Long-term survival after the Fontan operation: Twenty years of experience at a single center

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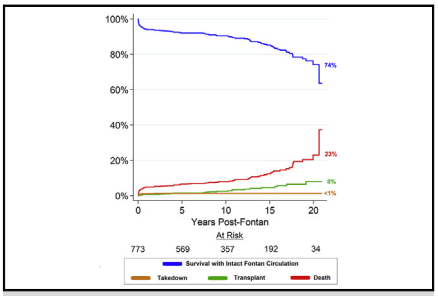
ABSTRACT

Objective: Existing studies of patients palliated with the Fontan operation are limited by heterogeneous patient populations and incomplete follow-up. This study aimed to describe long-term post-Fontan survival in a modern patient cohort.

Methods: All 773 patients who underwent a first Fontan operation at our institution between 1992 and 2009 were reviewed. The primary outcome was the composite endpoint of Fontan takedown, heart transplantation, or death before 2013.

Results: Follow-up rate was 99.2%. Survival with intact Fontan circulation was 94% at 1 year (95% confidence interval [95% CI], 92%-95%), 90% at 10 years (95% CI, 88%-92%), 85% at 15 years (95% CI, 82%-88%), and 74% at 20 years (95% CI, 67%-80%). Distinct risk factors were identified for early (≤1 year) and late composite outcomes. Independent risk factors for early outcome included prolonged pleural drainage (hazard ratio [HR], 4.4; $P < .001$), intensive care unit stay >1 week (HR, 2.4; $P < .001$), Fontan before 1997 (HR, 3.3; $P < .001$), preoperative atrioventricular valve regurgitation (HR, 2.0; $P < .001$), and longer crossclamp time (HR, 1.3 per 10 minutes; $P < .001$). Late outcome was predicted by atrioventricular valve regurgitation prior to Fontan (HR, 2.0; $P \leq .001$), and post-Fontan ICU stay >1 week (HR, 2.4; $P < .001$).

Conclusions: Long-term mortality after Fontan operation remains substantial. Risk factors for death or loss of Fontan circulation differ between the early and late postoperative periods. Long-term survival has not improved appreciably over the last decade, suggesting that alternatives to the Fontan are warranted. (J Thorac Cardiovasc Surg 2017;154:243-53)



Kaplan-Meier curves showing composite and individual post-Fontan outcomes.

Central Message

Patient-specific risk factors predict post-Fontan mortality, which remains substantial in the modern single ventricle population.

Perspective

This study examines post-Fontan outcomes in a modern single-ventricle population with a high prevalence of systemic right ventricles and exclusively total cavopulmonary connection-type operations. Patient-specific risk factors predict early and late post-Fontan mortality and need for heart transplantation. Twenty-year mortality remains substantial, and alternatives to the Fontan operation are needed.

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In the early 1970s, Fontan and Kreutzer independently described techniques to directly reroute systemic venous return to the pulmonary arterial circulation.[1,2] Although

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Abbreviations and Acronyms

AV = atrioventricular
AVVR = atrioventricular valve regurgitation
CHOP = Children's Hospital of Philadelphia
CI = confidence interval
EC = extracardiac conduit
HR = hazard ratio
ICU = intensive care unit
LT = lateral tunnel
PA = pulmonary artery
TCPC = total cavopulmonary connection

initially designed to alleviate cyanosis in patients with tricuspid atresia, the "Fontan" operation has since been applied to the vast majority of single-ventricle anatomies as the final planned stage of surgical palliation.[3-5] Subsequent modifications have improved early post-operative mortality,[6-8] but significant late consequences of this inherently abnormal circulation now are being appreciated.

Long-term mortality after Fontan operation has been described in several large, single-center cohorts.[9-14] Existing studies are limited, however, by a high prevalence of older atriopulmonary style operations, few patients with hypoplastic left heart syndrome or systemic right ventricle, and/or incomplete follow up, especially regarding transplant status. In this study we aimed to describe long-term survival with intact Fontan circulation in a large cohort of modern, single-ventricle patients with a high rate of follow-up.

METHODS

This was a single-center retrospective review of all patients who underwent a first Fontan operation at The Children's Hospital of Philadelphia (CHOP) between January 1, 1992, and December 31, 2009. Fontan operation was defined as any form of total cavopulmonary connection (TCPC), including the lateral tunnel (LT) and extracardiac conduit (EC) techniques, as well as extracardiac hepatic vein inclusion conduits in patients with a previous Kawashima operation. Patients undergoing Fontan revision or repeat Fontan after previous Fontan takedown were excluded. No atriopulmonary connections were performed at CHOP during this time period.

Baseline demographic, anatomic, preoperative, and perioperative characteristics were extracted from the medical record as reported previously.[15] Three surgical eras were defined based on relevant changes in surgical practice at our institution: 1992 to 1996 (Era 1, n = 226), 1997 to 2002 (Era 2, n = 196), and 2003 to 2009 (Era 3, n = 351). Routine use of modified ultrafiltration was introduced in 1996. In Era 1, almost all Fontan operations performed were of the LT variety, whereas in Era 3, the EC type predominated. Era 2 represented a period of transition in which the numbers of LT and EC Fontan procedures were nearly equal.

For patients currently followed at CHOP, outcomes were ascertained from the medical record. About one half (51%) of patients had no recent follow-up at our institution. For these subjects, current vital status was obtained via a query of the National Death Index, maintained by the National Center for Health Statistics (Atlanta, Ga). This contains a centralized database of death record information on file in United States vital statistics offices.[16] At the time of data analysis, information was available through December 31, 2012. Transplant status and history of transplant listing were obtained through collaboration with the Scientific Registry of Transplant Recipients (Minneapolis, Minn).[17] The primary endpoint was a composite of Fontan takedown, heart transplantation, or death before January 1, 2013. This study was approved by the institutional review board.

Statistical Analysis

Baseline demographic and clinical variables were summarized with standard descriptive statistics. Normally distributed variables were reported as mean ± standard deviation, and non-normally distributed variables were reported as median with range. Differences across eras were assessed with analysis of variance, Kruskal-Wallis, or Pearson χ^2 tests as appropriate. Multiple imputation based on all available demographic and clinical characteristics was used to handle the small proportion of missing data (3% across all covariates). Kaplan-Meier survival curves were constructed to estimate overall survival and survival with intact Fontan circulation. Time zero was defined as date of Fontan, and failure was defined as Fontan takedown, heart transplantation, or death within the study period. Patients alive without takedown or transplant were censored at the end of the study period. The small minority for whom current information could not be obtained from the National Death Index or Scientific Registry of Transplant Recipients were censored at the date of last available follow-up.

Risk factors for the composite endpoint were ascertained with multivariable Cox regression. Nonproportional hazards behavior was observed for several clinically relevant predictors, so extended Cox models that incorporated a binary measure of time (<1 year vs ≥1 year) were used for these time-dependent predictors. For time-dependent variables, hazard ratios (HRs) were reported separately for the early (<1 year) and late (≥1 year) post-Fontan periods. Variables considered in the analysis are presented in Appendix E1. Some continuous variables were dichotomized for ease of interpretation, with cut-points chosen based on sensitivity analysis to achieve a >90% specificity for the outcome of interest. Those with a P value <.1 in univariable analysis and observations in at least 90% of subjects were considered for entry into the multivariable models. Variables were retained if their addition to the model generated a likelihood ratio test P value <.1. When more than one significant multivariable model could be constructed, the model that produced the lowest Akaike information criterion score (post-test goodness-of-fit measure) was selected.

Because fewer than 90% of patients had a pre-Fontan catheterization, subset analyses were performed to examine the effects of hemodynamic parameters. These values could not be imputed because of the potential bias to refer patients with poorer physiology for catheterization at a greater rate. All P values reported are 2-sided, and statistical significance was established a priori at $P \leq .05$. Analyses were conducted with STATA, v. 12.0 (StataCorp, College Station, Tex) and SAS 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 773 patients underwent a first Fontan operation at CHOP between 1992 and 2009. The median number of operations performed per year was 42 (range, 26-68). Relevant demographic, preoperative, and perioperative characteristics of the study cohort are outlined in Table 1. Systemic right ventricles predominated, with 50% of patients carrying a diagnosis of hypoplastic left heart syndrome. Common atrioventricular (AV) valve was present in 11%. Ninety-seven percent of patients had staged