**Age at Fontan procedure impacts exercise performance in adolescents: results from Pediatric Health Network multicenter study.**

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**Abstract**

**Age at Fontan procedure impacts exercise performance in adolescents: results from Pediatric Health Network multicenter study.**

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**Background:** Fontan procedure is the palliative method of choice for patients with single ventricle physiology and involves separating the systemic and pulmonary circulations and placing them in series without the interposition of a normal ventricle. Optimal timing of the Fontan completion, particularly after an intermediate staging surgery, is controversial. The long-term impact of timing of Fontan completion on the exercise performance in adolescents is unknown.

**Methods:** We used The NIH/NHLBI Pediatric Heart Network Fontan Cross-Sectional Study dataset consisting of children and adolescents age 6-18 years recruited into the study in 2003-04 for analysis. Associations between demographic, disease- and procedure-related variables, including age at Fontan procedure, and risk of inadequate effort on exercise testing were evaluated using unconditional logistic regression.

Multivariate linear regression techniques were used to evaluate association of age at Fontan procedure with percent predicted V02 maximum, percent predicted O2 maximum pulse, and heart rate reserve in patients who achieved adequate exercise effort in hierarchically adjusted models.

**Results:** Retrospective data on 405 patients who had undergone only one Fontan operation and ramp cycle ergometry were analyzed. Mean age at Fontan surgery procedure was 3.4±2 years and mean age at the time of ramp cycle ergometry was 12.4±3.2 years; 58.5% were males and 78.8% were Caucasian. 312 patients reached ventilatory anerobic threshold (VAT) suggesting adequate effort. Although the age at Fontan procedure was not related to risk of reaching VAT (p=0.97) in the fully adjusted model, age age at first unloading surgery was associated with higher risk of an inadequate effort on exercise testing (OR 1.3, 95% CI 1.06-1.60). In patients who reached the VAT, each year increase in age at Fontan completion was associated with a decline of 1.5 (95% CI -2.5 to -0.5) points in percent predicted VO2 maximum after adjusting for demographic, disease related and surgical characteristics (p=0.003). Similarly, each year increase in age at Fontan completion was associated with a decline of 4.1 (95% CI -6.0 to -2.1) beats/min in heart rate reserve ($p < 0.001$).

**Conclusions:** Patients who undergo Fontan completion at an earlier age have better exercise performance than those who receive delayed surgery.

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# INTRODUCTION

*Single ventricle physiology and the Fontan procedure*

Several complex congenital cardiac malformations (e.g. Tricuspid atresia, hypoplastic left heart syndrome, double-inlet left ventricle and others) are characterized by a single functional ventricle. A single ventricle physiology is characterized by a combination of cyanosis and ventricular volume overload, with ventricular output 2-3 times the normal amount. Before the advent of palliative surgical procedures, this condition led to high rates of mortality, and a vast majority of the affected infants died within the first year of life.

A major advance in the management of single ventricle patients occurred in 1971 when Dr Francois Fontan separated the systemic and pulmonary circulations and placed them in series without the interposition of a normal subpulmonic ventricle in a patient with tricuspid atresia[1]. This approach directs all of the systemic venous return directly to the lungs and removes right to left shunting at the atrial or ventricular level. Soon, this surgical approach was applied to a wide range of patients with single functional ventricle whose anatomy precluded a biventricular repair. Although the original operation involved connecting the right atrium to the pulmonary artery (atriopulmonary connection), several modifications were proposed in the subsequent years. Most notably, de Leval et al. introduced the concept of total cavopulmonary connection (TCPC) in 1988, in which the inferior vena cava is connected to the pulmonary artery by incorporating either a lateral tunnel or an extra-cardiac conduit[2]. By the early 1990s, a staging approach (as described below) towards the TCPC was initially advocated for high risk patients but later adopted for even low to moderate risk patients because it significantly reduced the risk of mortality and morbidity at the subsequent Fontan procedure[3]. In the contemporary surgical era, the Fontan procedure is performed as a two staged procedure. The intermediate staging procedure, which is typically done in the first year (after 3 months of age) involves directing the superior cava blood flow to the pulmonary artery by performing either a Glenn (classic or bidirectional) or a Hemi-fontan procedure. This procedure partially (although significantly) improves the cyanosis and the volume-overloaded state of the ventricle. The ventricle is unloaded by virtue of a significant portion of the cardiac output going directly to the lungs. The Fontan completion procedure is done at a later age that ranges from 1 to 5 years at various institutions and results in resolution of cyanosis and further reduction of the volume overloaded state of the ventricle.

*Fontan procedure and long-term outcomes*

Despite the underlying severe congenital cardiovascular malformations for which the Fontan procedure is performed, the short-term and the medium-term results of this procedure have been excellent[4, 5]. However, the long-term survivors of the surgery develop several non-cardiac and cardiac complications. The non-cardiac complications include protein losing enteropathy, cirrhosis, plastic bronchitis and coagulation disorders. The cardiac complications include heart failure and arrhythmias are amongst the most common causes of late morbidity and mortality in Fontan patients. The pathogenesis of heart failure in Fontan patients is complex and likely multifactorial. It has been shown that the prolonged duration of the volume overloaded state of the single ventricle prior to palliative surgery often results in profound adverse alterations in myocardial contractility, which may persist even after surgery[6]. Secondly, the persistently elevated venous pressures and lack of pulsatile flow in the pulmonary vascular bed leads to increased pulmonary vascular resistance which may cause systemic ventricular preload limitation[7], given the lack of a subpulmonary ventricle to generate pressure to overcome the increased pulmonary vascular resistance. This chronic preload limitation has been shown to be associated with decreased ventricular compliance[8].

*Exercise performance in Fontan patients*

The ventricular dysfunction seen in Fontan patients has been implicated as one of several potential mechanisms that may lead to impaired exercise intolerance[9], which is common in patients who have undergone Fontan procedure. These patients have decreased peak oxygen uptake, have blunted heart rate response (chronotropic response) to exercise and may have decreased arterial oxygen saturation at peak exercise. The cardiac output is decreased likely due to reduced stroke volume, chronotropic incompetence and decrease pulmonary venous return. Ventilatory anaerobic threshold may be preserved or decreased and ventilatory equivalent for carbon dioxide is higher than the normal ranges. The most well characterized mechanism of exercise tolerance is the absence of adequate preload reserve that may lead to decreased cardiac output during exercise[10]. Besides the increase in pulmonary vascular resistance as mentioned above, other mechanisms that may lead to decreased mobilization of blood and decrease in pre-load are the maladaptive changes in the systemic venous system e.g. reduced venous compliance and capacitance, increased microvascular filtration pressures and increase in the venous tone[11].

*Age at Fontan completion and outcomes*

In the original selection criteria for patient selection for Fontan procedure, the optimal age range for the procedure was initially recommended as 4 to 15 years[12]. Therefore, the initial cohort of the patients undergoing Fontan procedure was much older in age as compared to the contemporary cohort. They also underwent Fontan procedure as a single staged repair. In two of the largest initial long-term follow-up studies, the mean age of the patients was almost 12 years at the time of repair[13, 14]. In these early studies, the age at Fontan was neither associated with changes in ventricular function[14], nor associated with exercise performance[13]. This suggested that the changes in ventricular contractility from chronic volume overload that may have occurred at younger age were not reversible after surgery.

With an improvement in surgical techniques, it became possible to do the Fontan procedure at an earlier age. In early short-term studies from this transitional period, it was noted that the patients who underwent Fontan procedure at an age <10 years had improvement in cardiac contractility in the follow-up period while those who were operated at a later age had no such improvement[6]. Similar results were reported by other investigators using cardiac catheterization[15]. However, these studies had only a few patients that had undergone Fontan procedure as a two-staged repair.

As the number of patients undergoing the two-staged Fontan repair at a younger age increased over the years, Mahle et al. in a study of 68 patients (in which 30% patients had prior intermediate staging surgery) demonstrated that the patients who were less than 2 years of age at the time of first unloading surgery had better exercise performance as preadolescents[16]. Similar results were reported by Shiraishi et a.l in their series of 65 patients that had left ventricular morphology and of which 28% had undergone intermediate staging procedure[17]. In both the studies, the number of patients undergoing an intermediate staging procedure was not enough to separately evaluate the impact of age at intermediate staging surgery and the impact of age at Fontan completion on long-term outcomes. In contemporary era, the two-staged Fontan repair is now done in majority of the patients with single ventricle. In the most recent large cohort of patients, the number of patients who had undergone an intermediate staging surgery exceeded 70%[18]. Therefore, the contemporary cohort of Fontan patients is significantly different than the cohort of patients that has been a part of the earlier studies.

*Current gaps in literature*

Relieving the volume overload of the single ventricle at a younger age is likely a good strategy to achieve better long-term outcomes. However, it is unclear if the completion of Fontan at an earlier age is necessary once a partial unloading surgery (such as bidirectional Glenn) has already been performed at a younger age. Delaying the Fontan completion by a couple of years after Glenn may prevent the long-term complications of Fontan circulation such as cirrhosis and protein losing enteropathy which are often attributed to increased hepatic venous pressure and venous mesenteric venous pressure. The evidence currently available about the association of early age at Fontan procedure with increased early postoperative mortality is also conflicting and adds to the controversy.

The optimal age at Fontan completion after an intermediate staging procedure remains controversial and ranges from less than one year of age at some institutions to 4-5 years at other institutions[19-21]. The impact of age at Fontan completion on long-term clinical outcomes remains unknown. Since exercise intolerance is associated with increased morbidity and mortality in patients with congenital heart disease including Fontan patients[22-24], we decided to investigate whether the age at Fontan completion is associated with the exercise performance measures in adolescent Fontan patients. The main objectives of this study were to: a) investigate the demographic, disease related and procedure related characteristics that may be associated with selection of age at Fontan completion ; b) Identify factors associated with inability to achieve ventilatory anerobic threshold (VAT), suggestive of inadequate effort on exercise testing; c) and investigate the association of age at Fontan completion with various exercise outcomes in patients who achieved adequate effort on exercise testing.

## METHODS

*Study population:*

The study design of the NIH-NHLBI funded multicenter Fontan cross-sectional study conducted by the Pediatric Health Network has been described earlier[18]. In this study, 546 patients age 6 to 18 years with a prior history of Fontan procedure but no cardiac surgical intervention in the preceding 6 months were recruited from 7 centers in the US and Canada between March 2003 to April 2004. Detailed anatomic, clinical and surgical data was collected and all pertinent studies (MR imaging, echocardiography and cardiopulmonary exercise testing) were obtained within 3 months of enrollment. For the purpose of this study, we analyzed the data on 412 patients who had undergone cardio-pulmonary exercise testing in our study. Patients (n=7) who had undergone any Fontan revisions (i.e. more than one Fontan procedure) were excluded.

*Cardiopulmonary exercise protocol:*

The detailed exercise protocol for the patients has been described earlier[25]. Prior to exercise testing, subjects underwent inspiratory and expiratory flow volume loops and performed hyperventilation for 10 seconds to measure maximum voluntary ventilation (MVV) (l/min). Maximal exercise testing was performed on the cycle ergometer using a ramp protocol that consisted of pedaling in an unloaded state for 3 min and then continuously increasing the workload to achieve each subject's predicted maximal work rate after 10 to 12 min of cycling. Metabolic measurements that were obtained were Oxygen consumption (VO2), carbon dioxide production (VCO2), and minute ventilation (VE), which were monitored on a breath-by-breath basis. Peak VO2 was defined as the highest VO2 achieved by the subject during the test. Ventilatory anaerobic threshold (VAT) was measured by V-slope method when it could be accurately determined. Values for VO2 were indexed to body weight and expressed as percentage of predicted values for healthy age- and gender-matched subjects. The ventilatory equivalents of carbon dioxide (VE/VCO2) were measured at VAT. The respiratory exchange ratio (RER) (i.e. VCO2/VO2) was measured continuously. The O2 pulse (VO2/heart rate [HR]) was measured at peak VO2 and indexed to body surface area and expressed as percentage of predicted values for healthy age and gender matches subjects. The O2 pulse reflects the amount of O2 extracted per heart-beat and can be used an estimator of stroke volume particularly in the patients who do not desaturate during exercise[26].

*Covariates and outcomes of interest:*

The patient and the surgery-related covariates adjusted in the models were chosen on the basis of their known or hypothesized association with outcomes from the available literature and are listed in Table 1. The primary outcomes of interest were the exercise parameters that have been shown to be of demonstrated value in predicting hospitalization and long-term survival in patients with congenital heart disease[22]. The primary outcomes of interest were:

a. Percent predicted peak VO2 maximum.
b. Heart rate reserve (HRR): which was defined as the difference between the maximal and the resting heart rate.

The secondary outcome of interest was percent-predicted maximum O2 pulse. The secondary outcome was chosen to explain the reasons for differences in exercise performance that may arise from delay in Fontan completion.

*Statistical analysis:*

After exclusions as noted above, 405 patients were stratified according to whether the subjects reached the VAT or not. These groups were subsequently referred to as "adequate effort or inadequate effort" groups[26]. Descriptive statistics, including N (%) or mean (standard deviation) were used to describe the demographic, disease and procedural characteristics and the exercise parameters of the two groups. Differences in the characteristics and the outcomes in the two groups were assessed by chi-square (for categorical variables) and unpaired t-tests (for continuous variables). To assess those variables that may affect age at Fontan procedure, univariate linear regression analyses using robust standard errors were used to assess the association of each variable listed in Table 1 with the age at Fontan completion. Multivariable regression analyses were then used to determine which covariates were independently associated with age at Fontan completion including all covariates in the model

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Associations between risk of inadequate effort on exercise testing (using a binary variable with 1 indicating inadequate testing) and demographic/surgical variables was assessed using unconditional logistic regression on all study participants. Models were run both unadjusted and adjusted for all variables that are listed in Table 1. The association between age at Fontan completion and exercise outcomes of predicted VO2 maximum, heart rate reserve and predicted O2 maximum, was determined using linear regression analyses in the 312 patients reaching VAT (i.e. the adequate effort group). The linear regression analyses assuming robust standard errors were done in a series of incremental models as follows: first unadjusted (model 1); then adjusted for demographics (age at exercise testing, BMI for age z score, gender and race) (model 2); then additionally adjusted for disease related characteristics (hypoplastic left heart syndrome, L-loop configuration, ventricular dominance) (model 3); and finally additionally adjusted for procedural characteristics (pacemaker, age at first unloading surgery, intermediate staging surgery, Fontan type, fenestration) (model 4). There was no significant multicollinearity (variance inflation factor >5) between the independent variables. All p values presented are 2 tailed; $p < 0.05$ was considered statistically significant for all analyses. Analyses were performed with STATA 12 statistical package (Stata Corp, College Station, TX)

## RESULTS

*Patient characteristics*

Of the 405 patients studied, 312 reached VAT on cardiopulmonary exercise testing and were classified into the 'adequate-effort' group; the remaining were considered as 'inadequate effort'. The reasons listed for not reaching VAT were primarily fatigue (31.2%), inability to follow instructions (17.2%) and inadequate effort (26.9%). The various patient related characteristics, underlying etiologies of the single ventricle and surgery related characteristics are shown in Table 2. The patients in the adequate effort group were more likely to be white with higher proportion of atriopulmonary and lateral tunnel intra-cardiac Fontan and less likely to have undergone intermediate surgery and extracardiac Fontan surgery. They also tended to be older than the patients in the 'inadequate-effort' group, although the difference was not statistically significant. No difference between the two groups was seen with respect to age at unloading surgery, age at Fontan completion, BMI for age z scores or etiology of the functional single ventricle.

*Association of age at Fontan completion with various covariates*

The linear associations of individual variables with age at Fontan completion is shown in Table 3. In unadjusted models, the variables that were positively associated with age at Fontan completion were age at exercise testing, age at unloading surgery, black race, Asian race, history of intermediate staging surgery and history of extracardiac Fontan procedures. The variables that were inversely associated with age at Fontan completion were male gender, higher BMI-for age z scores, hypoplastic left heart syndrome. On multivariate analysis, age at exercise testing, age at unloading surgery, black race, history of intermediate staging surgery and extracardiac Fontan procedures were independently associated with higher age at Fontan completion, whereas hypoplastic left heart syndrome and current pacemaker use were associated with lower age at Fontan completion.

*Predictors of inadequate effort*

The results of logistic regression to ascertain the factors associated with risk of achieving inadequate effort on exercise testing are shown in Table 4. In unadjusted models, the variables that were associated with higher risk of inadequate effort were black race, history of intermediate staging surgery and history of extracardiac Fontan repair. The variables that were associated with lower risk of inadequate effort were higher age at exercise testing and current pacemaker use.

In fully adjusted models, age at unloading surgery was associated with higher risk of achieving inadequate effort on exercise testing, whereas age at exercise testing was associated with lower risk of achieving inadequate effort on exercise testing. No other variables, including age at Fontan completion, were significantly associated with patients' inability to achieve VAT signifying inadequate effort.

*Cardiopulmonary exercise testing results*

The various exercise parameters obtained in the Fontan patients are shown in Table 5. For the entire study population, the percent predicted peak $VO_2$ max (normal > 84%) was decreased as compared to the normal subjects. Percent predicted maximum heart rate response was also decreased (normal >90%) suggestive of chronotropic incompetence. Percent predicted maximum O2 pulse was in normal range (normal >80%). The percent predicted peak work rate was decreased. The oxygen saturation decreased slightly on exercise but remained above 90%.

*Association of age at Fontan with exercise outcomes*

The results of incremental models evaluating the association of age at Fontan with percent predicted VO2 maximum are shown in Figure 1. The age at Fontan was negatively associated with percent-predicted VO2 maximum in the unadjusted model (Model 1). This relationship was attenuated in model 2 and model 3. However, in the fully adjusted model (model 4), each year increase in age at Fontan completion was associated with a decline of 1.5 (95% CI -2.5 to -0.5) points in percent-predicted VO2 maximum (p=0.003). The results of incremental models evaluating the association of age at Fontan with heart rate reserve are shown in Figure 2. In the fully adjusted model (model 4), each year increase in age at Fontan completion was associated with a decline of 4.1 (95% CI -6.0 to -2.1) beats/min in heart rate reserve (p<0.001). The results of incremental model evaluating the association of age at Fontan completion with percent-predicted maximum O2 pulse are shown in Figure 3. Age at Fontan completion was not associated with percent-predicted maximum O2 pulse in neither the unadjusted nor the adjusted models (p=0.25).

## DISCUSSION

In this analysis from a large multicenter study of adolescent Fontan patients, we have demonstrated that performing Fontan completion at an earlier age is associated with significantly improved exercise performance measures such as percent predicted $VO_2$ maximum and heart rate reserve in patients who were able to achieve adequate effort on cardiopulmonary exercise testing. Moreover, an older age at unloading surgery is associated with an increased risk of achieving inadequate effort on exercise testing. The lack of association of age at Fontan completion with percent predicted maximum $O_2$ pulse suggests that the effects of age at Fontan completion on exercise performance in adolescents are likely related to a decrease in heart rate response.

The association of older age at exercise testing with older age at Fontan completion may reflect a temporal trend over time to operate the patient at a younger age for the Fontan completion across hospitals participating in the NIH/NHLBI Pediatric Heart Network Fontan Cross-Sectional Study over the last years. Patients who underwent an intermediate staging surgery prior to Fontan had their Fontan completion at a later age likely because the risk of short-term mortality decreases substantially after the intermediate staging surgery. African American patients were also likely to have a delayed Fontan completion. A history of extracardiac Fontan repair was also associated with an older age at Fontan completion. This may be due to the synthetic conduit used to perform extra-cardiac Fontan procedure that does not increase in size with growth, but offers other potential advantages such as avoidance of sinus node manipulation, decreased suture lines and low potential for atrial dilation thus lessening the risk of future arrhythmias. In contrast, the surgeons performing Fontan completion at an earlier age may be performing lateral tunnel procedure because of its potential advantages for growth potential and avoidance of synthetic material that may possibly reduce the risk of thromboembolism in the low pressure, right-sided circulation. Presence of hypoplastic left heart syndrome was associated with a lower age at Fontan completion. This is likely due to the fact that the surgical advances in treatment for the hypoplastic left heart syndrome are more recent and secondly, these patients have high short-term mortality if not palliated at a younger age.

*Comparison with other studies*

Impaired exercise performance has been demonstrated in Fontan patients in several prior studies[13, 16, 17, 27-29]. However, the patient populations in the older studies were not representative of the contemporary Fontan patients. For example, in some of the prior studies, the mean age at Fontan repair has ranged from 12 years to 19 years[13, 27-29]. In these older studies, age at Fontan has not been shown to affect exercise tolerance. This suggests that irreversible changes in ventricular contractility may have occurred by the time these patients underwent surgery. In a few more recent single center studies, age at first unloading surgery[16] and age at Fontan repair[17] have been shown to be associated with improved exercise tolerance in pre-adolescents. However, in both the studies, the number of patients undergoing intermediate staging surgery was small and it could not be determined if the interval between intermediate staging surgery and Fontan completion affected exercise performance in these patients[16, 17]. Besides being the largest study in evaluating the effect of age at Fontan completion, our study is novel in that it more closely resembles a contemporary cohort of Fontan patients and encompasses a wider range of etiologies of functional single ventricle. The majority of our patients had undergone an intermediate staging surgery at a very young age and we have longer follow up time than most of the other studies.

*Age at Fontan completion*

Although younger age has been reported as a factor related to successful Fontan completion in older studies, more recent studies suggest that the Fontan operation can be safely performed at even younger ages than previously believed[16, 17]. The impact of early age at Fontan completion on long-term exercise performance certainly seems biologically plausible because in one short-term follow-up study using echocardiography, younger age at the time of Fontan was associated with reversal of abnormal contractile mechanics and the capacity for this improvement diminished with delay in surgery[6]. In another study, using cardiac catheterization, Uemura et al. demonstrated improvement in ejection fraction in patients who underwent Fontan operation at a younger age[15]. Similarly, a prior analysis of the Fontan cross-sectional study has revealed that the older age at Fontan completion was associated with higher degree of ventricular dysfunction as shown by worsening of measures of ventricular performance such as mean Tei index, higher E/E' as well as increased severity of atrioventricular valve regurgitation[18]. The presence of ventricular dysfunction raises the question of whether the blunted heart rate response to exercise (i.e. chronotropic incompetence) that was seen with increasing age at Fontan completion is related to concomitant beta-blocker use. We do not believe that this is likely the case as only a few of the patients in the current study were on beta-blocker therapy (3.5%). On the other hand, chronotropic incompetence is known to be widely prevalent in patients with heart failure[30]. The mechanisms underlying the chronotropic incompetence in ventricular dysfunction are poorly understood and are likely multifactorial. One of the potential mechanisms that have been proposed is post-synaptic desensitization of the beta-adrenergic receptors as seen in patients with heart failure[31]. Another possible mechanism may be that activation of cardiac mechanoreceptors in response to increased filling pressure may cause an inhibitory reflex leading to relative bradycardia (Bezold-Jarisch reflex)[32].

*Age at unloading surgery*

The association of age at first unloading surgery with the inability to exert adequate effort in exercise testing is difficult to explain. Since these patients did not exert themselves to VAT, we cannot explain the association of age at unloading surgery in terms of cardiac or pulmonary limitation. The two major reasons for inadequate effort on exercise testing were fatigue and inability to follow instructions. It is possible that the chronic cyanotic state before the first unloading surgery may have caused alterations in skeletal muscle function that might be contributing to fatigue.[33] Inability to follow instructions may have resulted from cognitive impairment. Delay in unloading surgery may expose the infant to a higher risk of shunt closure in the inter-stage period causing circulatory collapse and leading to neurologic injury. Secondly, chronic cyanosis may impair neurologic development and older age at repair has been shown to be associated with progressive impairment of cognitive function in cyanotic heart disease.[34]

*Clinical Implications*

Although statistically significant, whether the differences in percent-predicted VO2 max and the heart rate reserve for every year delay in Fontan completion are clinically relevant may be debated. Using the results from a large study of 1375 adult congenital heart disease patients that evaluated the risk of mortality by using cardiopulmonary exercise testing parameters[22], we came to the conclusion that a patient who underwent Fontan completion at an age of 5 years had 35% higher hazard of mortality than a patient who was operated at an age of 2 years. Therefore, we do believe that the differences observed in the current study are clinically meaningful. Fontan circulation may lead to several long-term problems. Most notably, protein-losing enteropathy has been shown to be an independent predictor of mortality or transplantation in perioperative Fontan survivors.[35] One might argue that performing the Fontan completion at an earlier age may cause these problems to develop sooner. We believe that this is unlikely to be the case because age at Fontan completion was not found to be associated with protein losing enteropathy in about 30 patients who had this complication and were part of this study (data not shown). Cirrhosis is another long-term complication of patients with Fontan physiology and may be related to duration of Fontan circulation. Long-term follow up data will be required to assess if a younger age at Fontan repair is associated with early development of cirrhosis.

*Strengths and Limitations*

Strengths of this study include a large contemporary cohort of Fontan patients with wider range of etiologies of functional single ventricle. Secondly, the data were collected from multiple centers across the US with standardized methods and procedures utilized across sites increasing quality of the data. We also had longer duration of follow-up than most of the other studies.

This study has several limitations. The retrospective and non-randomized design of the study exposes the data to a possibility of selection bias in the timing of Fontan completion. Significant variations in the management of single ventricle patients may exist at the referring physician or the institutional level and we cannot account for all the unknown variables by using this study design. Variations may also exist in the perioperative management at different institutions. Since, we do not have any data about where the patients were operated, we cannot adjust for these institutional level differences. Our analysis is limited to the Fontan patients who reached adolescence and the data on the patients who died post-operatively before getting enrolled in the current study is not available. Our results are derived from the patients who consented to be in the study. However, this is unlikely to be a major limitation of our work as the enrolled patients were of similar age and functional status as the non-consenting subjects.[36]

*Conclusions and directions for future research*

In one of the largest studies of contemporary adolescent Fontan patients, the majority of whom had undergone an intermediate surgery at a very young age, we have demonstrated that increasing age at Fontan completion is associated with decreased exercise performance. Longitudinal studies are required to assess if the benefit of Fontan completion at an earlier age on exercise tolerance, morbidity and mortality continues in adulthood and beyond.

Table 1. Variables from the NIH/NHLBI Pediatric Heart Network Fontan Cross-Sectional Study examined in the multivariate regression models.

| Patient related characteristics | Surgery related characteristics |
|---|---|
| Age at exercise testing | Intermediate surgery (Y/N) |
| Gender | Age at first unloading surgery |
| Race | Type of Fontan procedure |
| Z score for BMI for age | Fenestration of the Fontan baffle |
| Pacemaker present | |
| Ventricular dominance | |
| Hypoplastic left heart syndrome | |
| L-loop configuration | |

Table 2: Characteristics of the 405 adolescents who received the Fontan procedure and cardiopulmonary exercise testing participating in the NIH/NHLBI Pediatric Heart Network Fontan Cross-Sectional Study.

| **Variable** | **Total (n=405)** | | **Adequate effort (n=312)** | | **Inadequate effort (n=93)** | | |
|---|---|---|---|---|---|---|---|
| | **Mean±SD or N (%)** | **(Min,Max)** | **Mean±SD Or N (%)** | **(Min,Max)** | **Mean±SD or N (%)** | **(Min,Max)** | **p value*** |
| | | | | | | | |
| Age | | | | | | | |
| At exercise | 12.4 ± 3.2 | (6.9,18.8) | 12.9±3.0 | (6.9,18.8) | 10.6±3.1 | (6.9,18.7) | 0.59 |
| At unloading surgery | 1.7±1.7 | (0.0,14.0) | 1.8±1.7 | (0.0,14.0) | 1.6±1.6 | (0.3,9.0) | 0.93 |
| At Fontan | 3.4±2.0 | (0.7,14.0) | 3.4±2.0 | (0.7,14.0) | 3.6±2.2 | (0.8,12.4) | 0.95 |
| Z score for BMI-for age | 0.0±1.1 | (-4.9, 2.4) | 0.0+1.2 | (-4.9,2.2) | 0.0±1.1 | (-3.1,2.4) | 1.0 |
| Male Gender | 237 (58.5) | | 188 (60.3) | | 49 (52.7) | | 0.20 |
| Race | | | | | | | |
| White | 319 (78.8) | | 258 (82.7) | | 61 (65.6) | | <0.001 |
| Black | 44 (10.9) | | 29 (9.3) | | 15 (16.1) | | 0.09 |
| Asian | 11 (2.7) | | 8 (2.6) | | 3 (3.2) | | 0.38 |
| Other | 31 (7.6) | | 17 (5.4) | | 14 (15.0) | | 0.005 |
| Etiology | | | | | | | |
| Tricuspid atresia | 100 (24.7) | | 78 (25) | | 22 (23.7) | | 0.79 |
| Hypoplastic left heart syndrome | 71 (17.5) | | 51 (16.3) | | 20 (21.5) | | 0.25 |
| Double inlet LV | 64 (15.8) | | 52 (16.7) | | 12 (12.9) | | 0.35 |
| Heterotaxy | 29 (7.2) | | 21 (6.7) | | 8 (8.6) | | 0.56 |
| Double outlet RV | 8 (2) | | 7 (2.2) | | 1 (1.1) | | 0.42 |
| Mitral atresia | 20 (4.9) | | 16 (5.1) | | 4 (4.3) | | 0.74 |
| AV canal defect | 16 (3.9) | | 10 (3.2) | | 6 (6.5) | | 0.23 |
| Current pacemaker use | 46 (11.3) | | 41 (10.1) | | 5 (5.4) | | 0.10 |
| Dominant ventricle | | | | | | | |
| Right | 155 (38.3) | | 114 (36.5) | | 41 (44.1) | | 0.19 |
| Left | 224 (55.3) | | 179 (57.4) | | 45 (48.4) | | 0.13 |
| Mixed | 26 (6.4) | | 19 (6.1) | | 7 (7.5) | | 0.65 |
| Intermediate surgery | 293 (72.3) | | 215 (68.9) | | 78 (83.4) | | 0.002 |
| Fontan type | | | | | | | |
| Atriopulmonary | 63 (15.6) | | 54 (17.3) | | 9 (9.7) | | 0.04 |
| Lateral tunnel | 235 (58.0) | | 190 (60.9) | | 45 (48.4) | | 0.03 |
| Extracardiac lateral tunnel | 47 (11.6) | | 27 (8.6) | | 20 (21.5) | | 0.005 |
| Extracardiac conduit | 52 (12.8) | | 34 (10.9) | | 18 (19.3) | | 0.06 |
| Other | 8 (2.0) | | 7 (2.2) | | 1 (1.1) | | 0.42 |
| Fenestration done | 258 (63.7) | | 201 (64.4) | | 57 (61.3) | | 0.59 |

* p-values from chi-sqare or t-tests for categorical or continuous variables, respectively.

Table 3. Association between demographic, disease related and procedure related variables and age at Fontan completion using multivariate linear regression in 405 adolescent patients participating in the NHLBI etc.

| Variables | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Estimate | p value | Estimate | 95% CI |
| Age | | | | |
| At exercise | 0.17 (0.1 to 0.24) | <0.001 | 0.16 (0.09 to 0.23) | <0.001 |
| At unloading surgery | 0.66 (0.49 to 0.82) | <0.001 | 0.78 (0.5 to 1.05) | <0.001 |
| Males | -0.47 (-0.87 to -0.06) | 0.02 | -0.12 (-0.39 to 0.15) | 0.39 |
| Race | | | | |
| White | reference | | | |
| Black | 0.9 (0.17 to 1.63) | 0.02 | 0.77 (0.21 to 1.33) | 0.008 |
| Asian | 0.82 (0.07 to 1.56) | 0.03 | 0.23 (-0.42 to 0.88) | 0.49 |
| Other | 0.89 (-0.13 to 1.91) | 0.09 | 0.15 (-0.43 to 0.72) | 0.61 |
| Z score for BMI-for age | -0.19 (-0.37 to -0.01) | 0.04 | -0.05 (-0.17 to 0.07) | 0.4 |
| Hypoplastic left heart syndrome | -0.82 (-1.22 to -0.41) | <0.001 | -0.58 (-1.10 to -0.06) | 0.03 |
| L-loop configuration | -0.05 (-0.5 to 0.39) | 0.81 | -0.14 (-0.44 to 0.16) | 0.36 |
| Current pacemaker use | 0.16 (-0.38 to 0.71) | 0.5 | -0.46 (-0.86 to -0.06) | 0.02 |
| Dominant ventricle | | | | |
| Right | reference | | | |
| Left | -0.21 (-0.63 to 0.22) | 0.34 | -0.40 (-0.83 to 0.02) | 0.06 |
| Mixed | -0.11 (-1.0 to 0.79) | 0.81 | -0.05 (-0.61 to 0.51) | 0.86 |
| Intermediate surgery | 0.66 (0.27 to 1.06) | 0.001 | 1.98 (1.49 to 2.47) | <0.001 |
| Fontan type | | | | |
| Atriopulmonary | reference | | | |
| Lateral tunnel | -0.29 (-0.69 to 0.11) | 0.15 | 0.12 (-0.17 to 0.43) | 0.41 |
| Extracardiac lateral tunnel | 0.95 (0.28 to 1.62) | 0.005 | 1.44 (0.89 to 2.01) | <0.001 |
| Extracardiac conduit | 1.09 (0.25 to 1.94) | 0.01 | 1.54 (0.89 to 2.19) | <0.001 |
| Other | -0.11 (-1.16 to 0.95) | 0.84 | 0.06 (-0.37 to 0.49) | 0.78 |
| Fenestration done | 0.29 (-0.07 to 0.67) | 0.11 | 0.1 (-0.14 to 0.35) | 0.4 |

Table 4: Associations between demographic, disease related and procedure-related variables and risk of inadequate effort on exercise testing in 405 adolescents who received the Fontan procedure using multivariate logistic regression

| Variables | Unadjusted Odds Ratio (95% confidence interval) | p value | Adjusted * Odds Ratio (95% confidence interval) | 95% CI |
|---|---|---|---|---|
| Age | | | | |
| At exercise | 0.78 (0.71 - 0.85) | <0.001 | 0.77 (0.68 - 0.86) | <0.001 |
| At unloading surgery | 0.93 (0.8 - 1.09) | 0.36 | 1.32 (1.05 - 1.67) | 0.02 |
| At Fontan completion | 1.05 (0.94 - 1.17) | 0.38 | 0.99 (0.82 - 1.2) | 0.97 |
| Males | 0.73 (0.46 - 1.17) | 0.19 | 0.73 (0.43 - 1.24) | 0.25 |
| Race | | | | |
| White | reference | | | |
| Black | 2.19 (1.1 - 4.3) | 0.02 | 1.59 (0.72 - 3.53) | 0.25 |
| Asian | 1.59 (0.41 - 6.15) | 0.5 | 0.85 (0.19 - 3.88) | 0.84 |
| Other | 3.48 (1.63 - 7.45) | 0.001 | 2.18 (0.93 - 5.14) | 0.07 |
| Z score for BMI-for age | 1.02 (0.83 - 1.25) | 0.82 | 1.03 (0.82 - 1.30) | 0.77 |
| Hypoplastic left heart syndrome | 1.40 (0.79 - 2.51) | 0.25 | 1.45 (0.63 - 3.35) | 0.38 |
| L-loop configuration | 0.60 (0.32 - 1.56) | 0.13 | 0.74 (0.35 - 1.12) | 0.43 |
| Current pacemaker use | 0.37 (0.14 - 0.98) | 0.045 | 0.45 (0.16 - 1.30) | 0.14 |
| Dominant ventricle | | | | |
| Right | Reference | | | |
| Left | 0.69 (0.43 - 1.13) | 0.15 | 1.08 (0.55 - 2.14) | 0.82 |
| Mixed | 1.02 (0.40 - 2.61) | 0.05 | 1.32 (0.43 - 3.99) | 0.63 |
| Intermediate surgery | 2.35 (1.28 - 4.28) | 0.006 | 2.01 (0.84 - 4.81) | 0.12 |
| Fontan type | | | | |
| Atriopulmonary | Reference | | | |
| Lateral tunnel | 1.42 (0.65 - 3.09) | 0.37 | 0.79 (0.31 - 2.03) | 0.62 |
| Extracardiac lateral tunnel | 4.44 (1.78 - 11.07) | 0.001 | 1.22 (0.37 - 3.95) | 0.74 |
| Extracardiac conduit | 3.18 (1.28 - 7.87) | 0.01 | 1.25 (0.39 - 4.01) | 0.71 |
| Other | 0.85 (0.09 - 7.82) | 0.89 | 0.69 (0.06 - 7.84) | 0.77 |
| Fenestration done | 0.87 (0.54 - 1.41) | 0.58 | 0.63 (0.35 - 1.12) | |

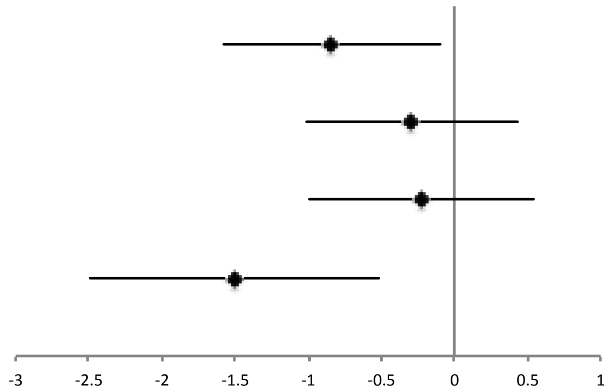
The fully-adjusted model included all variables shown in this table

Table 5 Exercise performance measures of adolescents participating in the NIH/NHLBI Pediatric Heart Network Fontan Cross-Sectional Study.

| | Total | | | | | Adequate effort group | | | | | Inadequate effort group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Variable* | *N* | *mean* | *sd* | *min* | *max* | *N* | *mean* | *sd* | *min* | *max* | *N* | *mean* | *sd* | *min* | *max* |
| Peak $Vo_2$ (ml/kg/min) | 396 | 26.3 | 6.9 | 8.1 | 46.5 | 312 | 27.3 | 6.6 | 11.0 | 46.5 | 84 | 22.6 | 6.9 | 8.1 | 39.8 |
| % predicted peak $VO_2$ | 396 | 64.7 | 16.4 | 19.3 | 111.8 | 312 | 67.0 | 15.7 | 26.2 | 111.8 | 84 | 56.2 | 16.1 | 19.3 | 94.8 |
| $VO_2$ at VAT (ml/kg/min) | 312 | 18.8 | 6.4 | 6.8 | 44.4 | 312 | 18.8 | 6.4 | 6.8 | 44.4 | | | | | |
| % predicted $VO_2$ at VAT | 312 | 78.2 | 24.6 | 28.1 | 170.8 | 312 | 78.2 | 24.6 | 28.1 | 170.8 | | | | | |
| VE/VCO2 at VAT | 312 | 43.3 | 9.8 | 26.0 | 93.0 | 312 | 43.3 | 9.8 | 26.0 | 93.0 | | | | | |
| % predicted peak work rate | 398 | 60.7 | 17.7 | 0.0 | 112.0 | 311 | 63.9 | 16.3 | 26.7 | 112.0 | 87 | 49.3 | 17.8 | 0.0 | 93.7 |
| Peak O2 pulse index (ml $O_2$/beat/BSA) | 395 | 5.5 | 1.4 | 1.8 | 12.5 | 311 | 5.7 | 1.4 | 2.3 | 12.5 | 84 | 4.7 | 1.4 | 1.8 | 8.7 |
| % Predicted max O2 pulse | 395 | 89.3 | 22.9 | 30.8 | 155.2 | 311 | 90.9 | 22.8 | 30.8 | 150.4 | 84 | 83.5 | 22.3 | 34.8 | 155.2 |
| Respiratory quotient at peak | 394 | 1.1 | 0.1 | 0.8 | 1.4 | 312 | 1.1 | 0.1 | 0.8 | 1.4 | 82 | 1.0 | 0.1 | 0.8 | 1.2 |
| Resting HR | 405 | 79.5 | 16.2 | 42.0 | 135.0 | 312 | 78.2 | 15.2 | 45.0 | 119.0 | 93 | 83.9 | 18.5 | 42.0 | 135.0 |
| Maximum HR | 398 | 154.8 | 23.0 | 57.0 | 206.0 | 311 | 157.3 | 22.4 | 57.0 | 206.0 | 87 | 145.8 | 22.9 | 88.0 | 206.0 |
| % Predicted peak HR | 398 | 74.6 | 11.1 | 27.2 | 98.3 | 311 | 75.9 | 10.8 | 27.2 | 98.3 | 87 | 69.6 | 10.9 | 42.4 | 97.2 |
| HR change | 398 | 75.3 | 27.6 | 3.0 | 143.0 | 311 | 79.2 | 25.6 | 3.0 | 143.0 | 87 | 61.2 | 30.1 | 5.0 | 133.0 |
| Resting O2 saturation | 398 | 94.1 | 4.2 | 76.0 | 100.0 | 308 | 94.3 | 3.9 | 81.0 | 100.0 | 90 | 93.5 | 5.1 | 76.0 | 100.0 |
| Peak O2 saturation | 365 | 91.0 | 6.0 | 58.0 | 100.0 | 290 | 91.2 | 5.8 | 58.0 | 100.0 | 75 | 90.4 | 6.8 | 62.0 | 100.0 |

Figure 1. Association of age at Fontan completion with percent predicted VO2 maximum in 312 patients who achieved adequate effort.

| Models | Beta-coefficient for age at Fontan (95% CI) | P-value |
|---|---|---|
| Model 1 | -0.84 (-1.58 to -0.10) | 0.03 |
| Model 2 | -0.29 (-9.06 to 3.44) | 0.425 |
| Model 3 | -0.23 (-1.01 to -0.54) | 0.55 |
| Model 4 | -1.50 (-2.49 to -0.51) | 0.003 |




Model 1: unadjusted
Model 2: adjusted for age at exercise testing, BMI for age z score, gender and race
Model 3: Model 2 + hypoplastic left heart syndrome, L-loop configuration, ventricular dominance
Model 4: Model 3+ age at first unloading surgery, intermediate staging surgery, Fontan type, fenestration, pacemaker use

Figure 2. Association of age at Fontan completion with Heart rate reserve in 312 patients who achieved adequate effort.

| Models | Beta-coefficient for age at Fontan (95% CI) | P-value |
|---|---|---|
| Model 1 | -0.84 (-2.46 to -0.77) | 0.30 |
| Model 2 | -0.67 (-2.42 to 1.07) | 0.45 |
| Model 3 | -1.12 (-2.94 to -0.69) | 0.22 |
| Model 4 | -4.09 (-6.04 to -2.14) | <0.001 |

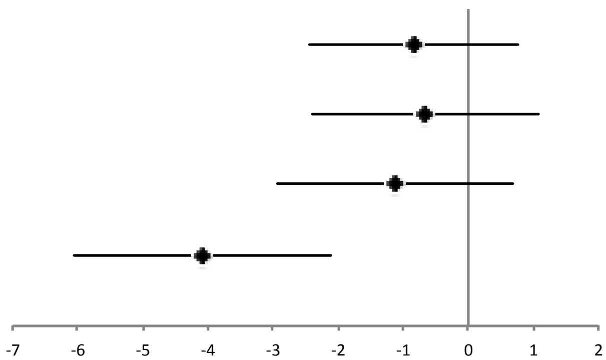
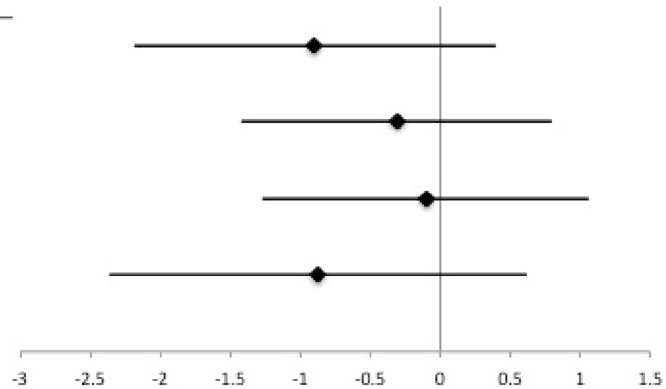


Figure 3. Association of age at Fontan completion with percent predicted maximum O2 pulse in 312 patients who achieved adequate effort

| Models | Beta-coefficient for age at Fontan (95% CI) | P-value |
|---|---|---|
| Model 1 | -0.9 (-2.19 to 0.38) | 0.17 |
| Model 2 | -0.31 (-1.42 to 0.79) | 0.58 |
| Model 3 | -0.11 (-1.27 to 1.05) | 0.86 |
| Model 4 | -0.87 (-2.36 to 0.61) | 0.25 |



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