Hypoplastic Left Heart Syndrome Is Not a Predictor of Worse Intermediate Mortality Post Fontan

Billie-Jean Martin, MD, PhD, Kandice Mah, MD, Luke Eckersley, MBBS, Joyce Harder, MD, Charissa Pockett, MD, Daryl Schantz, MD, John Dyck, MD, Mohammed Al Aklabi, MD, Ivan M. Rebeyka, MD, and David B. Ross, MD

Department of Cardiothoracic Surgery, Stanford University, Stanford, California; Department of Pediatrics, University of Alberta, Edmonton, Canada; Department of Pediatrics, University of Calgary, Calgary, Canada; Department of Pediatrics, University of Saskatchewan, Saskatoon, Canada; Department of Pediatrics, University of Manitoba, Winnipeg, Canada; and Department of Surgery, University of Alberta, Edmonton, Canada

Background. An increasing proportion of those living with single ventricle physiology have hypoplastic left heart syndrome (HLHS). Our objective was to assess the association between HLHS and outcomes post Fontan operation.

Methods. All pediatric patients who underwent a Fontan procedure at the University of Alberta between 1996 and 2016 were included. Follow-up clinical data collected included early and late surgical or catheter reintervention, echocardiography, and long-term transplant-free survival. Characteristics were compared between those with and without HLHS, and the association between outcomes and HLHS were assessed.

Results. A total of 320 children (median age 3.3 years, interquartile range 2.8 to 3.9 years; 121 [43.4%] female) underwent a Fontan procedure over the course of the study. Nearly one third of subjects had HLHS (107, 33.4%). Patients with HLHS were more likely to have abnormal ventricular function (19.6% versus 7.0%, $p = 0.003$) and worse than mild atrioventricular valve (AVV) regurgitation (23.4 versus 9.2%, $p = 0.001$) preoperatively. HLHS was not predictive of in-hospital Fontan failure (odds ratio 0.82, 95% CI 0.28, 2.39), late reintervention (hazard ratio [HR] 1.08, 95% CI 0.66, 1.76), or transplant-free survival (HR 1.58, 95% CI 0.72, 3.44). Subjects with HLHS were more likely to have more than mild AVV regurgitation (31.6% versus 13.3%, $p = 0.028$) and abnormal ventricular function (29.8% versus 10.7%, $p < 0.0001$) at late follow-up.

Conclusions. Patients with HLHS who survive to the Fontan procedure do no worse with the operation than those with other anatomy. Given worse late ventricular function and AVV regurgitation, equivalent survival may not persist throughout a patient's life course.

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The true long-term outcomes of the current Fontan operation are challenging to define, as the operation has only been used for 4 decades, and in that time the procedure itself has evolved rapidly—even more so, the patient population undergoing single ventricle palliation has dramatically changed.

An increasing proportion of those now living with single ventricle physiology have hypoplastic left heart syndrome (HLHS). Only recent outcomes data are available for this cohort, however, as HLHS has only been a survivable lesion for just over 2 decades. Patients with HLHS are therefore underrepresented in historical series of Fontan patients: in large long-term outcome studies, patients with an original diagnosis of HLHS comprise as little as 10% of the study cohorts [1, 2]. One of the largest series including a significant portion of HLHS patients

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Address correspondence to Dr Martin, 300 Pasteur Dr, Falk Building, Stanford, CA 94305; email: billieje@stanford.edu.

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was limited to in-hospital outcomes, and demonstrated no significant difference in the HLHS patients [3]. Further, no studies have considered longitudinal changes in echocardiographic parameters in a mixed-anatomy Fontan population.

Our objective was to determine whether there is an association between HLHS anatomy and long-term outcomes following a Fontan operation in a modern cohort of single ventricle patients, considering a broad spectrum of outcomes including echocardiographic endpoints.

Patients and Methods

All patients under 18 years of age who underwent an initial Fontan operation at Stollery Children's Hospital in Edmonton, Alberta, Canada, between 1996 and 2016 were included.

Detailed patient demographic, medical, and surgical information were obtained. Original cardiac anatomy and surgical details were confirmed by review of operative reports and echocardiograms. Preoperative cardiac catheterization and echocardiographic results were obtained for each patient. Procedural details, length of stay, perioperative complications, repeat surgical procedures, and timing of transplant were obtained through chart review and from the Western Canadian Children's Heart Network database. Follow-up echocardiogram results were obtained at hospital discharge, 1-year post-Fontan, and at last follow-up from local echocardiographic databases. Mortality was ascertained at each of the follow-up sites through direct contact with the families and attending physicians. Follow-up was complete to December 31, 2016. Survival and procedural follow-up was available for all children.

The large majority of patients had initial staged palliation at the Stollery Children's Hospital, with surgical technique as per the individual surgeon and patient anatomy. Prior to 2001, all Norwood operations were performed with a Blalock–Taussig shunt; a gradual transition to use of the Sano shunt was complete by 2006. Second-stage palliation was a bidirectional cavopulmonary shunt (BCPS) or similar procedure. The third-stage palliation was a Fontan operation, with a mix of lateral tunnel, extracardiac, and intra/extracardiac Fontan procedures, with all procedures still in use. Fenestration was also performed at each surgeon's discretion.

Outcomes of Interest

The primary outcome of interest was transplant-free survival. Secondary outcomes of interest assessed included early Fontan failure (death, transplant, Fontan takedown, Fontan revision, need for mechanical support during initial hospitalization) [2], postoperative length of stay, perioperative stroke, any late failure (death, transplant, or Fontan takedown post hospitalization), and any late adverse event (a composite of late failure, pacemaker implantation, any surgical procedure on bypass or nonbypass aortic surgery, any catheter procedure other than fenestration occlusion or collateral occlusion, or atrioventricular valve [AVV] regurgitation moderate or worse at last follow-up) [2].

Statistical Analysis

Continuous variables were tested for the normality of their distribution and are presented as means with standard deviation (SD) or medians with interquartile range (IQR) and analyzed using the t test or the Kruskal Wallis test. Categorical variables are presented as counts and percentages and were analyzed using the Fisher's exact or the χ^2 test. For multiple comparisons across categories, the Bonferroni correction (α/n) was applied. Baseline and operative characteristics were compared between those with and without HLHS. Moderate or worse AVV regurgitation was considered "significant regurgitation." All surgical reinterventions occurring after a patient was discharged from their Fontan hospitalization were considered "late." Patients who did not leave hospital with a Fontan circulation were excluded from long-term reintervention analysis. Actuarial survival and freedom from transplant were assessed using Kaplan-Meier survival analysis and differences between groups were analyzed using the log-rank test. Associations between all potential covariates of interest (demographics, era, anatomy, function, hemodynamics, operative characteristics) and time-dependent outcomes were initially assessed with univariable proportional hazards models. All variables associated with each outcome with a p value less than 0.100 were entered into a multivariable Cox regression model and then stepwise elimination with backward selection was used to select the most parsimonious set of predictive variables in multivariable models. As a sensitivity analysis, a propensity model was developed to predict HLHS anatomy, and HLHS patients were matched 1:1 with non-HLHS patients (see Appendix for details). For all outcomes other than survival, patients were censored at the time of death. All p values are two-sided and statistical significance was defined as a p value of less than 0.05. Analyses were conducted using Stata/IC v.14 (StataCorp, College Station, TX). The study was approved by the research ethics boards at the Universities of Alberta, Saskatchewan, and Manitoba, with a waiver of consent.

Results

Between 1996 and 2016, 320 pediatric patients underwent a first-time Fontan operation. Nearly all patients had the entirety of their palliation at the University of Alberta (93.1%). The most common original cardiac anatomy was HLHS (107 patients, 33.4%) (Table 1).

Preoperative Characteristics

The most common stage 1 procedure was a Norwood operation (Table 1). Post-BCPS length of stay did not differ by anatomy. Children with HLHS were more likely to have either poor ventricular systolic function or significant atrioventricular valve regurgitation pre-Fontan.