Risk Factors for Major Adverse Events Late after Fontan Palliation

Robert W. Elder, *Yale University*
Nancy M. McCabe, *Emory University*
Emir Veledar, *Emory University*
Brian Kogon, *Emory University*
Maan Jokhadar, *Emory University*
Fred Rodriguez III, *Emory University*
Michael McConnell, *Emory University*
Wendy Book, *Emory University*

Journal Title: Congenital Heart Disease
Volume: Volume 10, Number 2
Publisher: Wiley: 12 months | 2015-03-01, Pages 159-168
Type of Work: Article | Post-print: After Peer Review
Publisher DOI: 10.1111/chd.12212
Permanent URL: https://pid.emory.edu/ark:/25593/tvhcm

Final published version: http://dx.doi.org/10.1111/chd.12212

HHS Public Access

Author manuscript

Congenit Heart Dis. Author manuscript; available in PMC 2015 July 23.

Published in final edited form as:

Congenit Heart Dis. 2015 ; 10(2): 159–168. doi:10.1111/chd.12212.

Risk Factors for Major Adverse Events Late after Fontan Palliation

Robert W. Elder, MD[*], **Nancy M. McCabe, BSN**[†], **Emir Veledar, PhD**[‡], **Brian E. Kogon, MD**[§], **Maan Jokhadar, MD**[¶], **Fred H. Rodriguez III, MD**[¶,**], **Michael E. McConnell, MD**[**], and **Wendy M. Book, MD**[¶]

[*]Section of Cardiology, Pediatrics and Internal Medicine, Yale School of Medicine, New Haven, Conn, USA

[†]Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, Ga, USA

[‡]Baptist Health South Florida, Miami, Fla, USA

[§]Divisions of Cardiothoracic Surgery, Emory University School of Medicine, Atlanta, Ga, USA

[¶]Cardiology, Emory University School of Medicine, Atlanta, Ga, USA

[**]Children's Healthcare of Atlanta, Sibley Heart Center, Atlanta, Ga, USA

Abstract

Objective—Risk factors for major adverse events late after Fontan palliation are unknown. Prior studies have suggested ventricular function and morphology as important risk factors. The aim of this study is to (1) characterize the late major adverse event profile in adult Fontan patients and (2) identify additional risk factors that may contribute to adverse outcomes.

Design and Setting—A retrospective review of all adult patients >15 years post-Fontan seen at a tertiary academic center was conducted. Clinical, laboratory, cardiac data, and abdominal imaging were collected via chart review. Major adverse events (death, cardiac transplantation, or listing) were identified, and timing of events was plotted using Kaplan–Meier methods. Univariate and multivariate logistic regression was used to determine independent predictors of late-term events.

Corresponding Author: Robert W. Elder, MD, Yale University School of Medicine, P.O. Box 208064, 333 Cedar Street, 3 LCI, New Haven, CT 06520-8064, USA. Tel: 203-785-2022; Fax: 203-737-2786; robert.elder@yale.edu.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Author Contributions

Robert W. Elder, MD, was involved in design of the study, data analysis/interpretation, drafting the article, critical revision of the article, and approval of the article. Nancy M. McCabe, BSN, was involved in design of the study, data analysis/interpretation, drafting the article, critical revision of the article, and approval of the article. Emir Veledar, PhD, was involved in design of the study, data analysis/interpretation, statistics, and approval of the article. Brian E. Kogon, MD, was involved in design of the study, data analysis/interpretation, critical revision of the article, and approval of the article. Maan Jokhadar, MD, was involved in design of the study, data analysis/interpretation, critical revision of the article, and approval of the article. Fred H. Rodriguez III, MD, was involved in design of the study, data analysis/interpretation, critical revision of the article, and approval of the article. Michael E. McConnell, MD, was involved in design of the study, data analysis/interpretation, critical revision of the article, and approval of the article. Wendy M. Book, MD, was involved in design of the study, data analysis/interpretation, drafting the article, critical revision of the article, and approval of the article.

Conflict of interest: None.

Results—A total of 123 adult Fontan patients were identified (mean time post-Fontan 22.4 years [±4.4]). Major adverse events occurred in 19/123 patients (15%). In this 15-year survivor cohort, transplant-free survival rates were 94.6%, 82.9%, and 59.8% at 20, 25, and 30 years postoperation, respectively. Modes of death were Fontan failure with preserved function (4), congestive heart failure with decreased function (2), sudden death (2), thromboembolic event (1), post-Fontan conversion (2), and posttransplant (2). No differences in adverse outcomes were found based on morphology of the systemic ventricle, Fontan type, or systolic ventricular function. On the other hand, features of portal hypertension (OR 19.0, CI 4.7–77.3, $P < .0001$), presence of a pacemaker (OR 13.4, CI 2.6–69.8, $P = .002$), and systemic oxygen desaturation (OR 0.86, CI 0.75–0.98, $P = .02$) were risk factors for major adverse events in the multivariate analysis.

Conclusions—In adult Fontan patients surviving >15 years post-Fontan, portal hypertension, oxygen desaturation, and need for pacemaker were predictive of adverse events. Traditional measures may not predict late-term outcomes in adult survivors; further study of the liver's role in late outcomes is warranted.

Keywords

Fontan Procedure; Survival; Liver; Congenital Heart Defects; Mortality

Introduction

Infants born with functionally univentricular hearts have an estimated prevalence of 1 in 3000 live births.[1] The Fontan operation, first reported in 1971, remains the default palliative surgical procedure for pediatric patients with single-ventricle physiology.[2] With the dramatic improvement in perioperative and interstage mortality over the past 4 decades, many of these patients are now reaching adulthood.[3,4] Although the medium-term outcomes up to 20 years are well described,[5–7] there are limited data regarding outcomes later than 20 years after surgery in adults who have survived surgical palliation.

After the Fontan operation, adult congenital patients have a unique circulation, placing them at risk for significant morbidity and premature mortality in adulthood.[8] A number of factors, including arrhythmia burden, thromboembolic disease, protein-losing enteropathy, and single morphologic right ventricle, have been associated with adverse events among early survivors.[5] The development of symptoms of clinical heart failure is sometimes referred to as *Fontan failure* or *circulatory dysfunction*. Fontan failure can occur due to ventricular dysfunction (systolic, diastolic, or combined) or may occur in the presence of normal ventricular function or some combination of both. While some patients suffer from decreased systemic ventricular function, many adult Fontan patients exhibit circulatory failure, often referred to as *Fontan failure*, in the absence of decreased ventricular systolic function and in the setting of normal end-diastolic pressures. Patients with preserved ventricular systolic function remain at risk for adverse events.[9] Contributors to Fontan failure with preserved ventricular function include anatomic obstructions (pulmonary artery stenosis, stenosis of the Fontan baffle, etc.), pulmonary vascular remodeling, protein-losing enteropathy, plastic bronchitis, intractable atrial arrhythmias, chronotropic incompetence, cirrhosis, renal failure, and other late complications that affect the circulation.[1,10]

Recent attention has focused on the liver disease inherent to this population of late survivors and its potential involvement in major adverse events.[11,12] One recent study showed that adult and pediatric patients with features of portal hypertension had an eightfold-increased risk of major adverse events.[9]

The purpose of this study was to characterize risk factors and timing for the development of late-term major adverse events, including death and cardiac transplantation, in adult Fontan patients who have survived >15 years post-Fontan.

Methods

Subjects

All adult Fontan subjects >18 years of age evaluated at the Emory Adult Congenital Heart Center from May 1999 to March 2013 were identified through a retrospective review of available electronic records. The dataset included a minority of adult patients previously described.[9] Subjects <15 years from the time of the Fontan operation at latest follow-up were excluded. Demographic, medical history, and clinical data at time of latest outpatient follow-up were collected via chart review. Whenever possible, primary surgical data were reviewed. Approval was obtained from the Emory University IRB prior to data collection.

Data Collection

Demographic data collected included gender, age, and race. Medical history data included time since the Fontan operation (years), type of congenital heart disease (hypoplastic left heart syndrome, tricuspid atresia, double-inlet left ventricle, pulmonary atresia/intact ventricular septum, double-outlet right ventricle, or other), type of Fontan (atriopulmonary, lateral-tunnel, or extracardiac), and systemic ventricle morphology (left, right, or two ventricles of equal size). For statistical purposes, patients with an atriopulmonary Fontan who underwent Fontan conversion were analyzed as part of the atriopulmonary cohort. History or presence of clinical features of heterotaxy syndrome was documented.

Clinical data was collected from the latest outpatient adult congenital cardiology follow-up. Vital signs, including resting heart rate, oxygen saturation, and blood pressure were documented. Anthropomorphic data including weight (kg) and height (cm) were used to calculate body mass index (BMI, kg/m^2). Clinical exam findings of hepatomegaly, splenomegaly, or ascites were documented.

Medications used at the time of last cardiology clinic visit were documented. Laboratory values were collected within 1 year of the last outpatient clinic visit and included the following: sodium, creatinine, total bilirubin, total protein, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin, platelet count, and hepatitis serologies for A, B, and C.

Comorbidities including protein-losing enteropathy (defined as an elevated stool alpha-1 antitrypsin with associated serum hypoalbuminemia) or presence of mechanical valve.

Cardiac Data

The electrocardiogram was analyzed for rhythm and QRS duration. Presence of a pacemaker was recorded, as well as history of atrial arrhythmia.

The most recent echocardiographic data were reviewed for verification of the primary anatomic diagnosis. Systemic systolic ventricular function was determined by a blinded reviewer using subjective assessment, Simpson's method, or triplane three-dimensional reconstruction and was ultimately dichotomized as normal/mildly decreased vs. moderate/severely decreased.

Abdominal Imaging

All available abdominal imaging reports were reviewed, with imaging preference as follows: MRI > CT > US. All available endoscopic reports were reviewed. Varices were counted if present on any imaging modality or noted endoscopically. Ascites was considered present if seen on either imaging or clinical exam. Splenomegaly was counted if measured >13 cm in maximal diameter on any imaging modality or if present clinically.[13]

Definition of Events

The primary outcome was a major adverse event defined as death, heart transplant, or listing for heart transplant. In cases of multiple events, the censoring event was the first sequential event. In all cases, mode of death was determined by primary source material. Modes of death were defined as heart failure, Fontan failure, thrombosis, sudden death, perioperative death, or other. Heart failure death was defined as NYHA class III–IV symptoms with decreased systolic function by echocardiogram. Fontan failure death was defined as NYHA class III–IV symptoms with preserved systolic function. Death related to thrombosis was defined as death within 1 week of a clinically significant thromboembolic event without other proximal cause. Perioperative death was defined as death occurring within 30 days of cardiac surgery, whereas sudden death was defined as death occurring within 3 hours of symptom onset.

Statistical Methods

Descriptive statistics were calculated overall and stratified by those with or without a major adverse event. Differences between groups were determined using *t*-test and chi-square, as well as Fisher's exact test or Wilcoxon rank-sum test where appropriate. Transplant-free survival was plotted using the Kaplan–Meier method and compared by log-rank statistics. Univariate logistic regression was used to determine any significant relationships between study variables and major adverse events. Multivariate logistic regression was used to statistically evaluate the relationship between major adverse events and univariate predictors or variables known to be associated with major adverse events in this population. All variables were considered in the initial model as input to stepwise logistic regression. An alpha level of 0.05 was selected for significance as criterion for entry into and persistence in the model. The most parsimonious model was determined using receiver operating characteristics (ROC). The data was analyzed using SAS 9.3 at an alpha level of 0.05.

Results

A total of 136 adult Fontan patients were identified, of whom 123 patients were more than 15 years from the time of Fontan operation and were included in this analysis. The mean age of the cohort at latest follow-up was 28.5 years (±7.7), and mean duration since Fontan was 22.4 years (±4.4). Baseline patient characteristics are shown in Table 1.

Among the group, cardiac lesions included tricuspid atresia (54, 43.9%), double-inlet left ventricle (27, 22%), double-outlet right ventricle (12, 9.8%), pulmonary atresia with intact ventricular septum (9, 7.3%), hypoplastic left heart syndrome (8, 6.5%), and other (13, 10.7%). Of those patients with an atriopulmonary Fontan, 25 patients underwent Fontan conversion to a lateral-tunnel Fontan, with the most common indication being significant arrhythmia burden.

There were a total of 19 (15.4%) discrete, major adverse events in the group: 13 deaths and 9 cardiac transplants or listings for transplant, with 3 competing outcomes. Of these 19 events, 4 occurred in patients with a morphologic right ventricle and 15 occurred in patients with a morphologic left ventricle.

Clinical, laboratory, and cardiac variables as well as other comorbidities for the cohort are listed in Table 2. Notably, time since Fontan, systolic function of the systemic ventricle, and prior history of a thromboembolic event were not statistically different between the event and no-event groups. Six patients had positive hepatitis serology (B or C), but none of these patients experienced an event.

Of the deaths in this cohort, 4 patients died of Fontan failure with preserved systolic function, 2 died of congestive heart failure with decreased ventricular function, 2 experienced sudden death, and 1 patient had an embolic event leading to death. Two perioperative deaths occurred following Fontan conversion. After cardiac transplant, 2 additional patients died at 1 year and 6 years, respectively. One patient died while awaiting cardiac transplant (Table 3).

Among adult survivors of the Fontan operation >15 years post-Fontan, transplant-free survival rates were 94.6%, 82.9%, and 59.8% at 20, 25, and 30 years post-Fontan, respectively (Figure 1). Survival curves stratified by morphology of the systemic ventricle, Fontan type, and systolic ventricular function (normal/mild decreased vs. moderate/severely decreased) are shown in Figure 2A–C. There were no statistically significant differences in the stratified survival curves for any of the three features. There was a suggestion that patients with a morphologic right systemic ventricle tend to have worse outcomes starting after 20 years, though long-term data in this group are lacking and the difference was not significant.

Among the four components of the previously described VAST score (varices, ascites, splenomegaly, and thrombocytopenia),[9] three factors were significantly different between the event and no-event groups in univariate analysis: splenomegaly ($P < .0001$), ascites ($P < .0001$), and varices ($P < .0001$). Platelet count was not statistically different between the groups ($P = .09$).

Using a modified version of the score excluding platelets (VAS for varices, ascites, splenomegaly), we plotted Kaplan–Meier survival curves by each score: 0, 1, 2, 3 (Figure S1). Comparison revealed no difference between the Kaplan–Meier curves for a score of 0 vs. 1 ($P = .31$) and no difference between curves for a score of 2 vs. 3 ($P = .9$). When the score was dichotomized as 0–1 vs. 2–3, there was a significant separation of the survival curves of those with and without an adverse event ($P < .0001$, Figure 2D).

In multivariate analysis, the following variables were included in the initial model: VAS score, Fontan type, presence of any pacemaker, use of diuretic, lower resting oxygen saturation, creatinine, albumin level, alkaline phosphatase level, and history of thromboembolic event (Table 4). These variables were included for either their statistical significance in univariate analysis or for known causes of poor outcomes in this population. In stepwise logistic regression, the most parsimonious model included VAS score (OR 19.06, 95% CI [4.7–77.28]), presence of a pacemaker (OR 13.44, 95% CI [2.59–69.84]), and lower resting oxygen saturation (OR 0.86, 95% CI [0.75–0.98]). No additional variables met the 0.05 significance level for entry into the model.

Per ROC curve analysis, the final multivariate model of VAS score, presence of pacemaker, and resting oxygen saturation had an excellent ability to discriminate between persons with and without a major adverse event (area under the curve 0.905).

Discussion

Having survived a staged approach to palliation of a functionally univentricular heart, adult patients over 15 years from Fontan surgery face additional hemodynamic challenges. Late complications including heart failure, arrhythmias, thromboembolic disease, progressive cyanosis, and hepatic dysfunction may contribute to the development of major adverse events including death or cardiac transplantation.[1] While short- to medium-term results following Fontan palliation in a pediatric population are well described, to date there are limited data regarding late-term outcomes in adult survivors. This study used a cohort of adult single ventricle patients followed at a tertiary adult congenital heart disease center to examine outcomes of adult Fontan survivors and examine determinants of major adverse events.

In the report from Khairy et al. regarding long-term outcomes in 261 patients, Fontan type was associated with perioperative survival, but after excluding those patients who died in the early postoperative period, there was no difference in survival between Fontan types.[5] Although 25 patients in this study underwent Fontan conversion, they were analyzed based on their original Fontan operation, and thus no conclusions can be drawn regarding any potential advantage or disadvantage of conversion. Other groups have suggested a number of potential advantages to Fontan conversion.[14] In this cohort of survivors >15 years post-Fontan, of whom nearly half have undergone Fontan conversion, we find no difference in long-term survival between patients with an original atriopulmonary Fontan vs. those with a lateral-tunnel Fontan. Almost none of the patients in this cohort had an extracardiac Fontan, which does not fit with our current clinical practice but rather reflects the historical nature of this group.

Significant systolic ventricular dysfunction of the systemic ventricle occurred in 17% of our cohort. There was no difference in the proportion of patients with decreased ventricular function between those with an adverse event and those who did not have an event. Events may occur in adult post-Fontan patients related to “Fontan failure” in the absence of systolic ventricular dysfunction.[15] Interestingly, one report showed that among Fontan patients referred for heart transplantation, those with preserved systolic function had worse survival, with more episodes of infection and graft failure requiring mechanical support.[16] Although more sophisticated measures of ventricular function may provide additional insight, the heterogeneous nature of this group, with right, left, and mixed ventricular morphology, limits the applicability of such techniques. Clearly, systolic ventricular function alone does not capture the entire story of adverse events in this adult group, suggesting traditional cardiac measures used in a pediatric Fontan cohort do not adequately differentiate event risk in an adult survivor cohort.

In the multicenter Pediatric Heart Network study of Fontan patients, right ventricular morphology was associated with worse ventricular function.[17] Khairy and colleagues found an association between heart failure deaths and right ventricular morphology.[5] In the large Melbourne cohort of 499 Fontan patients followed from birth, having a dominant right ventricle had a hazard ratio of 2.2 for mortality, but only prior to the bidirectional cavopulmonary shunt stage.[18] After that, ventricular morphology was not associated with mortality. In our adult survivor cohort, we could not find an overall survival benefit for patients with left vs. right ventricular morphology. In part, this may be attributable to the fact that our data regarding patients with a systemic RV are limited to 25 years post-Fontan due to the relatively new survival of that group, including hypoplastic left heart syndrome. Indeed, at 25 years, there was only 1 remaining patient with a systemic RV as compared to 27 LV patients. It is also possible that the impact of right systemic ventricular morphology is more pronounced in early childhood and less important for conditional survival in adult Fontan patients. Future follow up of this important group is needed.

If traditional factors such as Fontan type, ventricular function, or morphology of the systemic ventricle do not discriminate among long-term survivors, what other factors may play a role? We previously reported that features of portal hypertension, as classified as a VAST score ≥2, was associated with worse outcomes in a group of adult and pediatric patients referred for liver evaluation.[9] In this significantly larger cohort including all adult Fontan patients >15 years from the time of surgery, varices, ascites, and splenomegaly were significant predictors of major events in univariate analysis. Platelet count was no longer different, which may relate to the variability of this marker depending on the volume status of the patient and time point at which it is measured. Volume overload can decrease platelet count by increasing portal pressures.

Using a modified score (VAS), we were able to demonstrate a clear separation between the survival curves for VAS ≥2 in this patient population (Figure 2D). This was also significant in the multivariate model. It is remarkable that at 30 years after the initial Fontan surgery, patients without those features were relatively well: 72.6% were free from death or cardiac transplant, compared with 30.1% who did have a VAS score ≥2.

In the multivariate analysis, presence of a pacemaker, regardless of type, was significantly related to outcomes. A recent report from the Pediatric Heart Network Fontan cross-sectional study showed that among >500 Fontan survivors, those with a pacemaker have poorer functional status and mildly decreased systolic ventricular function compared with Fontan survivors without a pacemaker.[19]

Resting oxygen saturation was another feature that was significant in the multivariate model, with lower oxygen saturation associated with worse outcomes. That is, for every unit increase in oxygen saturation, the odds of having an event are reduced by 14%. Among this heterogeneous group of Fontan survivors, the fate of a fenestration, if originally present, is variable. However, many adult Fontan patients have evidence of autofenestration or venovenous collaterals that cause systemic desaturation. Desaturation in the adult Fontan patient may be a marker of increased central venous and/or portal venous pressures that cause right-to-left shunting and was associated with worse outcomes in our patient group. Including those 3 features in the multivariate analysis, our final model was able to account for >90% of the adverse events in this adult survivor cohort.

Liver disease among Fontan patients is common, yet traditional markers of liver disease (transaminases and even markers of synthetic function) have been difficult to correlate with severity and outcomes.[20] Rather, consideration of the contribution of hemodynamic and physiologic consequences of Fontan liver disease and portal hypertension may aid in understanding outcomes in Fontan patients.[15] Since all Fontan patients have elevated postsinusoidal pressure by definition, we defined clinical features of portal hypertension as two or more signs of varices, ascites, or splenomegaly. One recent report was the first to suggest that Fontan patients with an elevated score on the Model for End-stage Liver Disease (MELD-XI) (excluding International Normalized Ratio), traditionally used for organ allocation in liver transplantation, had a hazard ratio of 7.76 for death or cardiac transplantation.[21]

Limitations

There are a number of potential limitations relevant to this dataset. Importantly, by the nature of the study design, we included only adult patients who were >15 years from Fontan palliation, and thus the survival data are only relevant to an adult survivor cohort. We captured all Fontan patients evaluated at a tertiary adult congenital heart disease center, but this group may be skewed towards sicker patients and may not represent the entire spectrum of adult Fontan patients, thus affecting the results. Data regarding medication usage, vital signs, physical findings, and so on were only recorded at the last outpatient visit and may vary over time and with treatment. While some of the patients had prior cardiac catheterization, data were not consistently available and thus not analyzed for this report.

With regard to the VAS score and features of portal hypertension, all abdominal imaging was reviewed, but at the onset of this study period there was no standardized protocol for all Fontan patients. Although abdominal imaging was available for nearly all patients, there is a potential for bias as to the modality of imaging and detection of components of the score. We attempted to overcome this by augmenting the score with clinical findings as well as

endoscopic findings. Additionally, heterotaxy patients with their variable splenic anatomy were included, although this may alter the results of the VAS score in regard to the potential for splenomegaly. Notably, less than 5% of the study patients had known or suspected heterotaxy syndrome.

Conclusions

In an adult survivor Fontan cohort >15 years post-Fontan completion, clinical features of portal hypertension (defined by a VAS score ≥2), need for a pacemaker, and decreased oxygen saturation were independent predictors of worse outcomes and together accounted for over 90% of the total events in this cohort. Previously described parameters such as ventricular function and morphology did not predict late adverse events in this group. Future prospective studies are needed to evaluate the importance of the VAS score to outcomes and define the time period between development of these features and significant adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

NMM was partially funded by T32NR012715 from the National Institute of Nursing Research and the Jonas Nursing Scholar Fund. The authors would like to thank Alicia Rangosh, RDCS, and Maria A. Pernetz, RDCS, for their critical help performing and reviewing complex echocardiograms for this project.

References

1. Khairy P, Poirier N, Mercier LA. Univentricular heart. Circulation. 2007; 115(6):800–812. [PubMed: 17296869]
2. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax. 1971; 26(3):240–248. [PubMed: 5089489]
3. Cetta F, Feldt RH, O'Leary PW, et al. Improved early morbidity and mortality after Fontan operation: the Mayo Clinic experience, 1987 to 1992. J Am Coll Cardiol. 1996; 28(2):480–486. [PubMed: 8800129]
4. Gersony WM. Fontan operation after 3 decades: what we have learned. Circulation. 2008; 117(1): 13–15. [PubMed: 18172049]
5. Khairy P, Fernandes SM, Mayer JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008; 117(1):85–92. [PubMed: 18071068]
6. d'Udekem Y, Iyengar AJ, Cochrane AD, et al. The Fontan procedure—contemporary techniques have improved long-term outcomes. Circulation. 2007; 116(11):I157–I164. [PubMed: 17846297]
7. Mair DD, Puga FJ, Danielson GK. The Fontan procedure for tricuspid atresia: early and late results of a 25-year experience with 216 patients. J Am Coll Cardiol. 2001; 37(3):933–939. [PubMed: 11693773]
8. Rychik J. Forty years of the Fontan operation: a failed strategy. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2010; 13(1):96–100. United States. [PubMed: 20307870]
9. Elder RW, McCabe NM, Hebson C, et al. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. Int J Cardiol. 2013; 168(4):3764–3769. [PubMed: 23849105]
10. Goldberg DJ, Shaddy RE, Ravishankar C, Rychik J. The failing Fontan: etiology, diagnosis and management. Expert Rev Cardiovasc Ther. 2011; 9(6):785–793. [PubMed: 21714609]

11. Wu FM, Ukomadu C, Odze RD, Valente AM, Mayer JE, Earing MG. Liver disease in the patient with Fontan circulation. Congenit Heart Dis. 2011; 6(3):190–201. [PubMed: 21443554]
12. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol. 2012; 33(7):1001–1012. [PubMed: 22534759]
13. Armitage, JO. Spleen. In: Walker, HK.; Hall, WD.; Hurst, JW., editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd. Boston: Butterworth-Heinemann; 1990. p. 717-719.
14. Dechert BE, Deal BJ. An integrated approach to the care of adult patients with prior atriopulmonary Fontan surgery. J Pediatr Health Care. 2008; 22(4):246–253. [PubMed: 18590870]
15. Mori M, Aguirre AJ, Elder RW, et al. Beyond a broken heart: circulatory dysfunction in the failing Fontan. Pediatr Cardiol. 2014; 35(4):569–579. [PubMed: 24531876]
16. Simpson KE, Cibulka N, Lee CK, Huddleston CH, Canter CE. Failed Fontan heart transplant candidates with preserved vs. impaired ventricular ejection: 2 distinct patient populations. J Heart Lung Transplant. 2012; 31(5):545–547. [PubMed: 22381208]
17. Anderson PA, Sleeper LA, Mahony L, et al. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study. J Am Coll Cardiol. 2008; 52(2):85–98. [PubMed: 18598886]
18. d'Udekem Y, Xu MY, Galati JC, et al. Predictors of survival after single-ventricle palliation: the impact of right ventricular dominance. J Am Coll Cardiol. 2012; 59(13):1178–1185. [PubMed: 22440217]
19. Williams RV, Travison T, Kaltman JR, et al. Comparison of Fontan survivors with and without pacemakers: a report from the Pediatric Heart Network Fontan Cross-Sectional Study. Congenit Heart Dis. 2013; 8(1):32–39. [PubMed: 22762157]
20. Kiesewetter CH, Sheron N, Vettukattill JJ, et al. Hepatic changes in the failing Fontan circulation. Heart. 2007; 93(5):579–584. [PubMed: 17005713]
21. Assenza GE, Graham DA, Landzberg MJ, et al. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. Heart. 2013; 99(7):491–496. [PubMed: 23406689]

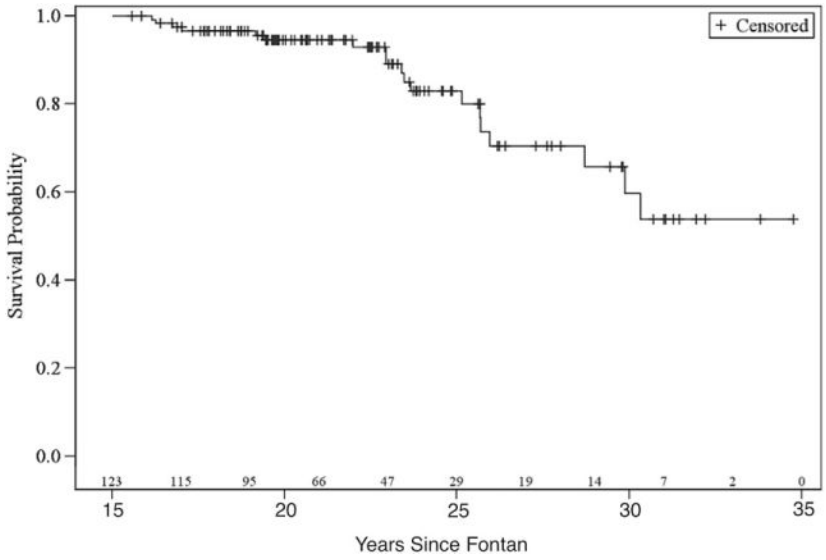
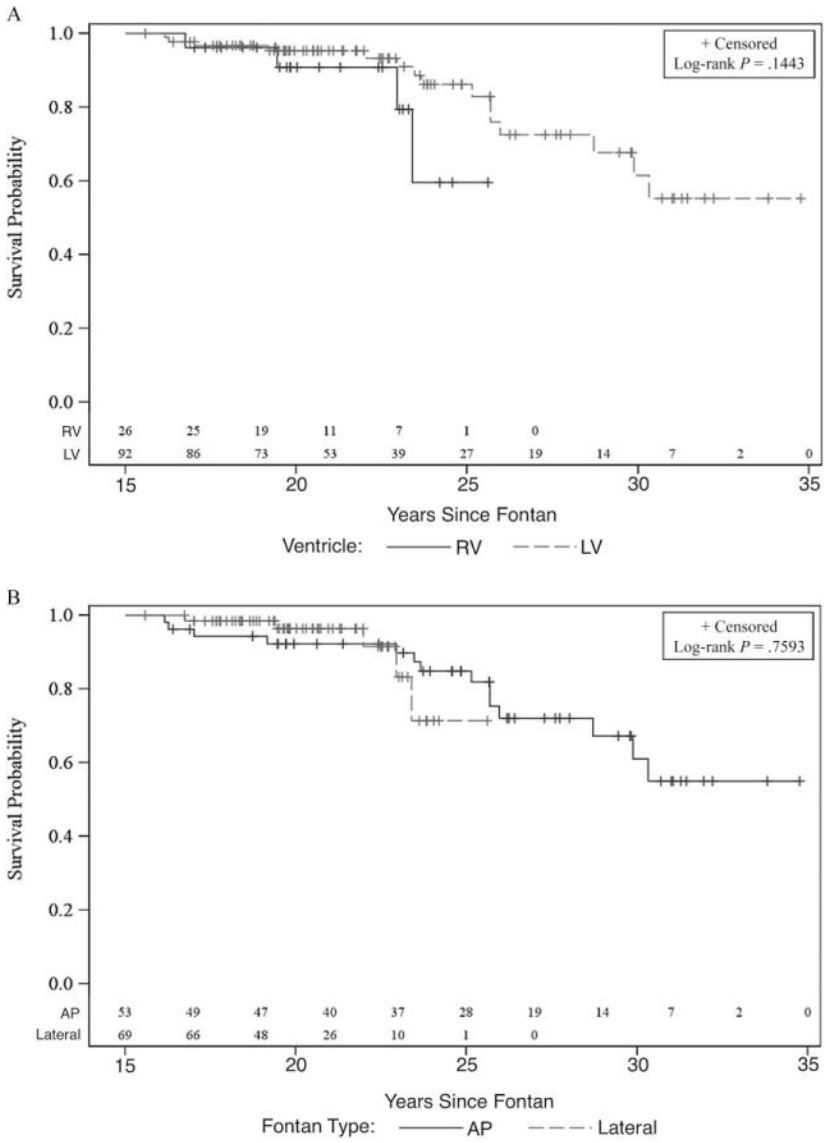


Figure 1.

Kaplan-Meier survival curve showing overall transplant-free survival of a cohort of 123 adult Fontan patients >15 years post-Fontan.



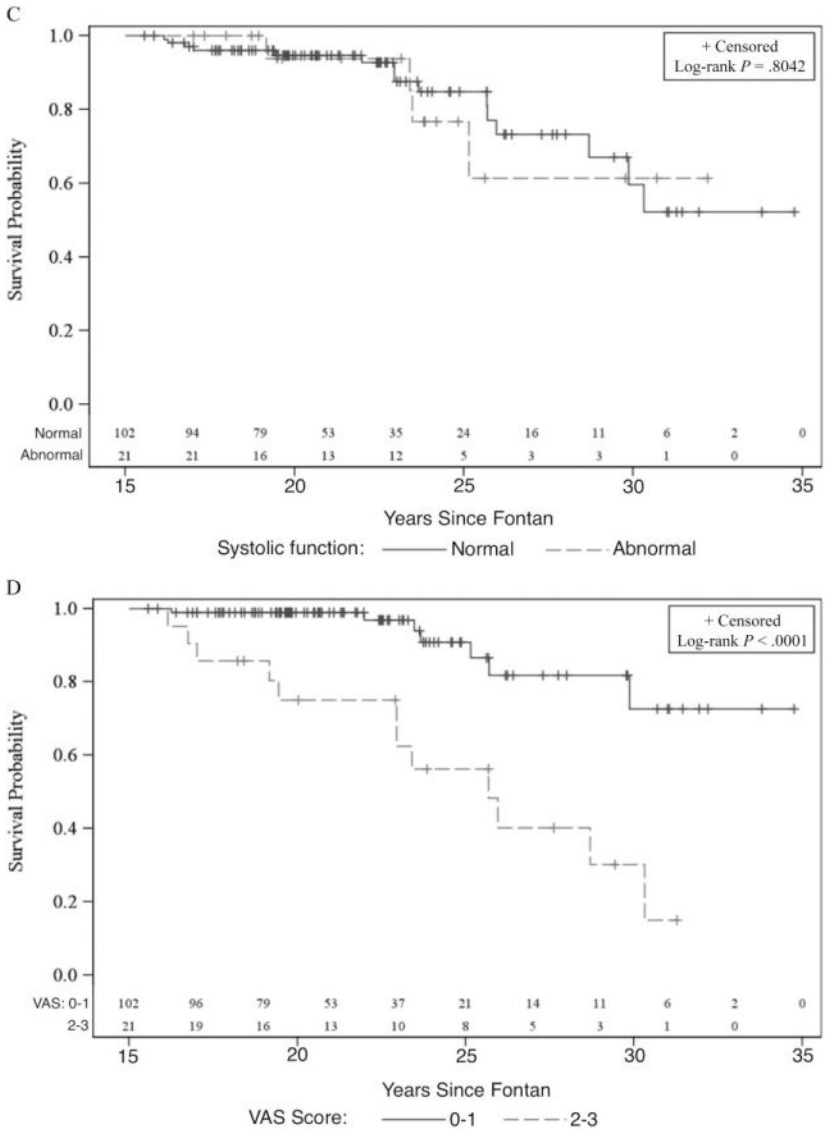


Figure 2.

Kaplan-Meier survival curves showing transplant-free survival, stratified by (A) systemic ventricular morphology (RV = right ventricle, LV = left ventricle), (B) Fontan type (AP = atriopulmonary Fontan, Lateral = lateral-tunnel Fontan), (C) systolic ventricular function (dichotomized as normal/mildly reduced vs. moderate/severely reduced), or (D) VAS score (VAS = varices, ascites, splenomegaly), dichotomized as 0–1 vs. 2–3.

Table 1

Baseline Patient Characteristics

Variable	Overall n = 123	No Event n = 104	Event n = 19	*P* Value
Demographics				
Age (years)*	28.5 (7.7)	27.7 (6.9)	33 (10.2)	.04
Female	54 (43.9)	50 (48.1)	4 (21.1)	.04
Caucasian	87 (70.7)	70 (67.3)	17 (89.5)	.06
Time since Fontan (years)*	22.4 (4.4)	22.3 (4.4)	22.8 (4.5)	.6
Ventricular morphology				.69
Right	26 (21.1)	22 (21.2)	4 (21.1)	
Left	92 (74.8)	77 (74)	15 (78.9)	
Biventricular	5 (4.1)	5 (4.8)	0 (0)	
Fontan type				.004
Atriopulmonary	53 (43.1)	39 (37.5)	14 (73.7)	
Lateral-tunnel	69 (56.1)	64 (52)	5 (26.3)	
Extracardiac	1 (0.7)	1 (1)	0 (0)	
Other				
Fontan revision	25 (20.3)	22 (21.2)	3 (15.8)	.76
Mechanical valve	10 (8.1)	6 (5.8)	4 (21.1)	.047
Any diuretic use	54 (43.9)	38 (36.5)	16 (84.2)	.0002
Any anticoagulation use	112 (91.1)	94 (90.4)	18 (94.7)	1
Heterotaxy	6 (4.9)	5 (4.8)	1 (5.3)	1

Values are n (%) unless otherwise indicated.

*Mean (SD).

Table 2

Clinical, Laboratory, and other Variables

Variable	Overall n = 123	No Event n = 104	Event n = 19	*P* Value
Clinical				
Resting HR	77.5 (12.4)	77.9 (12.8)	75.3 (10.2)	.41
Systolic BP	118.4 (13.4)	119.9 (12.8)	110.5 (13.9)	.004
Diastolic BP	67.7 (10)	67.9 (9.7)	66.5 (11.7)	.57
O_2 saturation	91.4 (4.7)	91.6 (4.3)	88.6 (5.8)	.03
BMI (kg/m^2)	25.9 (5.6)	25.8 (5.5)	26.6 (6.3)	.54
Laboratory				
Sodium	137.2 (3.2)	138.3 (1.9)	134.4 (5.6)	.007
Creatinine	0.9 (0.26)	0.87 (0.18)	1.1 (0.50)	.09
Total bilirubin	1.3 (0.66)	1.3 (0.67)	1.3 (0.57)	.87
Total protein	7.5 (0.74)	7.6 (0.66)	7.1 (0.98)	.005
ALP	79.6 (32.4)	74.6 (24.4)	107.7 (51.7)	.01
AST	30 (14.6)	29.5 (12.6)	33.1 (22.8)	.52
ALT	27.3 (13.7)	27.8 (13.9)	25.9 (13.2)	.6
Hematocrit	44.5 (6.6)	44.8 (6.8)	42.8 (5.1)	.22
Albumin	4.3 (0.54)	4.4 (0.46)	3.8 (0.68)	<.001
Other				
QRS duration	105.7 (19.4)	105.8 (20.9)	123.3 (27.6)	.002
Pacemaker	53 (43.1)	37 (35.6)	16 (84.2)	<.0001
History of atrial arrhythmia	69 (56.1)	54 (51.9)	15 (78.9)	.04
Moderate/severe ventricular function	21 (17.1)	17 (16.4)	4 (21.1)	.74
Thromboembolic event	24 (19.5)	18 (17.3)	6 (31.6)	.15
PLE	3 (2.4)	1 (1)	2 (10.5)	.06

Values are n (%).

HR, heart rate; BP, blood pressure; O2, oxygen; BMI, body mass index; ALP, alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; PLE, protein-losing enteropathy.

Table 3

Details of Fontan Patients who Died >15 Years Post Surgery

Year of Original Fontan	Age at Fontan (Yrs)	Dominant Ventricle	Fontan Type	Pacemaker (Y/N)	O_2 Saturation at Last Outpatient Visit	Ventricular Function	VAS Score	Age at Death (Years)	Mode of Death
1979	24	Left	AP	Y (atrial)	91	Preserved	3	50	Fontan failure
1980	4	Left	AP	Y (vent)	89	Preserved	2	36	Posttransplant
1982	3	Left	AP	Y (atrial)	91	Decreased	0	28	Heart failure
1982	19	Left	AP	Y (vent)	74	Preserved	3	42	Fontan failure
1987	4	Left	Lateral	Y (atrial)	91	Preserved	0	26	Embolic/PE
1987	5	Left	AP	N	80	Decreased	2	30	Posttransplant
1988	4	Right	Lateral	Y (dual)	86	Preserved	3	27	Fontan failure
1988	4	Right	Lateral	N	83	Decreased	2	27	Sudden death (while sleeping)
1988	1	Left	AP	Y (atrial)	91	Preserved	1	24	Post-op following TCPC conversion
1989	30	Left	AP	Y (atrial)	91	Preserved	2	49	Heart failure, listed for transplant
1990	5	Right	Lateral	Y (atrial)	97	Preserved	2	21	Fontan failure
1993	18	Left	AP	Y (atrial)	97	Preserved	0	34	Post-op following TCPC conversion
1993	4	Left	AP	Y (atrial)	88	Preserved	2	20	Sudden death (arrest)

VAS, score from 0–3 (1 point each for varices, ascites, splenomegaly); AP, atriopulmonary; PE, pulmonary embolus; TCPC, total cavopulmonary connection.

Table 4

Input and Final Multivariate Analysis

Variable	Hazard Ratio	95% CI	*P* Value
Univariate analysis			
VAS score ≥2	18.1	5.70–57.49	<.001
Classic Fontan	4.67	1.56–13.96	.006
Pacemaker	9.66	2.64–35.32	.001
Diuretic use	9.26	2.53–33.86	.001
O_2 saturation	0.88	0.80–0.97	.009
Creatinine	16.08	1.71–151.59	.015
Albumin	0.17	0.06–0.49	.001
ALP	1.03	1.01–1.05	.001
Thromboembolic event	2.21	0.74–6.58	.16
Multivariate analysis			
VAS score ≥2	19.06	4.70–77.28	<.0001
Pacemaker	13.44	2.59–69.84	.002
O_2 saturation	0.86	0.75–0.98	.02

VAS, score from 0–3 (1 point each for varices, ascites, splenomegaly).