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Heart failure after the Norwood procedure: An analysis of the Single Ventricle Reconstruction Trial

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[2]This study is registered with ClinicalTrials.gov at http://clinicaltrials.gov/show/NCT00115934.

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BACKGROUND: Heart failure results in significant morbidity and mortality in young children with hypoplastic left heart syndrome (HLHS) after the Norwood procedure.

METHODS: We studied subjects enrolled in the prospective Single Ventricle Reconstruction (SVR) Trial who survived to hospital discharge after a Norwood operation and were followed up to age 6 years. The primary outcome was heart failure, defined as heart transplant listing after Norwood hospitalization, death attributable to heart failure, or symptomatic heart failure (New York Heart Association [NYHA] Class IV). Multivariate modeling was undertaken using Cox regression methodology to determine variables associated with heart failure.

RESULTS: Of the 461 subjects discharged home following a Norwood procedure, 66 (14.3%) met the criteria for heart failure. Among these, 15 died from heart failure, 39 were listed for transplant (22 had a transplant, 12 died after listing, and 5 were alive and not yet transplanted), and 12 had NYHA Class IV heart failure but were never listed. The median age at heart failure identification was 1.28 (interquartile range 0.30 to 4.69) years. Factors associated with early heart failure included post-Norwood lower fractional area change, need for extracorporeal membrane oxygenation, non-Hispanic ethnicity, Norwood perfusion type, and total support time ($p < 0.05$).

CONCLUSIONS: By 6 years of age, heart failure developed in nearly 15% of children after the Norwood procedure. Although transplant listing was common, many patients died from heart failure before receiving a transplant or without being listed. Shunt type did not impact the risk of developing heart failure.

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The most common surgical treatment strategy for hypoplastic left heart syndrome (HLHS) is the Norwood procedure.[1] This palliative procedure has been used for over 35 years. Survival rates after the Norwood procedure have improved over time and 5-year survival currently exceeds 60%.[2,3] However, a significant proportion of children continue to develop heart failure after the Norwood procedure.

It is clear that heart failure in the single ventricle population often necessitates listing for heart transplantation.[4–7] Existing registries only capture data once children are listed for transplantation. Children with contraindications to heart transplantation or those who die from heart failure before listing for transplant are not included in such analyses. Some preliminary studies have suggested that the type of pulmonary artery shunt, that is, right ventricle-to-pulmonary artery shunt (RVPAS) vs modified Blalock–Taussig shunt (MBTS), may impact the likelihood of developing right ventricular failure.[8,9] In addition, little is known about children who are medically managed with symptomatic heart failure after the Norwood procedure.

The Single Ventricle Reconstruction (SVR) Trial and the follow-up extension study (SVR II Trial) provide a unique opportunity to enhance our understanding of heart failure after the Norwood procedure. A previous analysis of the SVR cohort demonstrated that subjects who underwent the Norwood procedure with RVPAS, as compared with those with the MBTS, had increased RV end-systolic volume and decreased right ventricular ejection fraction (RVEF) from the 14-month to pre-Fontan echocardiogram. However, it is not known how these echocardiographic findings relate to the clinical onset of heart failure. A detailed knowledge of the course of heart failure after the Norwood procedure can aid in determining if, and when, children with RV failure should be considered for heart transplantation. Thus, we sought to determine the incidence of heart failure in young children after the Norwood procedure. We also assessed the risk factors for development of heart failure, including echocardiographic findings at hospital discharge after the Norwood procedure.

Methods

The SVR Trial in infants undergoing the Norwood procedure randomly assigned subjects to either the MBTS or the RVPAS at 15 North American centers.[10] The study design permitted collection of extensive data from hospitalizations and subsequent follow-up assessments. After the Norwood procedure, but before hospital discharge, all subjects had a comprehensive echocardiogram evaluated at a central core laboratory for various measures, including fractional area change and tricuspid regurgitation.[11] Our analysis was limited only to those subjects who survived to hospital discharge after the Norwood procedure without transplant listing and includes all available follow-up until the last subject reached 6 years of age via the SVR II Trial. The institutional review board of each participating center approved this study, and parents/guardians of enrolled subjects provided informed consent.

Data were prospectively collected on heart failure symptoms and medical events, including listing for heart transplantation and, where applicable, subsequent transplantation. In the current study, heart failure was defined as having at least one of the following: listing for heart transplantation; death attributed to heart failure; or New York Heart Association (NYHA) Class IV heart failure.

To verify the classification of death due to heart failure, study investigators reviewed the annual vital status form records of all subjects whose primary cause of death had been attributed to heart failure. Heart failure symptoms were determined from annual follow-up by study coordinators using medical records and patient interviews. Heart failure symptoms were categorized according to

NYHA class in Years 5 and 6. Classification of symptomatic heart failure in those patients <5 years old was not undertaken owing to limitations of such scoring systems in the very young. Follow-up was limited to the 6-year annual assessment.

Statistical analysis

Statistical methods were similar to those previously used in an analysis of SVR data at 3 years.[12] Comparison of study outcomes was done according to treatment assignment to MBTS or RVPAS (intention-to-treat) unless otherwise specified. To assess for associations between echocardiographic findings and the subsequent development of heart failure, we utilized the protocol-mandated echocardiogram obtained after the Norwood procedure but before hospital discharge. We used a Wald test for comparison of 6-year event rates estimated by the Kaplan–Meier method and the log rank test to determine the distributions of time to the earliest occurrence of advanced heart failure using all available follow-up. Three subjects had their follow-up time censored at the time of biventricular repair. For subjects who were followed beyond 6 years, the follow-up was censored at 6 years. Onset of symptomatic heart failure (NYHA Class IV) was defined as the date the annual form was completed. Univariate Cox proportional hazards regression was used to identify potential pre- and intra-operative risk factors for transplant-free survival. Because a test of non-proportionality indicated non-proportional hazards for several predictors, including shunt type, in the multivariate modeling we used Cox regression with a time-dependent treatment indicator. Separate models were run for subjects who developed heart failure at <1 year of age (early) and ≥1 year of age (late). Multivariate modeling utilized a backward selection method within each time interval, starting with predictors significant at the 0.20 level in the univariate analysis. $p < 0.05$ was considered statistically significant in these multivariate models. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

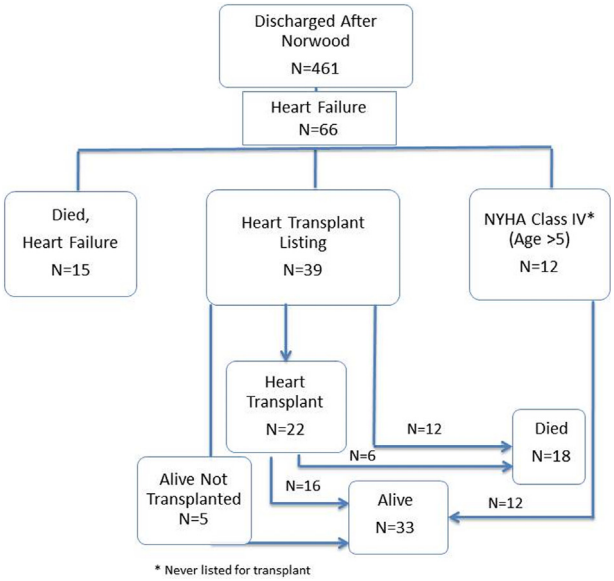

Figure 1 Diagram depicting clinical pathways for subjects with advanced heart failure.

Results

Of the 461 subjects discharged to home after the Norwood procedure without previous heart transplant listing, 226 had undergone an MBTS and 235 had undergone an RVPAS. During the follow-up period, 66 subjects (14.3%) subsequently met the definition of heart failure: heart transplant listing ($n = 39$); NYHA Class IV ($n = 12$); or heart failure death ($n = 15$) (Figure 1). Of the 353 subjects who survived to 6 years, 16 were post-transplant and, of the remaining 337, there were 297 who consented to the SVR II Trial and 287 completed the heart failure classification form. The heart failure criteria stratified by shunt type are shown in Table 1. Risk for developing heart failure was highest in the first year of life (Figure 2). After the first 12 months, the risk of developing heart failure was approximately 3% per year. The median age at heart failure onset was 1.28 (interquartile range 0.30 to 4.69) years. The median age for the various heart failure events is shown in Table 2. The median ages at heart failure, death, or transplant listing were all <1 year. With respect to stage of palliation at time of first heart failure event, there were 21 between Norwood procedure and Stage II, 28 between Stage II and Fontan, and 17 after Fontan. For transplant listing events there were 16 listed between Norwood procedure and Stage II, 19 between Stage II and Fontan, and 4 after Fontan.

Twelve participants died after heart transplant listing (12 of 39, 30.8%) but before receiving a transplant. The mean time interval between heart transplant listing and death for the 12 patients who died pre-transplant was 0.29 ± 0.30 year. Twenty-two subjects received a heart transplant. The mean interval from listing to heart transplant was 0.25 ± 0.40 year. Of the 22 subjects who underwent heart transplant, 6 died after transplant and 16 were alive at 6 years of age. For the 6 patients who died after transplant, the time interval between heart transplant and post-transplant death was 0.09 ± 0.13 year.

Among the 353 subjects surviving to 6-year follow-up, 287 completed the NYHA classification assessment, of whom 12 (4.2%) had NYHA Class IV heart failure. These 12 subjects were managed with a variety of medications, including angiotensin-converting enzyme inhibitors in 6, digoxin in 3, diuretics in 3, and sildenafil in 1. No patients were receiving β-blockers. Three subjects with NYHA Class IV heart failure were reported to not be receiving any conventional heart failure medications.

As the risk of developing heart failure varied by time since the Norwood procedure, 2 separate risk models were constructed. Risk factors associated with the development of early heart failure (<1 year) included perfusion and perioperative factors, such as need for extracorporeal membrane oxygenation (ECMO) at end of Norwood operation and use of predominant regional cerebral perfusion rather than deep hypothermic circulatory arrest during the Norwood (Table 3). A lower fractional area change on post-Norwood echocardiogram was associated with an increased risk of

Table 1 Heart Failure in Single Ventricle Reconstruction Trial Subjects Using All Available Follow-up Data

	All	MBTS	RVPAS
All heart failure	66 of 461 (14.3%)	31 of 226 (13.7%)	35 of 235 (14.9%)
Heart transplant listing	39 of 461 (8.5%)	19 of 226 (8.4%)	20 of 235 (8.5%)
Listed and not transplanted	17 of 39 (43.6%)	9 of 19 (47.4%)	8 of 20 (40.0%)
Listed and subsequent death	12 of 17 (70.6%)	6 of 9 (66.7%)	6 of 8 (75.0%)
Listed and alive at 6 years without transplant	5 of 17 (29.4%)	3 of 9 (33.3%)	2 of 8 (25.0%)
Listed and transplanted	22 of 39 (56.4%)	10 of 19 (52.6%)	12 of 20 (60.0%)
Transplanted and death before 6 years	6 of 22 (27.3%)	3 of 10 (30.0%)	3 of 12 (25.0%)
Transplanted and alive at 6 years	16 of 22 (72.7%)	7 of 10 (70.0%)	9 of 12 (75.0%)
Heart failure death	15 of 461 (3.3%)	7 of 226 (3.0%)	8 of 235 (3.4%)
NYHA Class 4 in Year 6*	12 of 287 (4.2%)	5 of 141 (3.5%)	7 of 146 (4.8%)

MBTS, Blalock–Taussig shunt; NYHA, New York Heart Association; RVPAS, right ventricle-to-pulmonary artery shunt.
The event status is reported as whether they ever had that event or not.
*There 337 transplant free survivors at their 6 years age, of which 297 of were consented to SVR Extension study. Of these, 287 completed the heart failure classification form.

early heart failure. Additional risk factors for early heart failure included non-Hispanic ethnicity and shorter total bypass time. The only peri-operative factor associated with late heart failure (>1 year) was the use of α-blockade at the time of the Norwood procedure, which was associated with a lower risk of late heart failure (hazard ratio $= 0.29$, 95% confidence interval 0.14 to 0.60). Anatomic variant of HLHS was not associated with the development of heart failure. Shunt type was not associated with the development of heart failure after hospital discharge for a Norwood procedure.

Discussion

In this study we have demonstrated that heart failure occurs not uncommonly in early childhood among children who undergo the Norwood procedure as young infants, and the risk of developing heart failure is greatest in infancy.

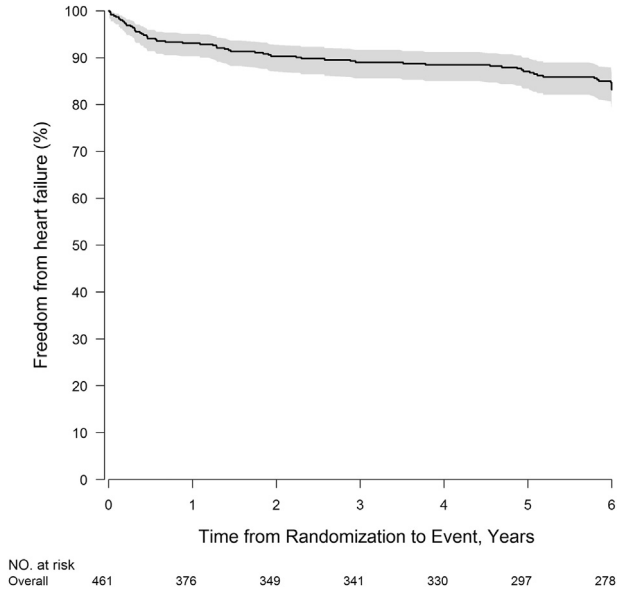

Figure 2 Freedom from heart failure using all available follow-up data until 6 years of age (72 months). Heart failure was defined as listing for heart transplantation, heart failure death, or NYHA Class IV heart failure.

Whereas many children are listed for and successfully undergo heart transplantation for severe heart failure, others die from heart failure while on the waitlist or, more often, without ever being listed. The number of children with heart failure who are managed medically at early school age is relatively low.

There has been concern regarding the impact of shunt type on the development of heart failure after the Norwood procedure because the RVPAS requires implantation of the proximal portion of the shunt directly into the RV free wall. Some have hypothesized that this would lead to local or global RV injury.[13] Ballweg and colleagues reported a higher degree of impaired RV function in those children receiving an RVPAS as compared with a MBTS[8]; however, the use of the 2 shunt types was not randomized, and those receiving the RVPAS were more likely to have aortic atresia. Frommelt and colleagues found that, on echocardiography performed between 14 months and the Fontan operation, the MBTS group had stable indexed RV volumes and ejection fraction, whereas the RVPAS group had increased RV end-systolic volume and decreased RV ejection fraction (RVEF).[14] This raised concerns about an increased long-term risk for RV failure in the RVPAS cohort. Our analyses demonstrated no differences between shunt groups in the composite measure of heart failure, or in transplant listing, symptomatic heart failure, or death from heart failure after discharge from Norwood hospitalization. This provides reassuring information regarding the medium-

Table 2 Follow-up Time From Norwood Discharge for Heart Failure in SVR Subjects

Event	Follow-up time, years [median (IQR)]
First heart failure ($n = 66$)	1.28 (0.30 to 4.69)
Heart transplant listing[a] ($n = 37$)	0.88 (0.28 to 2.23)
Heart failure death ($n = 15$)	0.57 (0.21 to 1.84)

[a]Two subjects were not included due to missing listing date. IQR, interquartile range; SVR, single ventricle reconstruction.

Table 3 Multivariate Risk Model for Early Heart Failure (<1 year)

Characteristics	Hazard ratio (95% CI)	*p*-value
Hispanic: yes vs no	0.28 (0.09 to 0.93)	0.038
Fractional area change: ≤0.35 vs >0.35	5.00 (1.37 to 18.22)	0.015
ECMO immediately after Norwood procedure	5.83 (1.75 to 19.46)	0.004
Norwood perfusion type		<0.001
DHCA only vs RCP/DHCA with DHCA time >10 min	0.05 (0.01 to 0.22)	
RCP and DHCA time ≤10 min vs RCP/DHCA with DHCA time >10 min	0.96 (0.27 to 3.44)	
Total bypass time	0.91 (0.87 to 0.95)	<0.001

For this model, $R^2 = 0.607$. A list of all variables included in the univariate model is provided in Table S1 in the Supplementary Material (available online at www.jhltonline.org). CI, confidence interval; DHCA, deep hypothermic circulatory arrest; ECMO, extracorporeal membrane oxygenation; RCP, regional cerebral perfusion.
DHCA- deep hypothermic circulatory arrest; ECMO- extracorporeal membrane oxygenation; RCP-regional cerebral perfusion

term adverse effects of the RVPAS and suggests that the decision to choose one shunt type over the other should be driven by factors other than risk of mid-term heart failure. It is important to recognize, however, that the present analysis was limited to those subjects discharged to home after the Norwood procedure and hence does not provide insights into implications of shunt type or immediate post-Norwood heart failure.

Several factors were associated with the development of heart failure in the first year. These include peri-operative factors such as the use of ECMO immediately after the Norwood procedure. Echocardiographic findings were also associated with the development of heart failure: a lower fractional area change at the time of Norwood hospital discharge was associated with early heart failure. This finding is logical and consistent with earlier studies.[15,16] Surprisingly, Hispanic ethnicity was associated with a lower risk of early heart failure. The mechanisms to explain such a link remain unclear, and a *p*-value close to 0.05 in the context of multiple testing could indicate a chance finding. The use of predominant deep hypothermic circulatory arrest (DHCA), compared with predominant regional cerebral perfusion, was associated with a lower risk of developing heart failure. It is possible that this represents center variation that is not accounted for completely in the model. Fewer peri-operative factors were associated with the development of heart failure beyond the first year. This suggests that clinical factors that come into play after discharge from the Norwood procedure, such as the peri-operative Stage II procedure course, the accommodation of the pulmonary vascular bed, and the development of volume-loading lesions, may have a greater impact on the development of heart failure after the first year of life.

Eight percent of subjects were listed for heart transplant. The risk for heart transplant listing was greatest in the first 18 months of life, with the highest risk occurring immediately after Norwood hospital discharge. This may not be surprising, as early single ventricle hemodynamics are less favorable and the Stage II procedure has the potential to reduce the volume load on the heart and create more efficient circulation.[17] Heart failure and ventricular function often impact the decision on timing of Stage II operation. In an analysis of the SVR cohort, Schwartz et al found that ventricular dysfunction was the reason for early Stage II development in 33 of the 199 (16.5%) non-elective cases.[18] After the first 12 months, the risk of developing heart failure is approximately 3% per year. It remains to be determined whether this same hazard rate persists into later school age and adolescence. Previous studies have shown the risk of death or transplant for those with HLHS is relatively low in the school-age group.[19]

Little has been reported about symptomatic heart failure in young children with HLHS. We found only a small proportion of children with advanced symptomatic heart failure at 6 years of age. One of the challenges of quantifying heart failure in young children relates to the standardized clinical measures. In the SVR Trial, we administered the Ross heart failure score at 1, 2, 3, and 4 years of age; starting at age 5 years, we administered the NYHA scale. We found the Ross heart failure score to be too inconsistent to use as a reliable clinical end-point. For this reason, we limited the analyses only to NYHA scores. We found that, at 6 years, only 4.2% of children were NYHA Class IV and not listed for heart transplant. This may reflect a strategy to list single ventricle patients for transplant once they reach Stage IV heart failure rather than pursue medical management.[20,21]

Our inability to reliably identify younger patients with advanced heart failure not listed for transplant, and our reliance on the NYHA classification for older children, limits the analysis in our study to children with very advanced heart failure, and it is not possible to draw conclusions regarding the incidence or management of mild to moderate heart failure in the SVR Trial cohort.

Although our sample size was small, we found that a number of therapeutic agents were used to manage those with NYHA Class IV heart failure. These included ACE inhibitors, diuretics, and digoxin. It is unclear which medical therapies should be employed to manage children with severe heart failure.[22] Surprisingly, none of the subjects were managed with a β-blocker, and several subjects were not receiving any heart failure medications. This may reflect uncertainty as to the value of conventional heart failure medications in this population, particularly after 2 pediatric trials demonstrated minimal benefit of these medications in the congenital heart disease population.

We found that, among subjects listed for heart transplantation, waitlist mortality was 30.7%. This is consistent with previous registry data reporting high waitlist mortality for young children with congenital heart disease.[23] Many factors account for this elevated waitlist mortality. Ventricular assist devices (VADs) are used much less commonly in the single ventricle population, and, when they have been used, success rates were found to be low.[24] In addition, patients palliated with the Norwood procedure have shown a

high rate of allosensitization due to the use of allograft material and frequent transfusions of blood products,[25] which further limits donor availability. Many centers seek to reduce the risks conferred by allosensitization through a strategy of virtual crossmatching, which often requires longer waitlist times.[26] The outcomes after transplant in this population with 72.7% of subjects surviving to 6 years of age are in keeping with published data. Young children with previous surgery for congenital heart disease are known to have an increased risk of post-transplant mortality.[27] The findings in this study support the recent modification of the heart transplant allocation system in the United States to prioritize those with congenital heart disease—modifications that took effect after the conclusion of the SVR Trial.[28]

One of the strengths of the SVR Trial is that all deaths had independent adjudication as to cause. This is important because most estimates of heart failure–related deaths have come from clinical databases or administrative data sets with recognized limitations.[29] Only very recently has a heart failure registry in children been established.[30] Moreover, in the single ventricle population, it cannot be assumed that every child with severe heart failure would come to heart transplant listing before death. Marked allosensitization, vascular complications, rapid deterioration, or parental preferences may have precluded heart transplant listing. We found that, among those children discharged to home after the Norwood procedure, the risk of heart failure death was highest in the first year. It is possible that prompt recognition of heart failure may have allowed some of these children to be stabilized, evaluated, and listed for heart transplantation. However, heart failure progression in this population can be rapid and deterioration may still occur in some patients despite optimal medical care.[31]

In conclusion, heart failure occurs in nearly 15% of children who achieve discharge after the Norwood procedure. Among transplant-free survivors to 6 years of age, $<5\%$ of children with palliated HLHS have advanced symptomatic heart failure. Future follow-up of the SVR cohort is needed to investigate the risk of developing heart failure in later school age or adolescence.

Disclosure statement

The authors have no conflicts of interest to disclose. This work is solely the responsibility of the authors and does not necessarily represent the official views of National Heart, Lung, and Blood Institute or National Institutes of Health.

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Appendix Single Ventricle Reconstruction Trial participants

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at www.jhltonline.org

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