not able to demonstrate a causal link between the presence of a pacemaker and any of the factors outlined above with the available data from the Fontan Cross-Sectional study, in general, Fontan patients with a pacemaker had a poorer overall clinical status than those without a pacemaker.

The percentage of Fontan survivors with pacemakers in our cohort was slightly higher (13%) than has been reported in other large series of single center Fontan survivors [3,14–16], and the percentage of Fontan subjects undergoing pacemaker placement at each participating site (4% to 37%) varied widely. In general, the percentage of Fontan patients requiring pacemaker placement is lower in reports with shorter follow-up periods [14,15]. In a large, single center report by Gentles *et al,* with a follow-up period similar to that of the Fontan Cross-Sectional Study, the percentage requiring pacemaker placement was 9.4% [16]. Because of the multicenter design, our findings may be more generalizable to the overall population of Fontan survivors than these single center reports.

The type of Fontan procedure did not differ between those with a pacemaker and those without a pacemaker in our cohort after adjusting for age at enrollment. The incidence of sinus node dysfunction is high following a lateral tunnel Fontan, however, the reported incidence of pacemaker placement is relatively low [17]. In a large single center cohort of patients undergoing an extracardiac Fontan procedure, epicardial pacemaker placement was the most common surgical re-intervention, with freedom from pacemaker implantation 89% at 10 years and 76% at 15 years [18]. In previous studies comparing Fontan patients with intracardiac lateral tunnels and extracardiac conduits, the groups with the longest follow-up period have the higher proportion of patients requiring pacemaker placement [19,20]. This suggests that the time since the Fontan procedure may be a more important risk factor for pacemaker placement in this population than type of Fontan.

After adjusting for age, Fontan survivors with pacemakers in our cohort were taking a greater number of medications, had undergone more cardiac procedures, and were more likely to have a history of arrhythmia than those without a pacemaker suggesting a poorer clinical status. Fishberger *et al.* reported similar long-term survival in Fontan patients with pacemakers and those without pacemakers, although there was a trend towards poorer survival in those patients with VVI pacemakers[3]. However, in a large single center series reported by Gentles *et al.*, prior pacemaker placement was associated with an increased risk

of late Fontan failure, defined as death, cardiac transplantation or take down of Fontan, with an odds ratio of 7.7 (confidence interval 2.9 – 20.6)[21].

Our study is the first to evaluate the association between pacemakers and functional health status following the Fontan procedure. Functional health status was significantly lower in the pacemaker subjects compared to those without a pacemaker. In the entire Fontan Cross-Sectional Study cohort, subjects with a lower heart rate had higher CHQ physical functioning summary scores [13]. In the group with pacemakers, the CHQ physical functioning summary scores were lower, but there was no significant correlation between physical summary scores and heart rate.

This study has important limitations. Due to the cross-sectional design of this study, there is no longitudinal information regarding outcomes. The study cohort was limited to relatively healthy Fontan survivors. The cardiac rhythm was determined from a single electrocardiogram obtained at the time of exercise testing. Data from Holter monitoring and pacemaker interrogations were not collected as part of this cross-sectional study, and, therefore, specific details regarding the specific type of device, pacing mode (including rate response), pacing intervals, and an estimate of the percentage of time paced could not be determined. The indications for pacemaker placement were likely not uniform across centers. In addition, although all echocardiographic measurements were made at a single core laboratory using a standard protocol, there are inherent limitations in calculating ventricular volumes in single ventricles with unusual geometry. Most importantly, no causal inferences can be made based on the results presented.

In summary, the Fontan survivors with a pacemaker enrolled in the PHN Fontan Cross-Sectional Study were on more medications, had a history of more surgical procedures, and were more likely to have suffered a medical morbidity. They also had lower functional health status, and decreased ventricular systolic function compared to Fontan survivors without a pacemaker. Further investigation is required to determine if these findings are a consequence of pacing in this population or if the need for a pacemaker is another finding associated with a poorer outcome after a Fontan procedure.

Acknowledgments

Supported by grants from the National Heart, Lung, and Blood Institute (HL068269, HL068270, HL068279, HL068281, HL068285, HL068292, HL068290, HL068288)

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Appendix

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Table 1

Demographics and Clinical Characteristics

	No Pacemaker	Pacemaker	P
N	475	71	
Age at enrollment	11.7±3.3	12.9±3.8	**0.01**
Age at Fontan, years	3.3±2.0	3.9±2.8	0.12
Years since Fontan	8.5±3.4	9.1±3.9	0.13
Male	62%	51%	0.09
Race			0.30
White	79%	87%	
Black	11%	4%	
Asian	3%	1%	
Other	8%	7%	
Hispanic	6%	11%	0.19
Anatomic diagnosis			**0.03**
SV, DILV	13%	28%	
SV, DIRV	2%	1%	
SV, MA	6%	1%	
SV, TA	22%	21%	
Unbalanced AVCD	4%	3%	
Heterotaxy	7%	10%	
HLHS	21%	14%	
Other	25%	21%	
L-loop	16%	31%	**0.01**
Ventricular Morphology			**0.02**
Left	46%	63%	
Right	35%	27%	
Mixed	19%	10%	
Type of Fontan			0.17 *
Atriopulmonary connection	12%	20%	
TCPC Intracardiac lateral tunnel	61%	55%	
TCPC extracardiac conduit	24%	27%	
Other	3%	0%	

* Age adjusted p value. AVCD = atrioventricular canal defect, DILV = double inlet left ventricle, DIRV = double inlet right ventricle, HLHS = hypoplastic left heart syndrome, MA = mitral atresia, SV = single ventricle, TA = tricuspid atresia, TCPC = total cavopulmonary connection.

Table 2

Post Fontan Medical History.

	No Pacemaker	Pacemaker	Age adjusted p value
N	475	71	
Additional cardiac surgical procedures (excluding pacemaker insertion)	13%	32%	**<.001**
Medical morbidity			
Stroke	2%	6%	0.09
Thrombosis	6%	17%	**<.001**
Protein losing enteropathy	3%	9%	**0.05**
Arrhythmia	13%	72%	**<.001**
New onset of ventricular dysfunction	10%	20%	**0.05**
Other complication	23%	24%	0.97

Table 3

Medication Usage at Study Enrollment

	No Pacemaker	Pacemaker	Site & Age Adjusted p Value
# current meds	2.1±1.7	3.8±2.5	**<.001**
Antithrombotic	66%	82%	**0.03**
Antithrombotic (excluding Aspirin)	11%	34%	**<.001**
Diuretics	12%	37%	**<.001**
Glycoside	22%	55%	**<.001**
ACEi	56%	73%	**0.03**
Antiarrhythmic	3%	8%	0.09

ACEi = angiotensin converting enzyme inhibitor.

Table 4

Study Outcomes

	No Pacemaker	Pacemaker	p Value
CHQ Summary Scores			
Physical Summary Score	46.1±11.2	39.7±14.3	**0.001**
Psychosocial Summary Score	47.3±10.8	46.6±10.6	0.63
CHQ Domain Scores			
Physical function domain z score	−0.4±1.1	−0.8±1.4	**0.02**
Role/Social limits - emotional domain z score	−0.4±1.5	−0.7±1.6	0.20
Role/Social limits - physical domain z score	−0.3±1.3	−0.9±1.8	**0.02**
Bodily pain domain z score	0.2±1.0	−0.1±1.1	0.11
General behavior domain z score	−0.1±1.1	0.0±1.0	0.61
Mental health domain z score	−0.2±1.1	−0.1±1.1	0.48
Self esteem domain z score	−0.2±1.0	−0.4±1.0	0.14
General health perceptions domain z score	−0.7±1.0	−1.1±1.0	**<.001**
Parental impact - emotional domain z score	−0.7±1.3	−0.9±1.3	0.09
Parental impact - time domain z score	−0.2±1.2	−0.4±1.3	0.21
Echo			
N	467	69	
EDV z-score	−0.73±1.76 (362)	−0.11±2.69 (52)	0.11
ESV z-score	0.10±2.27 (362)	1.04±3.28 (52)	**0.05**
Echo EF, %	58.9±10.4 (362)	55.8±9.8 (52)	**0.05**
Echo EF z score	−0.81±2.04 (362)	−1.40±1.92 (52)	**0.05**
Stroke volume z score	−1.09±1.71 (362)	−0.81±2.27 (52)	0.39
Mass:volume ratio	1.2±0.4 (356)	1.2±0.4 (50)	0.67
Mass:volume ratio z score	2.61±3.24 (356)	2.94±3.09 (50)	0.50
Atrioventricular valve regurgitation			0.81
None	118 (25.7%)	19 (27.5%)	
Mild	252 (54.9%)	39 (56.5%)	
Moderate/severe	89 (19.4%)	11 (15.9%)	
Semilunar valve regurgitation			0.13
None	145 (52.3%)	14 (37.8%)	
Mild	110 (39.7%)	17 (45.9%)	
Moderate	22 (7.9%)	6 (16.2%)	
Exercise			
N	362	49	
Achieved maximal exercise (Respiratory quotient ≥ 1.1)	39%	53%	
Peak VO2 (ml/kg/min)	27.5±6.2	25.5±6.8	0.15
Percent Predicted Peak VO2	67.3±14.4	64.5±16.6	0.38
VO2 at VAT (ml/kg/min)	17.8±6.5	16.4±6.8	0.32
Percent Predicted VO2 at VAT	77.1±21.6	76.0±23.6	0.82
BNP, pg/ml	23.3±40.1	40.2±81.0	0.72

	No Pacemaker	Pacemaker	p Value
Log BNP, pg/ml	2.6±0.9	2.8±1.2	0.74

BNP = B-type natriuretic peptide, CHQ = child health questionnaire, EF = ejection fraction, EDV = end-diastolic volume, ESV = end-systolic volume, VAT = ventilator anaerobic threshold, VO_2 = oxygen consumption.