Longitudinal Assessment of Growth in Hypoplastic Left Heart Syndrome: Results From the Single Ventricle Reconstruction Trial

ORIGINAL RESEARCH

Longitudinal Assessment of Growth in Hypoplastic Left Heart Syndrome: Results From the Single Ventricle Reconstruction Trial

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***Background*—**We sought to characterize growth between birth and age 3 years in infants with hypoplastic left heart syndrome who underwent the Norwood procedure.

***Methods and Results*—**We performed a secondary analysis using the Single Ventricle Reconstruction Trial database after excluding patients <37 weeks gestation (N=498). We determined length-for-age *z* score (LAZ) and weight-for-age *z* score (WAZ) at birth and age 3 years and change in WAZ over 4 clinically relevant time periods. We identified correlates of change in WAZ and LAZ using multivariable linear regression with bootstrapping. Mean WAZ and LAZ were below average relative to the general population at birth ($P<0.001$, $P=0.05$, respectively) and age 3 years ($P<0.001$ each). The largest decrease in WAZ occurred between birth and Norwood discharge; the greatest gain occurred between stage II and 14 months. At age 3 years, WAZ and LAZ were <−2 in 6% and 18%, respectively. Factors associated with change in WAZ differed among time periods. Shunt type was associated with change in WAZ only in the Norwood discharge to stage II period; subjects with a Blalock-Taussig shunt had a greater decline in WAZ than those with a right ventricle-pulmonary artery shunt ($P=0.002$).

***Conclusions*—**WAZ changed over time and the predictors of change in WAZ varied among time periods. By age 3 years, subjects remained small and three times as many children were short as were underweight (>2 SD below normal). Failure to find consistent risk factors supports the strategy of tailoring nutritional therapies to patient- and stage-specific targets.

***Clinical Trial Registration*—**URL: http://clinicaltrials.gov/. Unique identifier: NCT00115934. **(*J Am Heart Assoc*. 2014;3: e000079 doi: 10.1161/JAHA.114.000079)**

Key Words: growth • hypoplastic left heart syndrome • pediatrics • risk factors

Infants with hypoplastic left heart syndrome (HLHS) and related single morphological right ventricular (RV) anomalies most commonly undergo the Norwood procedure before 1 week of age and a superior cavopulmonary connection (stage II) at 4 to 6 months of age. These complex surgeries impose a significant metabolic stress on the infants, many of who are already underweight at the time of their operation.[1–4] Growth failure has received considerable attention as a major and potentially modifiable risk factor for increased morbidity, prolonged hospitalization, and impaired neurodevelopment.[3,5–7] Inferences regarding growth in this population have been handicapped by inclusion of a variety of single

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The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Heart, Lung, and Blood Institute.

An accompanying Appendix S1, which contains a complete list of the Single Ventricle Reconstruction Trial, is available at http://jaha.ahajournals.org/content/3/2/e000079/suppl/DC1

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Received February 10, 2014; accepted March 5, 2014.

ventricle morphologies, single center approaches, cross-sectional study design, failure to standardize measurements, and small sample sizes with limited power for multivariable analysis.[8–11]

The National Heart, Lung, and Blood Institute-sponsored Pediatric Heart Network Single Ventricle Reconstruction (SVR) Trial collected data prospectively on the largest cohort to date of subjects with HLHS and other single RV anomalies undergoing the Norwood procedure and randomized to either a modified Blalock-Taussig shunt (MBTS) or right ventricle-to-pulmonary artery shunt (RVPAS).[12] Consenting survivors from this trial were enrolled for longitudinal follow-up in the SVR Extension Study. This well-characterized cohort from a broad sample of North American centers provided a unique opportunity to evaluate early growth and to identify potential risk factors for poor growth. The goals of the present analysis were to describe growth patterns during the first 3 years of life and to explore patient characteristics, perioperative factors, shunt type, and other therapies that are associated with growth in the SVR cohort.

Methods

Subjects

The design and main results of the SVR trial have been reported previously.[12–14] Briefly, neonates with HLHS or a related single morphological RV anomaly and a planned Norwood procedure were eligible for inclusion in the trial. Those with a major congenital or acquired extracardiac abnormality that could independently influence transplant-free survival were excluded. Subjects undergoing a Norwood procedure were randomized to either a MBTS or RVPAS. Sociodemographic and clinical characteristics, medical and surgical variables, unanticipated procedures, complications, outcome data, and core laboratory analysis of echocardiographic images were collected on subjects from birth to 14 months of age (Table 1). Consenting survivors of the SVR trial were subsequently enrolled in the SVR Extension Study with annual data collection from review of the medical record. The study protocols were approved by each center's institutional review board or research ethics board and written consent was obtained from a parent or guardian.

Study Design and Measurements

We analyzed changes in weight and length/height over time to investigate growth patterns and assessed predictors of these patterns using all available data on subjects from birth through age 3 years. Because the factors contributing to impaired weight gain may change over time (often as the result of surgical or procedural alterations in physiology), the 3-year clinical course was divided into 4 clinically relevant periods: (1) birth to Norwood discharge, (2) Norwood discharge to stage II procedure (interstage), (3) stage II procedure to 14 months, and (4) 14 months to 3 years of age. Subjects who were premature (<37 weeks gestation, n=64) did not have a Norwood procedure (n=5), or whose parent/guardian withdrew consent in week 1 (n=1) were excluded from this analysis. Subjects who subsequently underwent heart transplantation or biventricular repair (n=23) had growth data included only up to the transplant or biventricular repair. Subjects who underwent the stage II procedure without being discharged after the Norwood procedure (n=22) were excluded from the analysis of the first 2 time periods. The shunt type in place when the subject left the operating room following the Norwood procedure was used for the analysis of the effect of shunt type on growth. Medical and surgical data were collected from the neonatal hospitalization, stage II hospitalization, and study visits up to and including age 3 years. If the stage III procedure occurred by 3 years of age, any surgeries and catheter interventions occurring during that hospitalization were also included in the predictor variables describing the number of procedures. Covariates considered as potential correlates of growth in the analysis are listed in Table 1.

Growth Assessment

All growth measurements were converted to age-adjusted *z* scores in standard deviations (SD) based on World Health Organization (WHO) standards.[15] The primary outcome was the change in weight-for-age *z* score (WAZ) for each of the designated time intervals. While a WAZ <-2 is a traditional screening criterion for growth failure in healthy individuals, prior studies have demonstrated that simple cross-sectional assessment using a single threshold is relatively insensitive.[16] To better assess the severity of impaired weight gain, we determined the proportion with WAZ <-1, which identifies a potentially at-risk population and also offers more statistical power, in addition to the more traditional abnormal classification of WAZ <-2. Weights were obtained at study visits, typically with infants weighed in a diaper and older children in light clothing and barefoot. Because the methodology for measuring height/length was not standardized for the SVR Trial and given the challenges inherent in obtaining length in infants,[17] we limited the analyses of change in height/length *z* scores (LAZ) to the time from birth to age 3 years. Changes seen over this longer time interval are more likely due to somatic growth rather than inaccuracies in measurement.[18] For this analysis, pre-Norwood length was defined as the LAZ at birth and barefoot height using a stadiometer at the 3-year study visit was defined as LAZ at 3 years.

Table 1. Candidate Predictors Considered in Models Predicting Change in Weight-for-Age *z* Score for the Designated Time Periods

Between birth and Norwood discharge:
General
Center
Socioeconomic Status (SES) and Hollingshead scores
Percentage of residents below federal poverty level
Medical insurance
Gender
Race/ethnicity
Anatomy subtype
Aortic atresia
Obstructed pulmonary return
Gestational age
Birth weight
Birth weight <2500 g
Multiple birth
Ever diagnosed with an identifiable genetic syndrome
Ever diagnosed with any genetic abnormalities
Pre-Norwood
Number of interventional catheterizations
Number/types of cardiac surgeries
Number/types of non-cardiac surgeries
Number of surgeries
Cardiopulmonary bypass time
Number of complications
Enteral feedings before Norwood
During Norwood hospitalization
Number/types of procedures performed concurrently
Number of interventional catheterizations
Number/types of cardiac surgeries
Number of non-cardiac surgeries
Number of complications
Length of hospital stay
Ventilator duration
Total bypass support time
Cross-clamp time
Regional perfusion time
Circulatory arrest time
Extracorporeal membrane oxygenation during Norwood procedure or hospitalization
At Norwood discharge
Oxygen saturation
Feeding method
Feeding type
Caloric density
Weight monitoring program
Oxygen monitoring program
Number of serious adverse events through discharge
Baseline echocardiogram
Right ventricular area change
Right ventricular ejection fraction
Neoaortic valve regurgitation
Tricuspid valve regurgitation
Between Norwood discharge and pre-stage II:
All of the above plus:
Post Norwood echocardiogram
Right ventricular area change
Right ventricular ejection fraction
Neoaortic valve regurgitation
Tricuspid valve regurgitation
Pre-stage II echocardiogram
Right ventricular area change
Right ventricular ejection fraction
Neoaortic valve regurgitation
Tricuspid valve regurgitation
Before stage II procedure
Feeding method
End diastolic ventricular pressure
Capillary wedge pressure
Number of interventional catheterizations
Number/types of cardiac surgeries
Number of non-cardiac surgeries
Cardiopulmonary bypass time
Number of complications
Number of serious adverse events
Between pre-stage II and 14 months:
All of the above plus:
During stage II hospitalization
Number/types of procedures performed concurrently
Reason for procedure (elective/nonelective)
Age at time of procedure
Total support time
Number of interventional catheterizations
Number/types of cardiac surgeries

Continued

Continued

Table 1. Continued

Number of non-cardiac surgeries
Number of complications
Length of hospital stay
Ventilator duration
Regional perfusion time
Circulatory arrest time
Extracorporeal membrane oxygenation during stage II procedure or hospitalization
Oxygen saturation at discharge
Any cardiopulmonary resuscitation used after stage II procedure
From post-stage II to 14 months
Number of interventional catheterizations
Number/types of cardiac surgeries (through 12 months)
Number of non-cardiac surgeries (through 12 months)
Cardiopulmonary bypass time
Number of complications
Number of serious adverse events
14 month echocardiogram
Right ventricular area change
Right ventricular ejection fraction
Neoaortic valve regurgitation
Tricuspid valve regurgitation
Between 14 months and 3 years and for change in weight-for-age z score between birth and 3 years, and change in height/length-for-age z score between birth and 3 years:
All of the above plus:
From 12 or 14 months to 3 years
Number of interventional catheterizations
Number/types of cardiac surgeries
Number of complications
Number of medications
Feeding method 13 to 24 months
Feeding method 25 to 36 months
Speech/language/occupational therapy 13 to 24 months
Speech/language/occupational therapy 25 to 36 months
Feeding issues 13 to 24 months
Feeding issues 25 to 36 months
Therapy for feeding issues 13 to 24 months
Therapy for feeding issues 25 to 36 months
Solid foods 13 to 24 months
Solid foods 25 to 36 months
Special foods 13 to 24 months
Special foods 25 to 36 months

Statistical Methods

Because of the high mortality over time in this population, the analysis of weight was performed at each time interval. Given that the analysis examined only survivors of each staged surgery, understanding the factors that predicted weight gain in each phase was most clinically relevant. Descriptive statistics include mean±SD for continuous variables and frequency with percentage for categorical variables. Each mean was based on data available at the respective time point (Figure 1A through 1C). Simple linear regression was used to obtain initial estimates of association of each candidate predictor with change in WAZ and LAZ at each time interval. Nonlinear relationships with continuous outcomes were assessed by categorizing continuous variables into groups based on quartiles; in addition, relationships between the natural logarithm of predictors with skewed distributions (for example, length of hospital stay) and the outcomes were explored. All variables with unadjusted $P<0.20$ were used as candidate predictors for multivariable modeling. For variables with >5% missing data (for example, socioeconomic predictors and the use of weight and/or oxygen monitoring programs), mean imputation was performed prior to conducting multivariable modeling. Stepwise linear regression was employed to develop multivariable models, in conjunction with bootstrapping (1000 samples) to obtain reliability estimates for each of the predictors. The criteria to enter and remain in the model were $P<0.15$ and $P<0.05$, respectively. Separate models were constructed adjusting, and not adjusting, for center. All terms in the final multivariable models have a reliability >50% and $P<0.05$. Only the models where center was not allowed as a potential covariate in the model are included in the Tables 3 through 8. Center effects are described in the text. All analyses were conducted using SAS version 9.3 (Statistical Analysis System, SAS Institute, Inc) and SAS macros for bootstrapping estimates of reliability.

Results

Study Cohort

Flow charts of the subjects included in the analysis of growth parameters at each time period are shown in Figures 1A through 1C. At birth, compared with a mean of 0 for the normative population, the mean for both WAZ and LAZ (Figure 2) was lower for subjects in the SVR cohort ($P<0.001$ for WAZ, $P=0.05$ for LAZ). Birth weight was >1 SD below expected population mean (WAZ <−1) in 24% and >2 SD below (WAZ <−2) in 6%. LAZ at birth was <−1 in 23% and <−2 in 10%.

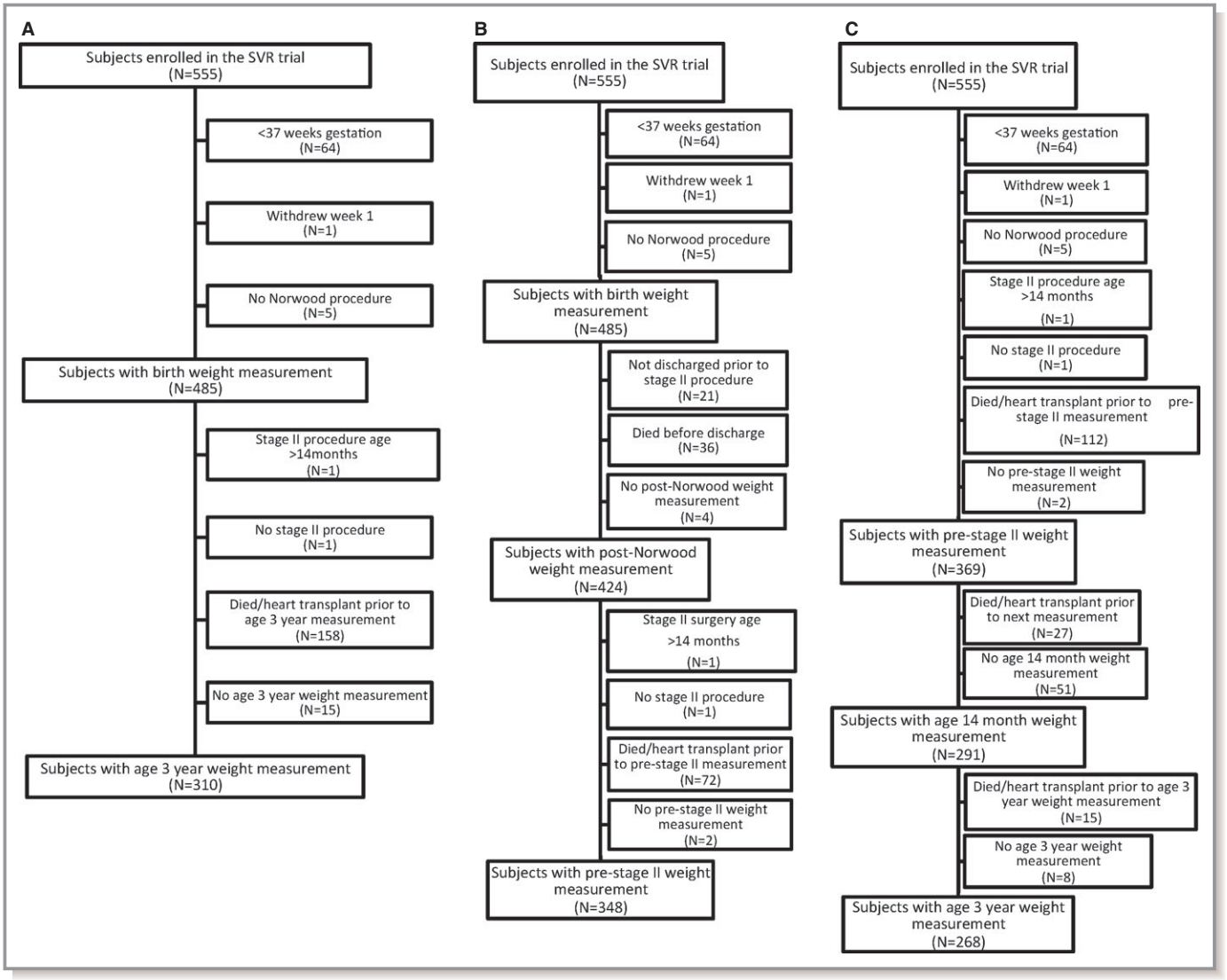

Figure 1. A, Flow diagram showing the study sample used for the growth analysis from birth to age 3 years (without intermediate time points). B, Flow diagram showing the study sample used for the growth analysis for birth weight to each of the first 2 time periods: (1) Birth to Norwood discharge; (2) Norwood discharge to pre-stage II. C, Flow diagram showing the study sample used for the growth analysis for pre-stage II and the last 2 time periods: (1) Pre-stage II to age 14 months, (2) Age 14 months to age 3 years. SVR indicates Single Ventricle Reconstruction.

Birth to Age 3 Years

Over the entire study period, the greatest drop in WAZ in this cohort was seen between birth and Norwood discharge with continued gradual decline through the interstage period to the stage II procedure, followed by the period of greatest gain occurring between stage II and 14 months (Table 2). At age 3 years, both mean WAZ and LAZ (Figure 2) were lower than the mean of the normative population ($P<0.001$); furthermore, WAZ was <-1 in 30% and <-2 in 6% and LAZ was <-1 in 58% and <-2 in 18% of subjects (Figure 1A).

We sought correlates of impaired growth and found that a higher birth weight was independently associated with a greater drop in both WAZ and LAZ by age 3 years. Longer Norwood hospitalization, a larger number of concurrent procedures at stage II, and moderate to severe tricuspid regurgitation at 14 months were independently associated with a greater decline in WAZ (Table 3) during this time period. The correlates of a decline in height were more difficult to interpret (Table 4). Cross clamp and total cardiopulmonary support times for the Norwood operation and total number of interventional procedures from 14 months to 3 years were independently associated with LAZ but the relationships were not linear. Although counterintuitive and nonlinear, lower right ventricular ejection fraction at the pre-stage II echo was also associated with a greater increase in LAZ at age 3 years. The type of shunt in place when leaving the operating room had no association with change in either WAZ or LAZ from birth to age 3 years.

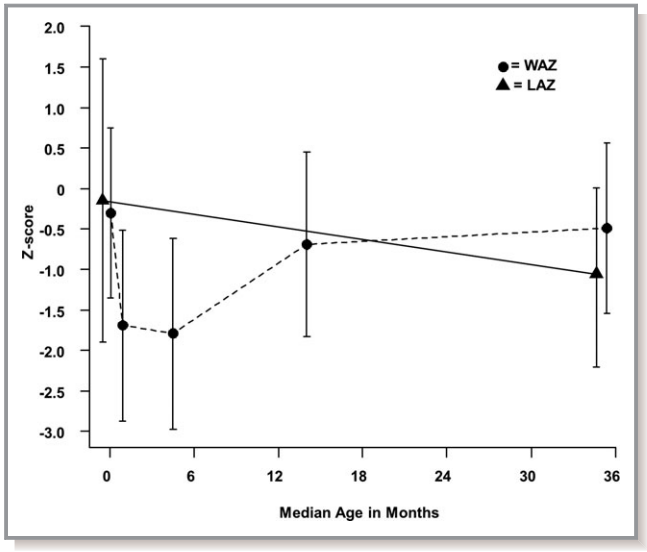

Figure 2. Graph demonstrating weight-for-age *z* score over all time periods and length-for-age *z* score at birth and age 3 years. Each mean is based on all data available at the respective time point, ranging from N=485 at birth to N=268 at age 3 years. The error bars represent one standard deviation. LAZ indicates length/height-for-age *z* score; WAZ, weight-for-age *z* score.

Birth to Norwood Discharge

The most dramatic drop in WAZ occurred from birth to Norwood discharge, with 91% of subjects having ≥0.5 SD drop in mean WAZ. WAZ was <−1 in 72% and <−2 in 37% of subjects at the time of discharge. The mean change in WAZ was −1.40±0.80 (95% CI −1.48 to −1.33, *P*<0.001, Table 2) and did not differ by shunt type. Male gender, higher birth weight, pre-Norwood enteral feeding, mechanical ventilation >5 days, and prolonged Norwood hospitalization were independent predictors of a decline in WAZ (Table 5). Total cardiopulmonary support time was also independently associated with a fall in WAZ and, although the relationship was nonlinear, support times >170 minutes had the largest drop in WAZ (Figure 1B).

Norwood Discharge to Stage II Procedure (Interstage)

The interstage period was characterized by a much smaller fall in WAZ than was observed during the birth to Norwood discharge interval. As a result, WAZ was <−1 in 72% at Norwood discharge and 72% at stage II. Compared with the 37% with WAZ <−2 at Norwood discharge, 39% of subjects had WAZ <−2 at stage II. In contrast to all other time periods, shunt type was associated with change in WAZ during the interstage period (*P*=0.002, Table 2). WAZ did not change in subjects with RVPAS (0.08±1.09, 95% CI −0.08 to 0.23, *P*=0.32) while there was a decline in WAZ in those with MBTS (−0.29±1.06, 95% CI −0.46 to −0.12, *P*=0.001). The relationship between shunt type and change in WAZ remained statistically significant when adjustment was made for center (Figure 1B).

Multivariable analysis for the interstage period demonstrated that higher birth weight, lower socioeconomic status score, absence of pre-Norwood enteral feeding, increased number of interstage complications, and method of feeding pre-stage II were independently associated with a mean interstage decrease in WAZ (Table 6). Infants receiving gastrostomy or gastrojejunostomy tube feedings in the interstage period had the greatest rise in WAZ.

Table 2. Changes in Weight-for-Age *z* Scores for Each Time Period

Time Period	Time Between Measurements	Change in Weight-for-Age *z* Score Mean±Standard Deviation (n)			*P* Value Comparing Shunts†
		All Subjects*	MBTS	RVPAS	
Birth to Norwood discharge (days)	32.5±26.4 (424)	−1.40±0.80 (424)	−1.44±0.84 (210)	−1.36±0.76 (214)	0.32
Norwood discharge to pre-stage II (months)	3.7±1.6 (348)	−0.08±1.09 (348)	−0.29±1.06 (153)	0.08±1.09 (195)	0.002
Pre-stage II to 14 (months)	9.5±3.2 (291)	1.00±0.97 (291)	1.12±0.92 (129)	0.91±1.00 (162)	0.06
Age 14 months to 3 years (months)	20.1±4.0 (268)	0.20±0.87 (268)	0.27±0.82 (123)	0.13±0.91 (145)	0.20
Birth to 3 years (years)	2.8±0.2 (310)	−0.25±1.28 (310)	−0.36±1.27 (144)	−0.16±1.29 (166)	0.18

MBTS indicates modified Blalock-Taussig shunt; RVPAS, right ventricle-to-pulmonary artery shunt.
*Each mean was based on data available at the respective time point (Figures 1A through 1C).
†The *P*-value used to compare shunts was derived from a two-sample t test.

Table 3. Main Effects Multivariable Model for Change in Weight-for-Age *z* Score From Birth to 3 Years (n=310, Adjusted R^2=0.41)

Variable	Estimate	Standard Error	*P* Value	Reliability (%)
Birth weight, kg	−1.654	0.116	<0.001	98
Tricuspid valve regurgitation at 14 month echo			0.01	70
≥Moderate	−0.421	0.148		
<Moderate	Reference			
Number of concurrent procedures at stage II procedure	−0.151	0.065	0.021	59
Length of stay for Norwood (ln days)	−0.261	0.091	0.005	54

Stage II Procedure to 14 Months

Stage II to 14 months was characterized by catch-up growth with 87% of subjects having a change in WAZ >0 (mean change in WAZ of 1.00±0.97; 95% CI 0.89 to 1.12; *P*<0.001, Table 2). WAZ was <−1 in 38% and <−2 in 12% of subjects and only 5% had a drop in WAZ of ≥0.5. Older age at stage II was associated with a greater drop in WAZ (Table 7). A greater number of complications between Norwood discharge and the stage II procedure were associated with a more positive change in WAZ in this period. The length of stay at the Norwood hospitalization and the Hollingshead Four Factor Index of Socioeconomic Status had an independent but nonlinear association with change in WAZ. Center was not significantly associated with growth in univariate analysis for this period and therefore was not included in the multivariable model (Figure 1C).

Age 14 Months to 3 Years

Although mean WAZ improved in this interval (0.20±0.87, 95% CI 0.09 to 0.30, *P*<0.001, Table 2), the increase was less

Table 4. Main Effects Multivariable Model for Change in Length-for-Age *z* Score From Birth to 3 Years (n=294, Adjusted R^2=0.27)

Variable	Estimate	Standard Error	*P* Value	Reliability (%)
Birth weight, kg	−1.478	0.18	<0.001	84
Total support time (Norwood)			<0.001	68
≤107 minutes	0.819	0.328		
108 to 139 minutes	−0.273	0.309		
140 to 170 minutes	−0.107	0.283		
>170 minutes	Reference			
Total cross clamp time (Norwood)			0.002	65
≤40 minutes	−0.431	0.330		
41 to 53 minutes	0.489	0.305		
54 to 67 minutes	0.249	0.302		
>67 minutes	Reference			
Number of interventional cardiac procedures from 14 months to 3 years			0.001	61
0	Reference			
1	0.023	0.231		
2	−1.793	0.527		
3+	1.128	0.547		
Right ventricular ejection fraction at pre-stage II echo			0.007	55
≤38.9%	0.207	0.291		
39.0% to 43.6%	0.011	0.291		
43.7% to 49.2%	0.360	0.285		
>49.2%	Reference			
Unknown/missing	0.868	0.274		

Table 5. Main Effects Multivariable Model for Change in Weight-for-Age *z* Score From Birth to Norwood Discharge (n=417, Adjusted R^2=0.33)

Variable	Estimate	Standard Error	*P* Value	Reliability (%)
Gender			<0.001	96
Female	0.302	0.068		
Male	Reference			
Birth weight, kg	−0.340	0.067	<0.001	73
Length of hospital stay for Norwood procedure		<0.001	72	
≤16 days	0.846	0.118		
17 to 24 days	0.474	0.114		
25 to 40 days	0.160	0.105		
>40 days	Reference			
Days on ventilator after Norwood procedure		0.04	72	
≤5 days or less	0.209	0.118		
6 to 7 days	−0.024	0.119		
8 to 12 days	0.017	0.117		
>12 days	Reference			
Total bypass support time during Norwood procedure			0.03	68
≤107 minutes	0.014	0.096		
108 to 139 minutes	0.057	0.096		
140 to 170 minutes	0.251	0.097		
>170 minutes	Reference			
Pre-Norwood enteral feeding				
No	0.276	0.108	0.01	53
Yes	Reference			

dramatic than the one SD deviation improvement seen in the stage II to 14 month period (Figure 2). The most counterintuitive independent correlate of an increase in WAZ during this time was the presence of pulmonary venous obstruction but this may be an artifact related to the small number with this pathology (N=5). Feeding method prior to stage II was associated with mean change in WAZ and nasojejunal/nasogastric feeding before stage II predicted the largest increase in WAZ (Figure 1C; Table 8).

Discussion

The SVR Trial and SVR Extension Study have collected data on the largest multicenter cohort of subjects with HLHS and related single RV anomalies to date, allowing us to perform a longitudinal assessment of both linear growth and weight gain from birth to age 3 years. Even at birth, mean weight and length of the SVR cohort were lower than the general population. The most dramatic decline in WAZ occurred between birth and Norwood discharge, with a relative plateau during the interstage period. The greatest increase in WAZ occurred after the stage II procedure, likely secondary to ventricular volume unloading, as suggested by other investigators.[8] Although growth improved after stage II, both the mean WAZ and LAZ of the SVR cohort remained below the mean of the normal population at age 3 years.

Predictors of change in WAZ varied with the time period being analyzed and no consistent practice improved growth from birth to age 3 years. This was not unexpected given the changes in surgery and physiology during each interval. In addition, interpretation of the models for prediction of change in WAZ was made more difficult by the fact that some time periods differed in length among subjects since the timing of Norwood discharge and the timing of the stage II procedure were inconsistent. Although it is possible to speculate about some of the observed associations, we preferred to avoid this in the absence of supportive data. However, some data are available to support several conclusions regarding predictors of growth in HLHS patients undergoing single ventricle palliation. The model for change in weight from birth to

Table 6. Main Effects Multivariable Model for Interstage Change in Weight-for-Age *z* Score From Norwood Discharge to Pre-Stage II (n=345, Adjusted R^2=0.21)

Variable	Estimate	Standard Error	*P* Value	Reliability (%)
Birth weight, kg	−0.716	0.111	<0.001	78
SES score* (per unit increase)	0.035	0.011	0.001	74
Pre-Norwood enteral feeding			<0.001	72
No	−0.701	0.176		
Yes	Reference			
Number of complications from Norwood discharge to pre-stage II	−0.105	0.036	0.004	70
Shunt (non-intention to treat)			0.009	70
MBTS	−0.282	0.107		
RVPAS	Reference			
Feeding method pre-stage II			<0.001	59
G/GJ tube	0.665	0.175		
NJ/NG tube	0.028	0.239		
Combination	0.104	0.141		
Other	−0.747	0.355		
Oral	Reference			

G/GJ indicates gastric/gastojejunal; MBTS, modified Blalock Taussig shunt; NJ/NG, nasogastric/nasojejunal; RVPAS, right ventricular to pulmonary artery shunt.
*SES score was assigned using a US census-based score derived from 6 measures related to income, housing, and occupation-related features of the subject's census block tract at the time of randomization.

3 years is particularly useful because it does not depend on the timing of either procedure or the length of stay for the Norwood hospitalization. In this model, longer total length of stay for the Norwood operation, a greater number of concurrent procedures at stage II, and moderate to severe tricuspid regurgitation at 14 months were associated with poor weight gain. These findings support the idea that imperfect results from initial palliation contribute to poor long-term weight gain. While it may seem counterintuitive that patients who are larger at birth (and would be expected to

Table 7. Main Effects Multivariable Model for Change in Weight-for-Age *z* Score From Pre-Stage II and 14 Months (n=290, Adjusted R^2=0.09)

Variable	Estimate	Standard Error	*P* Value	Reliability (%)
Norwood length of stay			0.02	60
≤16 days	−0.352	0.165		
17 to 24 days	−0.371	0.153		
25 to 40 days	−0.476	0.157		
>40 days	Reference			
Number of complications between Norwood discharge and stage II procedure	0.119	0.04	0.003	59
Ln age at stage II procedure, (months)	−0.507	0.175	0.004	58
Hollingshead category				
3.0 to 26.0	−0.571	0.256	0.03	53
27.0 to 40.0	−0.346	0.259		
41.0 to 54.9	−0.695	0.253		
55.0 to 66.0	−0.522	0.26		
Missing	Reference			

Table 8. Main Effects Multivariable Model for Change in Weight-for-Age *z* Score From 14 Months to 3 Years (n=268, Adjusted R^2=0.06)

Variable	Estimate	Standard Error	*P* Value	Reliability (%)
Feeding method before stage II procedure			0.006	77
1. G/GJ tube	−0.153	0.171		
2. NJ/NG tube	0.597	0.216		
3. Combination	−0.148	0.131		
4. Other	−1.622	0.85		
5. Oral	Reference			
Obstructed pulmonary venous return			0.008	54
Yes	1.020	0.383		
No	Reference			

G/GJ indicates gastric/gastojejunal; NJ/NG, nasogastric/nasojejunal.

have better outcomes) actually have poorer weight gain, this finding has been reported by other investigators.[8] It most likely reflects a regression to the mean where those with lower birth weights simply have more opportunity to catch up and therefore a greater improvement in WAZ.[19,20]

The interstage model was largely consistent with what we expected, including less weight gain in patients with higher birth weight and more complications. Weight improved in patients with higher socioeconomic status. Importantly, the type of systemic-to-pulmonary-artery shunt affected weight gain only during the interstage interval, when subjects with MBTS had poorer weight gain than those with RVPAS. This finding may be explained by the higher energy expenditure associated with MBTS physiology.[21–23] Mortality was also higher in the group with the MBTS during the interstage.[12] Ultimately, shunt type did not have long-term effects on weight as the MBTS subjects who survived started to gain weight after the volume unloading of the stage II procedure. The variability in timing of stage II measurements and inclusion of subjects who were not discharged after the Norwood confound the model for the pre-stage II to 14-month time period. Despite this, it appears that on average even the sickest patients with the most complications and those with unfavorable anatomy (obstructed pulmonary veins) gained weight after stage II, if they survived.

The greater percentage of subjects who are short compared with those underweight at age 3 years cannot be explained by caloric intake alone. Typically, weight is more affected than height by inadequate caloric intake.[23] However, at age 3 years, 3 times as many children were short as were underweight (>2 SD below normal). The recovery of weight without recovery of height should be viewed with caution as it may represent an excessive increase in adipose rather than an accumulation of lean body mass.[24,25] Cross-sectional studies of stage II and Fontan survivors reported both a lower LAZ and a positive correlation between lower LAZ and developmental problems.[8,26] It is unclear if this interaction is a direct relationship or the result of an undiagnosed genetic defect. Genetic syndrome was not associated with linear growth or weight gain in this analysis but the SVR Trial relied on expert physical examination, rather than contemporary genomic technologies, so the ability to diagnose syndromes that are not phenotypically apparent was limited.[27] As the knowledge gap narrows with increasing investigations into the genetic, epigenetic, and environmental basis for congenital heart disease, we may better understand the variations in phenotypes and difficulty in impacting both linear growth and weight gain in children with HLHS and other single RV anomalies.[28–31] Future studies evaluating abnormal body composition may be informative and promote consideration of therapies commonly used in other severe catabolic or genetically based growth impaired states.

Limitations

Our study should be interpreted in light of some limitations. First, it is important to note that the anthropometric data presented in this report are conditional on transplant-free survival to each respective time point, using all available data to maximize precision of our estimates. As a result, qualitative comparisons of the change in WAZ amongst the time intervals, while of clinical interest, are based on cohorts of decreasing size and subject to survivor bias. Second, genotyping was not used to define genetic syndromes in the SVR Trial. Children with potentially pathogenic copy number variants or other genetic abnormalities often do not have obvious clinical findings so are not diagnosed with a syndrome,[27] potentially accounting for the failure to find an association between genetic syndrome and poor linear growth

or weight gain in this study. Third, because the WHO normative data do not allow adjustment for gestational age at birth, we attempted to minimize the effect of differences in gestational age by restricting our analysis to term infants. Finally, detailed data regarding feeding practices and calories were not collected in the SVR Trial, limiting our inferences about their effect on weight and length.

Conclusions

Early patterns of weight gain in children with HLHS and other single RV anomalies vary over time. Predictors of poor weight gain also vary among time intervals and are difficult to interpret. Survivors of the Norwood procedure, including those with complicated courses and unfavorable anatomy, demonstrate catch-up weight gain following volume-unloading surgery but both WAZ and LAZ remain below average at age 3 years. Since length was affected more than weight at age 3 years, it is unlikely that addressing caloric intake alone will address growth impairment. Further investigation into genetic and epigenetic causes for alterations in body composition may suggest treatments to be tested in future clinical trials.

Sources of Funding

Supported by U01 grants from the National Heart, Lung, and Blood Institute (HL068269, HL068270, HL068279, HL068281, HL068285, HL068292, HL068290, HL068288, HL085057).

Disclosures

None.

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