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ORIGINAL ARTICLE

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Trajectory of right ventricular indices is an early predictor of outcomes in hypoplastic left heart syndrome

Andrew S. Kim MD[1] | Colleen M. Witzenburg PhD[2] | Mark Conaway PhD[3] | Jeffrey E. Vergales MD[1] | Jeffrey W. Holmes MD, PhD[2,4] | Thomas J. L'Ecuyer MD[1] | Peter N. Dean MD[1]

[1]Division of Cardiology, Department of Pediatrics, University of Virginia, Charlottesville, Virginia

[2]Department of Biomedical Engineering, University of Virginia, Charlottesville, Virginia

[3]Division of Translational Research and Applied Statistics, Department of Public Health Sciences, University of Virginia, Charlottesville, Virginia

[4]Department of Medicine, University of Virginia, Charlottesville, Virginia

Correspondence
Andrew S. Kim, Division of Cardiology, Department of Pediatrics, University of Virginia, 1215 Lee St. Charlottesville, VA 22903.
Email: Akim@childrensheartcenter.com

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Abstract

Background: Children with hypoplastic left heart syndrome (HLHS) have risk for mortality and/or transplantation. Previous studies have associated right ventricular (RV) indices in a single echocardiogram with survival, but none have related serial measurements to outcomes. This study sought to determine whether the trajectory of RV indices in the first year of life was associated with transplant-free survival to stage 3 palliation (S3P).

Methods: HLHS patients at a single center who underwent stage 1 palliation (S1P) between 2000 and 2015 were reviewed. Echocardiographic indices of RV size and function were obtained before and following S1P and stage 2 palliation (S2P). The association between these indices and transplant-free survival to S3P was examined.

Results: There were 61 patients enrolled in the study with 51 undergoing S2P, 20 S3P, and 18 awaiting S3P. In the stage 1 perioperative period, indexed RV end-systolic area increased in patients who died or needed transplant following S2P, and changed little in those surviving to S3P (3.37 vs −0.04 cm^2/m^2, $P = .017$). Increased indexed RV end-systolic area was associated with worse transplant-free survival. (OR = 0.815, $P = .042$). In the interstage period, indexed RV end-diastolic area increased less in those surviving to S3P (3.6 vs 9.2, $P = .03$).

Conclusion: Change in indexed RV end-systolic area through the stage 1 perioperative period was associated with transplant-free survival to S3P. Neither the prestage nor poststage 1 indexed RV end-systolic area was associated with transplant-free survival to S3P. Patients with death or transplant before S3P had a greater increase in indexed RV end-diastolic area during the interstage period. This suggests earlier serial changes in RV size which may provide prognostic information beyond RV indices in a single study.

KEYWORDS

echocardiography, hypoplastic left heart syndrome, outcomes, predictor, right ventricular area, serial measurements, single ventricle palliation

Abbreviations: FAC, fractional area change; HLHS, hypoplastic left heart syndrome; RV, right ventricular; RVEDA, right ventricular end-diastolic area; RVESA, right ventricular end-systolic area; S1P, stage 1 palliation; S2P, stage 2 palliation; S3P, stage 3 palliation.

1 | INTRODUCTION

Hypoplastic left heart syndrome (HLHS) is a rare congenital heart defect occurring in about 2 per 10 000 live births.[1,2] The hallmark feature of HLHS is an underdeveloped left ventricle that is inadequate to support systemic circulation and, without intervention, this condition is invariably fatal. Since there is no cure, treatment options for these patients include heart transplantation or more typically, three-staged palliative procedures that allow these patients to grow to adulthood with a systemic right ventricle (RV). Survival after staged palliation of HLHS has drastically improved over the past decade, but mortality remains significant with data from the Single Ventricle Reconstruction Trial showing a 6-year overall mortality/transplantation of 39%.[3]

The relatively poor survival in patients with HLHS is likely due in large part to the inability of the single RV to adapt and perform as the systemic ventricle through staged palliation. When the RV dysfunction occurs typically, cardiac transplantation is the only long-term option. Given the high rate of transplant wait list mortality,[4] measurements to predict which patients will require transplantation prior to staged palliation completion and which patients will successfully complete the staged palliative procedures are needed, but not available.

HLHS patients are regularly assessed via echocardiography and clinic visits. Objective echocardiographic measurements such as fractional area change (FAC) and two-dimensional (2D) tricuspid annular plane systolic excursion (TAPSE), however, are not routinely performed for the purpose of predicting outcomes. Previous studies have looked at 2D echocardiographic indices of the RV in HLHS patients at various stages of palliation.[5-15] Of these studies, only three to our knowledge have associated these indices to patient outcomes[5,6,9] and none have looked at the trajectory of right ventricular (RV) indices and related the change in these indices to outcomes.

The aim of this study was to determine whether the trajectory of RV indices from serial echocardiograms in the first year of life (during the first two-staged palliative procedures) was associated with transplant-free survival to stage 3 palliation (S3P, Fontan procedure). We anticipate that better measures of RV function during the first year of life, quantified by indexed ventricular areas, FAC and 2D TAPSE, will be associated with transplant-free survival to S3P. We further hypothesize that smaller increase in RV diameter and area over time will be associated with improved transplant-free survival to S3P and that the trajectory of these RV indices will be better associated with transplant-free survival compared to measurement at a single time point.

2 | METHODS

2.1 | Study design

A retrospective review of all patients with HLHS who underwent stage 1 palliation (S1P) between October 2000 and October 2015 at the University of Virginia's Children's Hospital and survived the initial hospitalization was performed. The study was approved by the University of Virginia's Institutional Review Board. Patients were recruited from the institutional database according to diagnosis and surgical interventions. The diagnosis of HLHS was made on the basis of echocardiographic imaging showing mitral valve stenosis or atresia as well as aortic valve stenosis or atresia with a diminutive left ventricle, ascending aorta, and aortic arch. Per center protocol and preference, all patients had a Norwood/Sano procedure as S1P, a bidirectional Glenn procedure as stage 2 palliation (S2P), and a Fontan procedure as S3P. Patients with unbalanced atrioventricular canal defects or double outlet RVs were excluded as the echocardiogram parameters which would be inherently different. The primary endpoint was death or transplant prior to S3P. Patients who survived to S3P were included in Group 1 and patients who underwent transplant or died prior to S3P were included in Group 2.

2.2 | Echocardiographic analysis

All echocardiograms were performed as a part of routine patient care. Echocardiograms were performed by congenital cardiac sonographers using either Philips Epiq 7 or Philips iE33 ultrasound machines. Measurements of the RV from the apical four-chamber view were done post hoc by the primary author using Philips Xcelera R4.1 Build 1173 software for studies completed after 2012 and AGFA IMPAX CRS software for studies done prior 2012.

ASK analyzed the echocardiograms done prior to S1P, at discharge from S1P hospitalization, prior to S2P and at discharge from S2P hospitalization. RV measurements were done per guidelines established in previous studies.[17-19] A tracing of RV endocardial border from the lateral tricuspid annulus along the free wall to the apex and back to the medial tricuspid annulus along the interventricular septum was performed to quantify RV area. The area of the RV was measured both at end-systole (RVESA) and end-diastole (RVEDA) allowing for the quantification of RV FAC ([RVEDA-RVESA/RVEDA]). RV areas indexed to body surface area were measured. Body surface area was determined using the Boyd equation.[20] RV basal diameter was measured at the maximal transverse diameter of the basal 1/3 of RV inflow at end-diastole.[18] RV mid-cavity diameter was measured approximately halfway between the maximal basal diameter and the apex at the level of the papillary muscles at end-diastole.[18] RV longitudinal length was measured from the level of the tricuspid valve annulus to the apex.[19] Finally, 2D TAPSE was measured as the difference in distance from the lateral tricuspid valve annulus to the skin-transducer interface between systole and diastole.[17]

2.3 | Statistical analysis

Two-tailed *t* test with equal variance was used to analyze continuous demographic variables (gestational age and birthweight). The chi-squared test was used to analyze categorical variables. Repeated measures regression models were used to compare RV indices preprocedure and postprocedure between groups defined by outcomes following the procedures. Logistic regression, using Firth penalized

regression, was used to assess the association of echo parameters on the probability of transplant-free survival. Survival analysis using a Kaplan-Meier estimator was used using the median change in RV indices. A *P* value of < .05 was defined as statistically significant.

3 | RESULTS

There were a total of 61 patients that met inclusion criteria. Of these 61 patients, 51 patients underwent S2P. In the group of 10 that did not undergo S2P, 1 was transplanted and the remaining 9 died. Of the 51 patients that underwent S2P, 13 (26%) died or were transplanted prior to S3P, 20 (39%) underwent S3P, and the remaining 18 (35%) are alive awaiting S3P (Figure 1). The 18 patients that were alive and awaiting S3P were not included in the analysis. There were no significant differences in patient gender, gestational age, birth weight, HLHS type, or the degree of initial tricuspid valve regurgitation in our study population between groups (Table 1).

3.1 | Echocardiographic indices at single time point during palliation

Figure 2A,B shows the evolution indexed RV end-systolic area and indexed RV end-diastolic area throughout the study. In the pre-S2P echocardiogram, both indexed RV end-diastolic and end-systolic areas were significantly higher in Group 2: (36.54 vs 29.06 cm^2/m^2, $P = .021$) and (26.36 vs 19.31 cm^2/m^2, $P = .013$). Both differences in RV indices were associated with increased risk of transplant or mortality (OR = 0.9, 95% CI 0.84, 1, $P = .05$ for indexed RV end-diastolic area, OR = 0.89, 95% CI 0.8, 0.99, $P = .04$ for indexed RV end-systolic area). At the discharge echocardiogram from S2P hospitalization, only indexed RV end-systolic area was significantly higher (26.95 vs

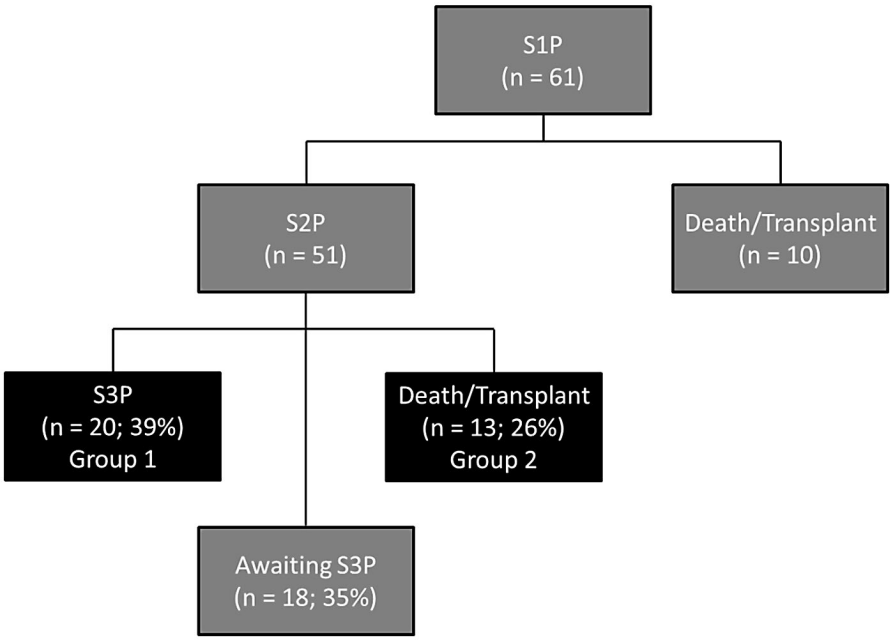

FIGURE 1 Flowchart showing the clinical course for our study population. Group 1 consists of patients with transplant-free survival to S3P and Group 2 consists of patients who underwent transplantation or died followed S2P

TABLE 1 Patient population

Characteristic	Group 1 (survived to S3P)	Group 2 (mortality or transplant prior to S3P)	*P* value
Gender	Male: 13	Male: 12	0.110
	Female: 7	Female: 1	
Gestational age (wks)	38.3	38.8	0.392
Birth weight (kg)	3.1	3.3	0.218
HLHS type	MS/AS: 9	MS/AS: 6	0.453
	MS/AA: 3	MS/AA: 0	
	MA/AA: 8	MA/AA: 7	
Degree of tricuspid valve regurgitation at initial echocardiogram	None: 11	None: 5	0.111
	Trivial: 1	Trivial: 4	
	Mild: 8	Mild: 4	

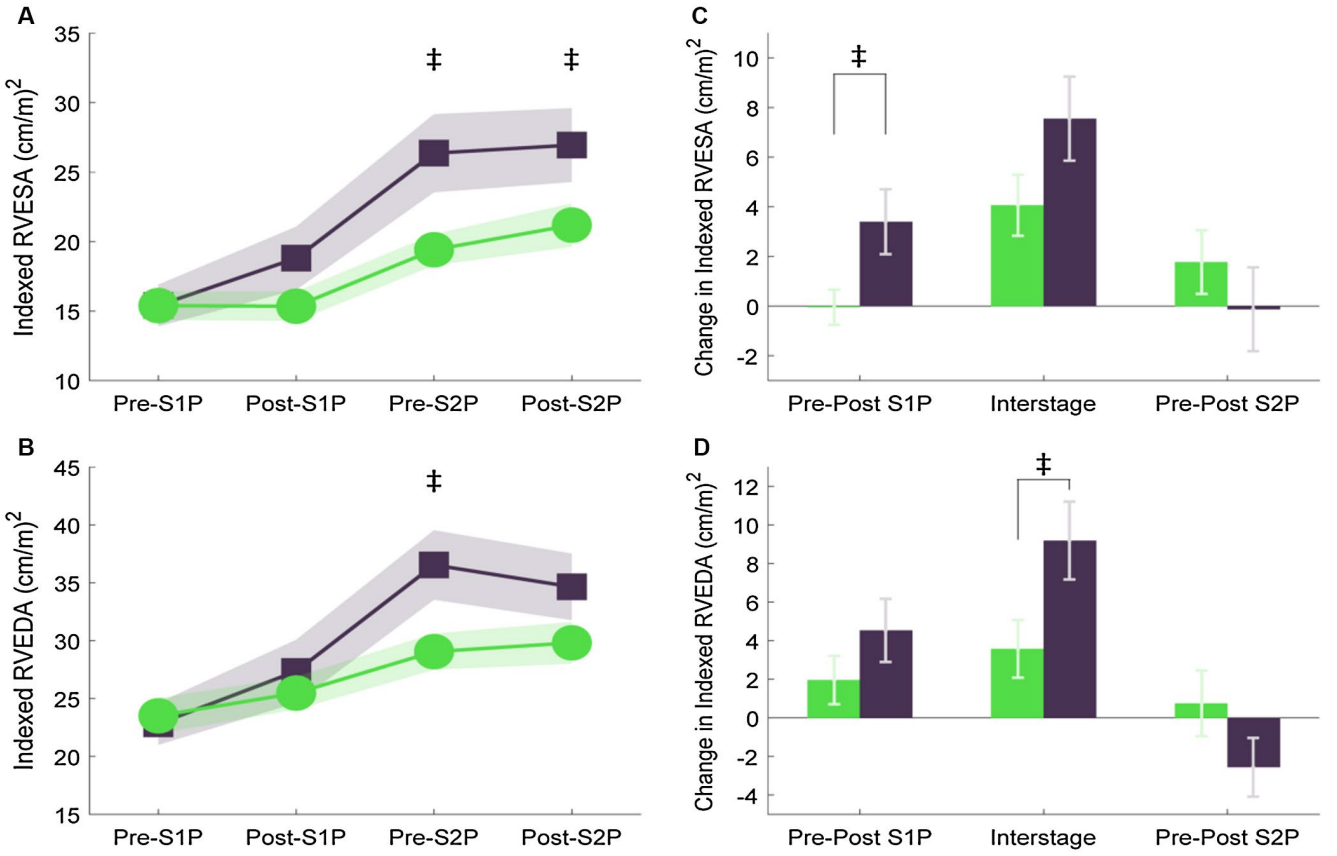

FIGURE 2 Indexed right ventricular end-systolic area (RVESA) (A) and indexed right ventricular end-diastolic area (RVEDA) (B) at different time points throughout the study for Group 1 (light green circles) and Group 2 (dark purple squares). Shaded regions indicate mean ± SEM and ‡ indicate $P < .05$. The changes in indexed RVESA (C) and indexed RVEDA (D) between time points throughout the study for Group 1 (light green bars) and Group 2 (dark purple bars). Error bars indicate mean ± SEM and ‡ indicate $P < .05$

21.18 cm^2/m^2, $P = .05$). This was not associated with increased risk of transplant or mortality.

3.1.1 | Changes between pre-S1P and post-S1P

In the stage 1 perioperative period (before vs at discharge from S1P), indexed RV end-systolic area changed little in Group 1 (survival to S3P) but increased in Group 2 (death or transplant following S2P) (−0.04 vs 3.40 cm^2/m^2, $P = .017$) (Table 2, Figure 2C). This increase in indexed RV end-systolic area was associated with increased risk of transplant or mortality (OR = 0.815, 95% CI 0.668, 0.993, $P = .042$) (Table 3).

RV diameters, FAC, indexed end-diastolic area, and TAPSE were not significantly different between the two groups and were not associated with risk of transplant or mortality.

3.1.2 | Changes during the interstage (between S1P and S2P) period

In the period between S1P discharge and S2P ("interstage period"), indexed end-diastolic area increased in both Group 1 and Group 2 (Figure 2D), but had a significantly greater increase in Group 2 (9.2 vs 3.6, $P = .03$) (Table 2). This greater increase trended toward an association with increased risk of transplant or mortality, but was not statistically significant (OR = 0.897, 95% CI 0.8, 1.006, $P = .063$) (Table 3).

RV diameters, indexed end-systolic area, TAPSE, and FAC were not significantly different between groups and were not associated with reduced risk of transplant or mortality.

In addition, in the interstage period between S1P and S2P, overall survival was 42% for those with median indexed RV end-diastolic area change greater than 5 cm^2/m^2 and 83% for those with median indexed RV end-diastolic area change less than 5 cm^2/m^2 ($P = .05$) (Figure 3).

3.1.3 | Changes between pre-S2P and post-S2P

In the stage 2 perioperative period (before and at discharge from S2P), no change in RV size or function was significantly different between groups or associated with transplant-free survival to S3P.

4 | DISCUSSION

In this study, in a population of patients with HLHS, changes in echocardiographic indices in the first 6 months of life (stage 1 perioperative

TABLE 2 RV indices

Time interval	RV indces	Group 1 Mean (SD)	Group 1 n	Group 2 Mean (SD)	Group 2 n	*P* value
Pre-Post-S1P						
	Mid-cavity diameter (cm)	0.32 (0.42)	20	0.36 (0.49)	13	0.771
	TAPSE (cm)	−0.02 (0.15)	19	−0.05 (0.11)	13	0.531
	Indexed RV end-diastolic area (cm^2/m^2)	1.97 (5.62)	20	4.53 (5.9)	13	0.218
	Indexed RV end-systolic area (cm^2/m^2)	−0.04 (3.18)	20	3.40 (4.71)	13	0.017
	Fractional area change (%)	5.39 (9.47)	20	−0.6 (11.87)	13	0.118
Interstage period						
	Mid-cavity diameter (cm)	0.56 (0.55)	20	0.76 (0.61)	13	0.33
	TAPSE (cm)	0.1 (0.17)	20	0.07 (0.21)	13	0.749
	Indexed RV end-diastolic area (cm^2/m^2)	3.58 (6.68)	20	9.19 (7.28)	13	0.03
	Indexed RV end-systolic area (cm^2/m^2)	4.06 (5.51)	20	7.56 (6.11)	13	0.098
	Fractional area change (%)	−6.79 (12.6)	20	−2.98 (8.09)	13	0.342
Pre-Post-S2P[a]						
	Mid-cavity diameter (cm)	0.06 (0.6)	20	−0.01 (0.5)	12	0.729
	TAPSE (cm)	−0.05 (0.16)	20	−0.11 (0.21)	12	0.408
	Indexed RV end-diastolic area (cm^2/m^2)	0.76 (7.61)	20	−2.56 (5.27)	12	0.195
	Indexed RV end-systolic area (cm^2/m^2)	1.77 (5.73)	20	−0.13 (5.85)	12	0.374
	Fractional area change (%)	−3.73 (8.17)	20	−5.8 (9.45)	12	0.517

[a]1 patient had mortality shortly after S2P thus did not have a post-S2P echocardiogram.

period, the "interstage" period, and stage 2 perioperative period) were found to be associated with transplant-free survival to staged palliative completion. We identified two changes in echocardiographic indices that were significantly associated with the risk of transplant or mortality prior to S3P. First, a perioperative increase in RV indexed end-systolic area during the S1P hospital stay (Figure 2C) was associated with worse outcomes, suggesting a potential long-term impact of RV enlargement at this early time point. Second, a larger increase (Figures 2D and 3) in RV end-diastolic area between S1P and S2P was associated with worse outcomes, suggesting that dilation during this period may be a marker for adverse remodeling. Future studies could investigate the potential positive effect of congestive heart failure medications on this remodeling. Importantly, these *changes* in RV size occurred early in the course of surgical palliation, preceding the observation of significant differences in RV size at a single time point. While prior studies have evaluated RV function or size at a single time point, to our knowledge, this is the first to look at changes in serial indices and relate those to outcomes.

Between stage 1 and stage 2, we observed mortality/transplantation of 16%, comparable to mortality/transplantation of 12%, 17%, and 15% reported by the Single Ventricle Reconstruction Trial[3], a meta-analysis[21] and recent study with standardized management,[22] respectively. Additionally, the overall mortality/transplantation of 38% we observed was comparable to the 3-year rate of 36% reported in the Single Ventricle Reconstruction Trial[4] and the 3-year rate of 30% reported by Hansen et al.[23]

TABLE 3 Regression: predicting survival to S3P

Time interval	RV indices	Odds ratio	95% CI	*P* value
Pre-Post-S1P				
	Mid-cavity diameter	0.794	(0.158, 3.982)	0.780
	TAPSE	5.147	(0.024, >999)	0.549
	Indexed RV end-diastolic area	0.928	(0.818, 1.054)	0.252
	Indexed RV end-systolic area	0.815	(0.668, 0.993)	0.042
	Fractional area change	1.053	(0.98, 1.133)	0.160
Interstage period				
	Mid-cavity diameter	0.557	(0.160, 1.947)	0.360
	TAPSE	1.768	(0.038, 82.42)	0.771
	Indexed RV end-diastolic area	0.897	(0.8, 1.006)	0.063
	Indexed RV end-systolic area	0.906	(0.792, 1.035)	0.147
	Fractional area change	0.971	(0.909, 1.037)	0.381
Pre-Post-S2P				
	Mid-cavity diameter	1.250	(0.342, 4.566)	0.735
	TAPSE	5.244	(0.085, 325)	0.431
	Indexed RV end-diastolic area	1.070	(0.952, 1.203)	0.254
	Indexed RV end-systolic area	1.055	(0.925, 1.204)	0.423
	Fractional area change	1.027	(0.944, 1.118)	0.534

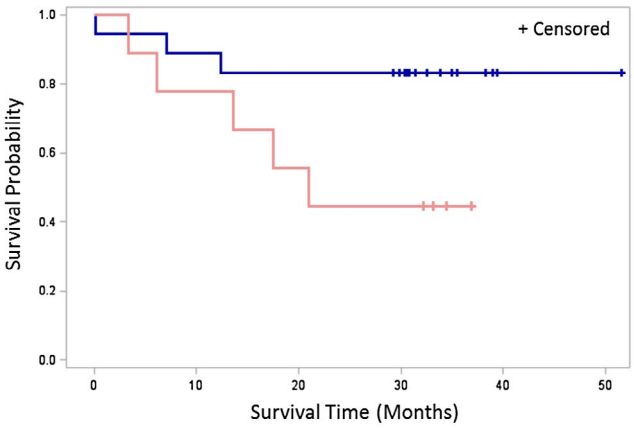

FIGURE 3 Median change in RV indexed end-diastolic area is 5 cm^2/m^2. Survival analysis showing the overall survival probability as a function of months in patients with a change in RV indexed end-diastolic area of less than 5 cm^2/m^2 (blue) and greater than 5 cm^2/m^2 (pink) during the interstage period. Patients with a smaller increase are significantly ($P = .05$) more likely to survive to S3P

Survival of patients with HLHS has improved with advances in surgical technique and experience, but an inherent limitation remains the fact that the patient is reliant on a RV as the systemic pumping chamber. This increased morbidity and mortality was shown in a study by d'Udekem et al.,[24] who found that the most potent risk factor for negative outcome after single ventricle palliation was RV dominance. A study by Kutty et al.[15] looked at 18 patients with HLHS at four time points from diagnosis of HLHS to S2P using real-time three-dimensional echocardiography. Indexed end-systolic volume was noted to increase throughout staged palliation and there was an increase in indexed end-diastolic volume from pre-S1P to post-S1P. In addition, they found a trend toward decreasing ejection fraction throughout staged palliation, with significant decreases noted in the stage 1 and stage 2 interstage periods. These changes, however, were not associated with outcomes. With the established importance of the systemic RV as a risk factor for negative outcome and the RV anatomic and functional changes noted to occur over time, our study sought to elucidate how these changes in the systemic RV in HLHS patients are associated with outcomes.

Multiple prior studies have tried to relate RV functional and/or volumetric indices at a single time point to outcomes. One of the earliest studies relating RV indices in a single echocardiogram to outcome was done by Altmann et al.,[5] who looked at the impact of initial RV function in a single echocardiogram prior to the Norwood operation on outcomes. They found that initial RV dysfunction did not impact early survival, but intermediate and overall survival was significantly decreased in those with initially diminished RV function. Frommelt et al.,[10] looked at the impact of shunt type on echocardiographic indices in children with single RV anomalies using the SVR Trial dataset and found that at the 14-month echocardiogram, a larger RV indexed end-systolic and end-diastolic volumes and areas, lower RV ejection fraction, and moderate or greater tricuspid valve regurgitation were associated with an increased risk of transplant or death between the 14-month echocardiogram and Fontan palliation.

In contrast to Altmann et al., none of the analyzed RV indices at our pre-S1P echocardiogram were associated with transplant-free survival in our study. Additionally, none of the analyzed RV indices at the post-S1P echocardiogram were associated with transplant-free survival. This difference may possibly be attributable to a different patient population as well as differences in surgical technique and improvements in postoperative care allowing better management (and thus survival) of patients who previously may have had mortality. When considering the perioperative period around S1P, only the *change* in indexed RV end-systolic area was associated with transplant-free survival to S3P, suggesting that the early trajectory of change in RV indices may be better associated with outcomes rather than measurement at a single time point. Using area as a 2D surrogate for Kutty et al.'s measurement of volume, there was an overall increase in both end-systolic and -diastolic areas and an overall decline in FAC through staged palliation. What is interesting to note, however, is that in the peri-S1P period, indexed RV end-systolic area increased in those who died or had transplant prior to S3P, while it changed little in those who had transplant-free survival to S3P.

Through the course of staged palliation, there are different and changing hemodynamic loading conditions inherent in proceeding through staged single ventricle palliation. With S1P, the systemic RV is volume loaded so an increase in area between S1P and S2P is not surprising. Indeed, in our study, indexed areas increased in both groups, but the change in indexed end-diastolic area during the "interstage period" was larger for patients who died or required transplant prior to the third-staged palliative procedure. This is an important finding because young patients who are identified as higher risk of not surviving to S3P may benefit from increased surveillance, more intensive medical management, and earlier listing for cardiac transplant.

With S2P, the systemic RV is volume unloaded so one could predict that either RV area would decrease as has been described previously,[11] or the rate of increase in area would diminish. During the stage 2 perioperative period, both indexed end-diastolic and systolic area rates of increase appeared to diminish in our study.

5 | LIMITATIONS

There are a number of limitations that must be considered. First, this was a single-center study where only Norwood procedures with Sano modifications were performed; thus, these results may not be generalizable to other centers, particularly centers that perform the Blalock-Taussig shunt modification of the Norwood procedure. Second, since this was a retrospective review, the timing of the echocardiograms was not standardized. While the timing of the prepalliation echocardiograms was fairly standardized, the postpalliation studies were performed at hospital discharge which varied in regard to time from the operation and age of patient. We must also consider the long-time frame of the cohorts of the study during which time surgical techniques, operative strategies, as well as postoperative ICU management are likely to have been refined and changed.

6 | CONCLUSIONS

In summary, our findings suggest that following serial measurements of the RV, particularly early changes in indexed area, may assist clinicians in better recognizing those patients who will survive without transplant to S3P and those who will either die or require heart transplant prior to S3P. In addition, the absolute change of RV indices appears to be better associated with transplant-free survival compared to measurement of RV indices at a single time point.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest with the contents of this article.

AUTHORS' CONTRIBUTIONS

The authors' contributions were as follows: The study was conceived by ASK, CMW, JEV, JWH, and TJL. ASK made all echocardiographic measurements. ASK, CMW, and PND designed the study and analyzed the data. MC performed statistical calculations. ASK and CMW wrote the first draft of the manuscript. JWH and PND critically revised the manuscript. All authors have read and approved the final manuscript.

ORCID


Andrew S. Kim https://orcid.org/0000-0002-1253-0506

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