Survival in Children With Down Syndrome Undergoing Single-Ventricle Palliation

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Background. We describe survival in patients with Down syndrome (DS) with single-ventricle anatomy and palliation and characterize risk factors associated with mortality.

Methods. All patients with DS and single-ventricle anatomy documented in the electronic medical record at our institution from January 1, 1992, to May 1, 2014, were compared with patients with unbalanced atrioventricular septal defects and single-ventricle anatomy, without DS or heterotaxy, during the same period. Survival analysis was performed to evaluate factors associated with mortality, including the presence of DS.

Results. There were 28 patients with DS and 30 patients without DS. One-year survival with DS was 75% (95% CI: 55% to 87%); 5-year survival was 61% (95% CI: 40% to 76%). All DS deaths except one occurred before 2 years of age. One-year non-DS survival was 93% (95% CI: 76% to 98%); 5-year survival was 85% (95% CI: 64% to 94%). Factors associated with death by univariable analysis included DS ($p = 0.04$), pulmonary vascular resistance (PVR) of at least 3 Wood units × meter^2 (WUm^2) in the first year of life ($p = 0.03$), and moderate-to-severe atrioventricular valve regurgitation ($p = 0.1$). In combined analysis, when accounting for PVR of at least 3 WUm^2 (hazard ratio [HR] 9.8, 95% CI: 1.1 to 83.5, $p = 0.04$), DS was not associated with increased mortality (HR 1.5, 95% CI: 0.3 to 7.8, $p = 0.66$). No patient with DS with PVR less than 3 WUm^2 died.

Conclusions. Children with DS and single-ventricle anatomy have excellent survival when PVR is less than 3 WUm^2 in the first year of life, with minimal mortality beyond 2 years of age. When accounting for PVR, DS alone is not associated with increased mortality in patients with single-ventricle anatomy.

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Patients with Down syndrome (DS) and congenital heart disease who undergo single-ventricle palliation (SVP) represent a population considered to be at high risk for morbidity and mortality compared with their euploidic peers. Low transpulmonary pressures are necessary for successful palliation, but children with DS are inherently predisposed to higher pulmonary vascular resistance (PVR) [1–3]. Recent large administrative database studies have shown increased hospital deaths after staged palliation procedures in patients with DS compared with patients without DS [4, 5]. Other studies have reported on mortality in DS after total cavopulmonary connection (TCPC) [2, 6–9], with inconsistent findings about mortality risk compared with patients without DS. Overall, little has been published on the clinical and surgical outcomes of patients with DS, particularly before TCPC. The purpose of this study is to describe survival in patients with DS and single-ventricle anatomy, to compare survival in patients with and without DS who undergo SVP, to characterize risk factors associated with mortality in DS and SVP, and to investigate whether DS alone is a risk factor for death.

Patients and Methods

This study was approved by the Institutional Review Board at Baylor College of Medicine. Patients cared for between January 1, 1992, and May 1, 2014, were identified with institutional electronic databases. Search criteria included diagnosis of DS and single-ventricle anatomy. Single-ventricle anatomy was defined as the inability to surgically separate pulmonary and systemic cardiac output. For patients who underwent a surgical procedure, this included pulmonary artery banding, pulmonary artery banding with superior cavopulmonary connection (SCPC; also known as pulsatile Glenn), and intact pulmonary artery with SCPC (also known as one-and-a-half repair). In most patients, suitability for septation was determined by echocardiogram; however, in some, it was determined on intracardiac inspection during the operation. Patients without DS who had an unbalanced atrioventricular septal defect (AVSD) considered unsuitable for septation were selected for comparison with the

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use of the same search criteria. Patients with unbalanced AVSD were chosen for comparison, given that this lesion was present in most of the DS cohort. Patients with heterotaxy complex (isomerism) were excluded because of a known increased risk of death [10, 11]. Clinical diagnosis, demographic characteristics, gestational age, dominant ventricle (morphologic left versus right), age at surgical procedure, and type of pre-SCPC surgical procedure (pulmonary artery band, systemic-to-pulmonary artery shunt, or other) were recorded. Preterm was defined as birth less than 37 weeks' gestation. Preoperative data collected included degree of atrioventricular valve regurgitation, mean pulmonary artery pressure, ventricular end-diastolic pressure, and calculated PVR as obtained by echocardiography and cardiac catheterization. The degree of atrioventricular valve regurgitation was estimated qualitatively and was divided into 1, none to mild, and 2, moderate to severe. Highest PVR in the first year of life was collected when available. PVR is reported in Wood unit $\times$ meter^2 (WUm^2). Pre-SCPC PVR was defined as the PVR measured on the catheterization most closely preceding the SCPC surgical procedure.

Statistical Methods

Wilcoxon rank sum and Pearson χ^2 tests were used to compare continuous and categorical variables, respectively, and Cochran-Armitage trend test was applied for ordinal variables. Cardiac survival (from birth to death or heart transplantation) was estimated with the Kaplan-Meier method. Birth was time zero, and all living patients without transplantation were censored at the date of last contact. Kaplan-Meier analysis was first used, including patients with and without DS, to perform univariable analysis to determine which factors were associated with mortality. A receiver operating characteristic curve analysis was created to identify a threshold value of PVR that maximized sensitivity and specificity for mortality to delineate a clinically useful cutoff. An exploratory multivariable Cox regression model was then created, initially including all covariates associated with mortality with p less than 0.2 by univariable analysis. Given the small dataset, backward elimination was used to discard covariates with p values greater than 0.05, retaining DS in the model to assess its effect estimate. Given high collinearity between PVR and mean pulmonary arterial pressure, only PVR was used in the model. A p value less than 0.05 was considered statistically significant. Analysis was performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Twenty-eight patients with DS and single-ventricle anatomy and 30 patients without DS with unbalanced AVSD were included. Patient characteristics are listed in Table 1. Median age at last follow-up was approximately 5 years in both groups (range, 2 months to 33 years in both). Statistically significant differences between the groups included older median age at SCPC ($p = 0.03$), higher pre-SCPC PVR ($p = 0.02$), and higher pre-SCPC mean pulmonary artery pressure ($p = 0.01$) in the DS group. The DS group was evenly divided between morphologic left (50%) and right (50%) ventricles, whereas 70% of the non-DS group had a morphologic right ventricle ($p < 0.01$). The majority of patients with DS had an unbalanced AVSD (26 of 28, 93%); one patient had hypoplastic left heart syndrome and another had tricuspid atresia.

The clinical course of patients with DS is shown in Figure 1. The majority of patients were initially palliated with a pulmonary artery band (22 of 28, 79%), including 5 patients with a concomitant arch repair. Three had a Blalock-Taussig shunt (3 of 28, 11%), 1 of whom underwent a Norwood procedure. Of the remaining 3, 1 died before any operation and the other 2 underwent SCPC as their first palliation.

SCPC was performed in 16 patients with DS (16 of 28, 57%) at a median age of 1.1 years (range, 3 months to 13.4 years). In contrast, median age at SCPC in patients without DS was 6 months (range, 3 months to 6.6 years; $p = 0.03$). The median SCPC date for patients with DS and patients without DS was September 12, 2006 (range, June 23, 1997 to March 8, 2011) and March 18, 2008 (range, February 1, 1992 to April 14, 2014), respectively. Of the DS group, 8 remain with only SCPC, 3 have undergone TCPC, 1 has undergone a one-and-a-half ventricle repair, 2 died before another operation, and 2 underwent SCPC takedown for failing physiology. PVR before takedown in those 2 patients was 5.4 and 3.4. Data, including current management plan for patients with DS with SCPC, are found in Table 2. Presently, 3 patients who underwent SCPC are considered candidates for TCPC and are awaiting an operation.

Two patients with DS underwent single-stage TCPC after pulmonary artery banding (ages at TCPC were 1.9 and 3.5 years). Thus, a total of 5 patients with DS achieved TCPC (18%; 5 of 28), at a median age of 3.5 years (range, 1.9 to 4.8 years). The median TCPC date for patients with DS and patients without DS was July 9, 2007 (range, June 23, 1997, to April 28, 2009) and September 19, 2009 (range, January 18, 1995, to June 17, 2013), respectively. The patients with DS with hypoplastic left heart syndrome and tricuspid atresia both successfully achieved TCPC. Four of the 5 are alive (age range at follow up, 5 to 11 years). TCPC was achieved in 16 patients without DS (53%). Sixteen patients with DS (57%) and 15 patients without DS (50%) underwent cardiac catheterization in the first year of life. Hemodynamic data are listed in Table 1.

In patients with DS, 1-year Kaplan-Meier survival was 75% (95% CI: 55% to 87%); 5-year survival was 61% (95% CI: 40% to 76%). All deaths occurred before 2 years of age, except for 1 patient, which occurred at age 18 years. For patients without DS, 1-year Kaplan-Meier survival was 93% (95% CI: 76% to 98%); 5-year survival was 85% (95% CI: 64% to 94%; univariable comparison of overall Kaplan-Meier survival in DS and non-DS $p = 0.03$). Median age at death was 11 months (range, 2 months to 18 years) for patients with DS and 2.3 years (range, 2 months to 5.7 years) for patients without DS. No patients with DS received a transplant. One patient without DS received a transplant; another is currently on the waiting list. Data