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ORIGINAL ARTICLE

Right Ventricular Remodeling in Hypoplastic Left Heart Syndrome is Minimally Impacted by Cardiopulmonary Bypass: A Comparison of Norwood vs. Hybrid

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Abstract

Right ventricular (RV) remodeling in hypoplastic left heart syndrome (HLHS) begins prenatally and continues through staged palliations. However, it is unclear if the most marked observed remodeling post-Norwood is secondary to cardiopulmonary bypass (CPB) exposure or if it is an adaptation intrinsic to the systemic RV. This study aims to determine the impact of CPB on RV remodeling in HLHS. Echocardiograms of HLHS survivors undergoing stage 1 Norwood ($n=26$) or Hybrid ($n=20$) were analyzed at pre- and post-stage 1, pre- and post-bidirectional cavo-pulmonary anastomosis (BCPA), and pre-Fontan. RV fractional area change (FAC), vector velocity imaging for longitudinal & derived circumferential deformation (global radial shortening (GRS) = peak radial displacement/end-diastolic diameter), and deformation ratio (longitudinal/ circumferential) were assessed. Both groups had similar age, clinical status and functional parameters pre-stage 1. No difference in RV size and sphericity at any stage between groups. RVFAC was normal (> 35%) throughout for both groups. Both Norwood and Hybrid patients had increased GRS ($p=0.0001$) post-stage 1 and corresponding unchanged longitudinal strain, resulting in decreased deformation ratio (greater relative RV circumferential contraction), $p=0.0001$. Deformation ratio remained decreased in both groups in subsequent stages. Irrespective of timing of the first CPB exposure, both Norwood and Hybrid patients underwent similar RV remodeling, with relative increase in circumferential to longitudinal contraction soon after stage 1 palliation. The observed RV remodeling in HLHS survivors were minimally impacted by CPB.

Keywords Single ventricle · Hypoplastic left heart syndrome · Adaptation · Cardiac function

Abbreviations

RV	Right ventricle
HLHS	Hypoplastic left heart syndrome
CPB	Cardiopulmonary bypass
BCPA	Bidirectional cavo-pulmonary anastomosis
FAC	Fractional area change
DHCA	Deep hypothermic circulatory arrest

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Introduction

Right ventricular dysfunction has long been known to be an independent risk factor for early and long-term mortality in hypoplastic left heart syndrome (HLHS) patients [1]. Recent studies have shown that RV deformation is associated with poor clinical outcomes in HLHS [2, 3], highlighting its potential as a clinical marker of early RV dysfunction, especially in the first interstage. Progressive change in RV deformation toward increasing reliance on circumferential contraction has been noted in HLHS patients prenatally [4] with progression through postnatal palliative surgical stages [5, 6], with changes being the most prominent post-stage 1 Norwood [5–7]. Yet the pathophysiology for this phenomenon is unclear and is postulated to be a result of maladaptive response to increased afterload and preload, inadequate coronary artery flow reserve, and/or effects of ischemia from neonatal cardiopulmonary bypass (CPB) [8, 9]. Similar temporary and permanent deformation changes are observed following repair of other congenital heart diseases following CPB [10, 11].

This study aims to assess the impact of CPB on RV contraction patterns in HLHS survivors (survival to BCPA), by comparing those who have an earlier CPB (Norwood palliation) to those with later CPB (Hybrid procedure), at BCPA palliation.

Methods

Study Population

This was a multicenter, retrospective cohort study of patients with "classic" HLHS at two quaternary-level pediatric cardiac surgical centers, one specializing in the Norwood-Sano procedure (Stollery Children's Hospital, Edmonton) and the other in the Hybrid procedure (SickKids Hospital, Toronto), with follow-up to pre-Fontan. The patients undergoing the Hybrid procedure were randomly assigned to this intervention as part of a clinical protocol. Norwood-Sano procedure involves aortic arch repair, Damus–Kaye–Stansel anastomosis, Sano shunt insertion (5 mm RV-PA conduit) and atrial septectomy. The Hybrid procedure consists of bilateral 3.0 mm to 3.5 mm polytetrafluoroethylene graft pulmonary artery bands tightened to obtain oxygen saturations of 85% and a PDA stent (10 or 20 mm length). Atrial septostomies are routinely deferred to a separate procedure if the atrial communication becomes restrictive.

Patients who survived the first and second stages of surgical repair between January 2007 and December 2011 were included in the study in order to assess longitudinal changes. The study was continued to Pre-Fontan as both groups would have undergone CPB at this point in time with several years of follow-up, and it limits additional chronic factors that can influence cardiac function. We excluded variants of HLHS such as critical aortic stenosis, unbalanced atrioventricular septal defects and heterotaxy, as well as patients who were converted from a Hybrid to Norwood during the study period. The study was approved by the research ethics boards in both institutions.

Chart Reviews

Demographic and clinical data were collected at each time point and included preoperative bloodwork (arterial pH, lactate) and surgical information (age at surgery, CPB time, cross clamp time, intervention).

Two-Dimensional Echocardiography

Echocardiograms from five time points were analyzed in a longitudinal fashion: pre-stage 1 (birth till stage 1), post-stage 1 (2–4 weeks post-stage 1), pre-BCPA (preoperative echo for BCPA), post-BCPA (2–4 weeks post-BCPA), and pre-Fontan (preoperative echo for Fontan). Each time point was selected to assess the timing and persistence of changes—with the period immediately post-procedure reflecting acute changes and period immediately prior to the next palliative procedure reflecting chronic changes. Conventional measures of RV function and size were collected on 2D echocardiograms including, RV end-diastolic and end-systolic area (RVEDA, RVESA) indexed to body surface area (BSA), sphericity index and RV fractional area change (FAC).

Measurement of Ventricular Function Using Velocity Vector Imaging (VVI)

Stored 2D grayscale DICOM images (frame rate 30 Hz) were analyzed using TomTec Image Arena Version 4.6, which enabled cases from both centers to be exported to a centralized location and was assessed by an observer (KM) blinded to the stage 1 procedure of each patient. Cardiac loops from 4-chamber view showing the RV were analyzed. The endocardium was traced at end-systole (frame before the atrioventricular valve begins to open) and the myocardium was automatically tracked over the entire cardiac cycle based on the software's algorithm. Tracking accuracy was checked and manual adjustments were made when required. Measurements were made for three cardiac cycles and averaged measures were reported. Interobserver reliability testing of this method was performed and detailed in a previous study at our institution [4].

As in previous study, we recorded longitudinal displacement, strain, radial displacement, and calculated global radial shortening (GRS = peak radial displacement/end-diastolic diameter, a surrogate for circumferential "strain") and longitudinal to circumferential deformation ratio (Deformation ratio = longitudinal strain/GRS, which represents the relative contribution of longitudinal to circumferential contraction). Due to patient growth throughout the stages, longitudinal and radial displacement were indexed to BSA.

Statistical Analysis

Statistics are expressed as a mean and its standard error using Stata (v.13). T test with Bonferroni's correction assessed differences between procedures at baseline ($p < 0.01$). RV evolution over time was analyzed using longitudinal models based on generalized estimation equations [12]. Post-estimation pairwise comparisons with Bonferroni's correction ($p < 0.006$) assessed differences between the time periods within procedures. Statistical differences between procedures by time were assessed by *t* test with Bonferroni's correction ($p < 0.01$).

Results

Forty-six HLHS patients (26 Norwood, 20 Hybrid) were included in the study. Echocardiograms for Norwoods were performed at age 3.2 ± 3.6 days pre-Norwood, 22.3 ± 6.8 days post-Norwood, 5.4 ± 2.2 months pre-BCPA, 6.6 ± 1.9 months post-BCPA and 3.0 ± 1.1 years pre-Fontan. Echocardiograms for Hybrids were performed at age 5.9 ± 19.8 days pre-Hybrid, 24.7 ± 18.9 days post-Hybrid, 5.0 ± 1.0 months pre-BCPA, 6.7 ± 1.4 months post-BCPA and 3.2 ± 1.2 years pre-Fontan. Most clinical variables were equivalent between the groups at pre-stage 1 (Table 1). Norwood group had bypass time of 101 ± 32 min at the Norwood procedure and 57 ± 34 min at the Glenn procedure, whereas the Hybrid group had bypass time of 205 ± 61 min at the Glenn procedure. In the first interstage, Norwood group had 10 reinterventions for coarctation, 7 of the 10 were performed by catheterization, and Hybrid group had 3 reinterventions for coarctation, 2 of the 3 were performed by catheterization. Norwood patients initially had a slightly lower BSA than Hybrid patients at pre-stage 1 (0.20 vs. 0.22m^2, $p = 0.003$) and post-stage 1 (0.21 vs 0.24m^2, $p = 0.002$), but this difference was no longer significant from pre-BCPA to pre-Fontan.

Table 1 Baseline clinical statistics (mean ± standard error) by group

	NORWOOD ($n = 26$)	HYBRID ($n = 20$)
pH	7.37 ± 0.02	7.35 ± 0.02
Saturation (%)	85 ± 1.65	83 ± 2.58
Lactate (mmol/L)	1.07 ± 0.07	1.72 ± 0.12
BSA (m2)	0.20 ± 0.005	0.22 ± 0.005*
Age at first OR (days)	10.3 ± 0.12	10.7 ± 4.21

*p value < 0.01 relative to Norwood

RV Size and Function Comparison (Statistical Significance is $p < 0.006$ for within Intervention Comparisons Between Stages (Table 2), and Statistical Significance is $p < 0.01$ for Comparison Between Interventions)

There were no differences in RVEDAi, RVESAi or sphericity at any stage for each intervention and between the interventions. RVFAC was normal throughout the stages for both groups. There were no significant changes in RVFAC throughout the stages for both interventions, with normal systolic function throughout (RVFAC > 35%). However, Norwoods had a greater FAC post-stage 1 (Norwood 46.6% vs. Hybrid 37.5%, $p = 0.002$), while comparison between interventions at other stages were not significantly different. We did note that Hybrid FAC at pre-Fontan trended higher (Norwood 37.1% vs Hybrid 41.4%, $p = 0.03$) but was not statistically different (Fig. 1).

Norwood changes Through the Stages (Table 3, Statistical Significance $p < 0.006$)

An increase in GRS at post-Stage 1 ($p = 0.0001$), pre-BCPA ($p = 0.0001$) and pre-Fontan (p = 0.0001) was observed. Longitudinal strain increased (more negative) at pre-BCPA ($p = 0.005$); however, there was a return to baseline post-BCPA and pre-Fontan. A reduction in deformation ratio reflected these changes (a relative increased circumferential compared to longitudinal contraction) post-stage 1 ($p = 0.0001$) with a trend of persistent reduction through the other stages ($p < 0.04$).

Hybrid Changes Through the Stages (Table 4, Statistical Significance $p < 0.006$)

There was an increase in GRS post-Stage 1 ($p = 0.0001$), with a transient return to baseline pre- and post-BCPA, before a reduction at pre-Fontan ($p = 0.002$). Longitudinal strain was unchanged, except for a reductive trend (less negative) at post-BCPA ($p = 0.006$) that is followed by a return to baseline at pre-Fontan. A reduction in

Table 2 Right ventricular size, shape (sphericity index), and function comparison between stages (mean ± standard error)

	Pre-stage 1	Post-stage 1	Pre-BCPA	Post-BCPA	Pre-Fontan
Norwood					
RVEDAi (mm^2/m^2)	3278.70 ± 193.87	3439.44 ± 221.98	3359.28 ± 171.53	3023.85 ± 136.14	2877.29 ± 128.77$^{\wedge}$
RVESAi (mm^2/m^2)	1967.33 ± 132.06	1756.26 ± 157.30	1956.82 ± 139.34	1892.48 ± 99.94	1819.77 ± 100.20
Sphericity index	0.69 ± 0.04	0.72 ± 0.04	0.72 ± 0.04	0.72 ± 0.05	0.81 ± 0.06*
FAC (%)	39.90 ± 2.51	46.61 ± 2.45*	41.65 ± 2.13	37.73 ± 1.10	37.15 ± 1.28
Hybrid					
RVEDAi (mm^2/m^2)	2812.70 ± 126.20	2921.50 ± 165.88	3344.70 ± 180.89*	3062.43 ± 213.76	2894.12 ± 165.31
RVESAi (mm^2/m^2)	1683.60 ± 96.48	1814.95 ± 97.03	2111.60 ± 126.70*	1943.32 ± 173.60	1706.49 ± 119.70
Sphericity index	0.69 ± 0.05	0.74 ± 0.05	0.730 ± 0.04	0.74 ± 0.04	0.80 ± 0.04*
FAC (%)	40.32 ± 1.69	37.50 ± 0.95	37.15 ± 0.98	37.88 ± 1.65	41.42 ± 1.31

BCPA bicaval pulmonary anastomosis, *FAC* fractional area change, *RVEDAi* indexed right ventricular end-diastolic area, *RVESAi* indexed right ventricular end-systolic area

**p* value < 0.006 relative to Pre-stage 1, $^{\Upsilon}p$ value < 0.006 relative to Post-stage 1, ^*p* value < 0.006 relative to Pre-BCPA, $^{\#}p$ value < 0.006 relative to Post-BCPA

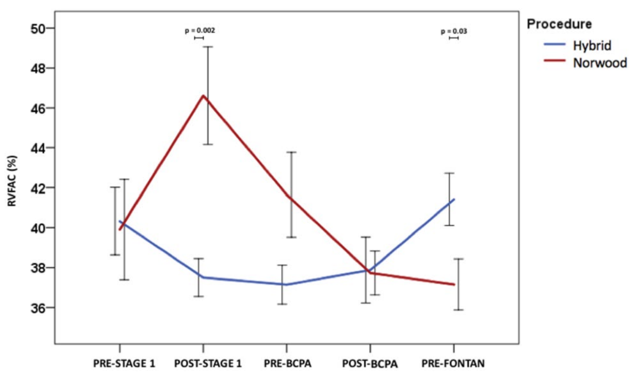

Fig. 1 RVFAC trends between procedures. Both groups had preservation of normal RVFAC throughout the stages. Decline in RVFAC in the Hybrid group compared to the Norwood group corresponds to the relative decrease in contribution of circumferential deformation compared to longitudinal deformation during interstage-1. (Statistical significance $p < 0.01$). *BCPA* Bicaval pulmonary anastomosis, *RVFAC* right ventricular fractional area change

deformation ratio reflected these changes (a relative increase in circumferential contraction), post-stage 1 ($p = 0.0001$) with a transient return to baseline pre- and post-BCPA, and subsequently a decrease at pre-Fontan ($p = 0.0001$).

RV Deformation Comparison Between Intervention Groups Using Velocity Vector Imaging (Figs. 2–4, Statistical Significance $p < 0.01$)

There were minimal differences between the groups' circumferential function except for during the first interstage, where the Norwood group had greater GRS (post-stage 1 $p = 0.02$, pre-BCPA $p = 0.008$) (Fig. 2). No significant difference in longitudinal strain between interventions (Fig. 3). The deformation ratio (Fig. 4) was similar, except the Norwood group showed more reliance on circumferential contraction pre-BCPA ($p = 0.008$).

Table 3 Deformation—comparison between stages—Norwood

	Pre-stage 1	Post-stage 1	Pre-BCPA	Post-BCPA	Pre-Fontan
Global radial shortening	− 0.06 ± 0.006	− 0.09 ± 0.007*	− 0.08 ± 0.005*	− 0.07 ± 0.006$^{\wedge\Upsilon}$	− 0.08 ± 0.006*$^{\Upsilon\wedge}$
Longitudinal strain (%)	− 12.32 ± 0.41	− 12.54 ± 0.43	− 13.80 ± 0.51*$^{\Upsilon}$	− 10.52 ± 0.48*$^{\Upsilon\wedge}$	− 13.39 ± 0.65$^{\#}$
Deformation Ratio	232.25 ± 20.98	157.61 ± 14.26*	179.7 ± 12.27	179.46 ± 13.53	194.03 ± 15.20

BCPA bicaval pulmonary anastomosis

**p* value < 0.006 relative to pre-stage 1, $^{\Upsilon}p$ value < 0.006 relative to post-stage 1, ^*p* value < 0.006 relative to pre-BCPA, $^{\#}p$ value < 0.006 relative to post-BCPA

Table 4 Deformation—comparison between stages—Hybrid

	Pre-stage 1	Post-stage 1	Pre-BCPA	Post-BCPA	Pre-Fontan
Global radial shortening	− 0.06 ± 0.003	− 0.07 ± 0.006*	− 0.06 ± 0.006	− 0.06 ± 0.008	− 0.07 ± 0.004*
Longitudinal strain (%)	− 12.94 ± 0.52	− 12.40 ± 0.49	− 12.17 ± 0.48	− 10.16 ± 0.82*$^{\Upsilon\wedge}$	− 13.36 ± 0.59$^{\#}$
Deformation ratio	240.07 ± 16.14	184.94 ± 12.99*	226.53 ± 16.35$^{\Upsilon}$	187.69 ± 20.76	189.17 ± 8.27*

BCPA bicaval pulmonary anastomosis

*p value < 0.006 relative to pre-stage 1, $^{\Upsilon}p$ value < 0.006 relative to post-stage 1, ^p value < 0.006 relative to pre-BCPA, $^{\#}p$ value < 0.006 relative to post-BCPA

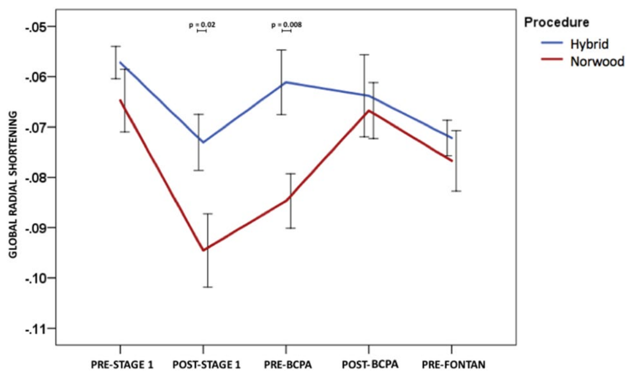

Fig. 2 Global radial shortening (GRS) between procedures. Increase in GRS is greater in the Norwood group than Hybrids at both post-stage 1 and pre-BCPA, with an overall higher GRS in Norwoods than hybrids through all the stages. (Statistical significance $p < 0.01$). *BCPA* bicaval pulmonary anastomosis

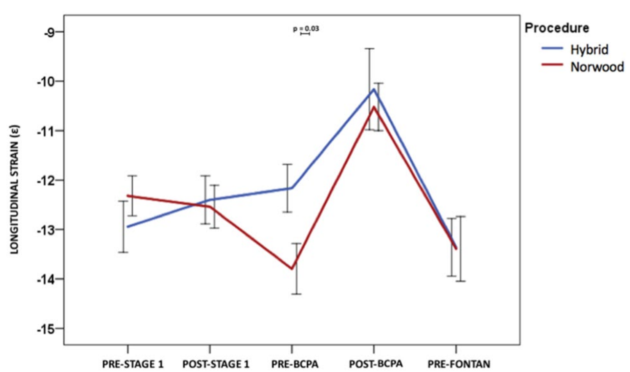

Fig. 3 Longitudinal strain between procedures. There was no significant patterns in the longitudinal strain alone in either group. Assessment of longitudinal strain alone can provide an incomplete picture of single RV function. (Statistical significance $p < 0.01$). *BCPA* bicaval pulmonary anastomosis

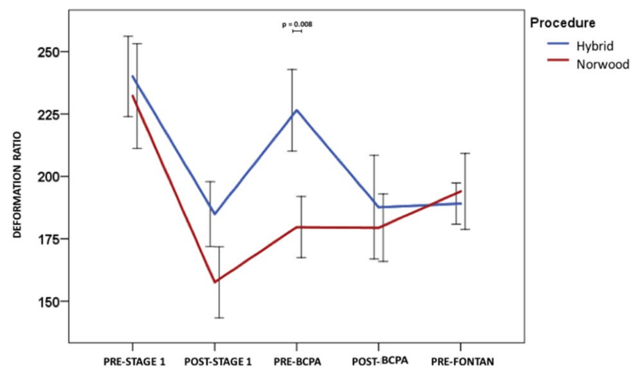

Fig. 4 Deformation ratio between procedures. Norwoods have a greater dependence on circumferential deformation (lower deformation ratio relative to baseline) immediately post-stage 1. Hybrids also have an initial dependence on circumferential deformation post-stage 1 but this resolves pre-BCPA which corresponds with a decrease in RVFAC. By Pre-Fontan both groups continue to show a greater reliance on circumferential contraction with stable RVFACs, irrespective of timing to CPB. *BCPA* bicaval pulmonary anastomosis

Discussion

The main finding of this study was a reduction in the longitudinal to circumferential deformation ratio secondary to an acute increase in circumferential contraction (GRS) after stage 1 palliation regardless of whether they underwent Norwood-Sano or Hybrid procedure. Our findings suggest CPB had minimal impact on the observed changes in RV contraction pattern through staged palliations.

Changes in RV Contraction Pattern

In normal biventricular hearts, the RV contraction has greater longitudinal shortening than circumferential [13]. However, in congenital lesions where the RV is under systemic pressure, the RV contraction has a greater reliance on circumferential contraction [14]. This has been postulated to be an adaptive response to systemic pressure and has been documented in patients with transposition of the great arteries after an atrial switch operation, congenitally corrected transposition of the great arteries, idiopathic pulmonary arterial hypertension and HLHS [8, 9, 15]. This change in HLHS RV contraction pattern was observed to begin during fetal life [4] and found to continue postnatally throughout the stages of palliation [6, 7] until early post-Fontan [7]. The lack of change in the RV contraction to lower longitudinal to circumferential deformation ratio at pre-BCPA is associated with greater mechanical dyssynchrony, ventricular dilation, increased ventricular mass and cardiac dysfunction [6, 7, 16]. This finding supports the concept that the RV contraction change in HLHS may be an adaptive and potentially beneficial process in response to the chronic increase in RV afterload and preload. However, studies have consistently found that the greatest alteration in RV contraction pattern for HLHS occurred after the Norwood-Sano procedure [6, 7], leading us to question whether CPB played a significant role in its progression.

Effects of CPB

The immediate and persistent negative impact of CPB on the myocardium and myocardial function has been documented in animal models, children and adults [11, 17, 18]. Animal studies showed that myocardial ischemic reperfusion injury from CPB and cardioplegic arrest provokes a systemic inflammatory and metabolic response that facilitates an apoptotic process, increases oxidative stress, elevates plasma fatty acids and inhibits glucose oxidation processes that are toxic to the myocardium, particularly in immature hearts which are more reliant on carbohydrate metabolism for energy [18–20]. In Tetralogy of Fallot, with prolonged bypass and cross clamp times [21], CPB has been linked with persistently decreased RV longitudinal strain and strain rate at follow-up, as late as 2 years post-repair [10]. In pediatric and adult cardiac transplantations, donor hearts undergoing ischemic times from 120 to 240 min, also consistently demonstrate decreased RV longitudinal strain immediately post-transplant with recovery in some, but not all, at 1 year post-transplant [17]. In comparison, our Norwood and Hybrid group both had similar combined CPB times over the two stages and were mostly greater than 120 min. Hence, the exposure to CPB during staged palliation may influence RV contraction patterns, especially in the neonatal period.

Early Changes in RV Contraction Pattern in HLHS

In this study, our findings in the Norwood group is consistent with our previous findings of an early increase in RV circumferential contraction (increased GRS, unchanged longitudinal strain and decreased deformation ratio), occurring less than 1 month after stage 1 palliation. In the Hybrid group, we also observed an early increase in RV circumferential contraction and maintained longitudinal strain. When comparing the two groups, there was no additional detrimental effect detectable in the Norwood group relative to the Hybrid group from the neonatal CPB, supporting the concept that the observed early changes in RV contraction patterns was minimally impacted by CPB. We speculate that the early change in RV contraction pattern maybe an adaptation to acute changes in loading conditions afterload post-stage 1 palliation.

We did note a relative decrease in RVFAC of the Hybrid group post-stage 1. This is somewhat consistent with Grotenhuis et al. observation of decreased RVFAC in Hybrids when compared to Norwood-BT shunts in their longitudinal study, raising the possibility that Hybrid procedure may have a transient risk of RV dysfunction in the early post-procedure period [22]. During the first interstage, Norwood patients did show a slightly greater reliance on circumferential contraction, the significance of which is unclear. There was no difference in longitudinal function between the groups for the other stages.

Post-BCPA, the reduction in both longitudinal and circumferential contraction in both groups, which may be secondary to reduction in RV preload. Again, even though the Hybrid patients underwent their first CPB at BCPA, no significant difference in RV deformation and function between the two groups could be found, again supporting the concept that CPB had minimal impact on RV remodeling. The lack of differences between both groups in all functional parameters at pre-Fontan suggests that no matter what time point CPB occurs, both groups eventually display the same adaptive phenomenon, with a greater dependence on circumferential contraction relative to its baseline soon after birth. We did note the Hybrid group RVFAC trended toward being greater at pre-Fontan which warrants further exploration as long-term detrimental impact of the Sano shunt on RV function has been previously postulated [23–25].

Clinical Implication

RV dysfunction is a recognized predictor of morbidity and mortality in HLHS [26, 27] and efforts to understand its pathophysiology and a search for potential beneficial therapeutic interventions remains an important endeavor. This paper adds to our understanding of the determinants of RV function and adaptation in HLHS during staged palliations. Our findings indicate that the changes in RV deformation pattern are present in both Hybrids and Norwoods, irrespective of CPB and should shift our focus to other potential early modifiers of RV remodeling. It remains unclear whether the increased reliance on circumferential contraction represents adaptation or maladaptation; however, its presence in these early survivors and current data in the literature would suggest this may be beneficial [5, 6, 8, 14, 15]. Nevertheless, longer term outcome studies are required to clarify. Lastly, this study highlights the importance of assessing both circumferential and longitudinal function parameters in single ventricular hearts for complete assessment of RV function and should be included in future investigations.

Limitations

The retrospective nature of this study limited our ability to obtain complete clinical data such as saturations at the time of imaging and short axis views on all patients. We calculated circumferential contraction based on assumed geometry from radial displacement parameters from the 4-chamber view [4]. As the assumptions regarding RV geometry was made equally in both cohorts, any error in estimation of absolute circumferential contraction is likely to be similar in both groups.

Conclusions

Irrespective of timing of the first CPB exposure, both Norwood and Hybrid patients underwent similar RV remodeling, with relative increase in circumferential to longitudinal contraction soon after stage 1 palliation. The observed RV remodeling in HLHS survivors were minimally impacted by CPB. Research into other potential modifiers of RV remodeling should be pursued.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interest.

Ethical Approval His retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The research ethics boards at the University of Toronto and Alberta approved this study.

Informed Consent This study is retrospective and was approved by both institutions research ethics boards.

References

1. Barber G, Helton G, Aglira BA, Chin AJ, Murphy JD, Pigott JD et al (1988) The significance of tricuspid regurgitation in hypoplastic left-heart syndrome. Am Heart J 116:1563–1567
2. Lin LQ, Conway J, Alvarez S et al (2018) Reduced right ventricular fractional area change, strain, and strain rate before bidirectional cavopulmonary anastomosis is associated with medium-term mortality for children with hypoplastic left heart syndrome. J Am Soc Echocardiogr 31:831–842
3. Colquitt JL, Loar RQ, Morris SA et al (2019) Serial strain analysis identifies hypoplastic left heart syndrome infants at risk for cardiac morbidity and mortality: a pilot study. J Am Soc Echocardiogr 32:643–650
4. Brooks PB, Khoo NS, Mackie AS et al (2012) Right ventricular function in fetal hypoplastic left heart syndrome. J Am Soc Echocardiogr 10:1068–1074
5. Tham EB, Smallhorn JF, Kaneko S et al (2014) Insights into the evolution of myocardial dysfunction in the functionally single RV between staged palliations using speckle-tracking echocardiography. J Am Soc Echocardiogr 27:314–322
6. Khoo NS, Smallhorn JF, Kaneko S et al (2011) Novel insights into RV adaptation and function in HLHS between the first 2 stages of surgical palliation. J Am Coll Cardiol 4:128–137
7. Kaneko S, Khoo NS, Smallhorn JF et al (2012) Single RV have impaired systolic and diastolic function compared to those of left ventricular morphology. J Am Soc Echocardiogr 25:1222–1230
8. Tan JL, Prati D, Gatzoulis MA et al (2007) The RV response to high afterload: comparison between atrial switch procedure, CCTGA, and idiopathic pulmonary arterial hypertension. Am Heart J 153:681–688
9. Hauser M, Bengel FM, Hager A et al (2003) Impaired myocardial blood flow and coronary flow reserve of the anatomical right systemic ventricle in patients with ccTGA. Heart 89:1231–1235
10. Li Y, Xie M, Wang X et al (2015) Impaired right and left ventricular function in asymptomatic children with repaired tetralogy of Fallot by two-dimensional speckle tracking echocardiography study. Echocardiography 32:135–143
11. Nawaytou HM, Yubbu P, Montero AE et al (2016) Left ventricular rotational mechanics in children after heart transplantation. Circ Cardiovasc Imaging. https://doi.org/10.1161/CIRCIMAGING.116.004848
12. Rabe-Hesketh S, Skrondal A (2008) Multilevel and longitudinal modeling using Stata, 2nd edn. Stata Press, USA
13. Hamdan A, Thouet T, Sebastian K et al (2008) Regional right ventricular function and timing of contraction in healthy volunteers evaluated by strain-encoded MRI. J Magn Reson Imaging 28:1379–1385
14. Pettersen E, Helle-Valle T, Edvardsen T et al (2007) Contraction pattern of the systemic RV shift from longitudinal to circumferential shortening and absent global ventricular torsion. J Am Coll Cardiol 49:2450–2456
15. Moceri P, Bouvier P, Baudouy D et al (2017) Cardiac remodelling amongst adults with various aetiologies of pulmonary arterial hypertension including Eisenmenger syndrome-implications on survival and the role of right ventricular transverse strain. Eur Heart J Cardiovasc Imaging 18:1262–1270
16. Friedberg MK, Silverman NH, Dubin AM et al (2007) RV mechanical dyssynchrony in children with HLHS. J Am Soc Echocardiogr 20:1073–1079
17. Monivas Palomero V, Mingo Santos S, Goirigolzarri Artaza J et al (2016) Two-dimensional speckle tracking echocardiography in heart transplant patients: two-year follow-up of right and left ventricular function. Echocardiography 33:703–713
18. Lopaschuk GD, Collins-Nakai R, Olley M et al (1994) Plasma fatty acid levels in infants and adults after myocardial ischemia. Am Heart J 128:61–67
19. Kantor P, Dyck J, Lopaschuk G (1999) Fatty acid oxidation in the reperfused ischemic heart. Am J Med Sci 318:3–27
20. Karimi M, Wang LX, Hammel JM et al (2004) Neonatal vulnerability to ischemia and reperfusion: cardioplegic arrest causes greater myocardial apoptosis in neonatal lambs than in mature lambs. J Thorac Cardiovasc Surg 127:490–497
21. Van Arsdell G, Maharaj G, Tom J et al (2000) What is the optimal age for repair of Tetralogy of Fallot? Circulation 102:123–129

22. Grotenhuis HB, Ruijsink B, Chetan D et al (2016) Impact of Norwood versus hybrid palliation on cardiac size and function in HLHS. Heart 102:966–974
23. Fischbach J, Sinzobahamvya N, Haun C et al (2013) Interventions after Norwood procedure: comparison of Sano and modified BT-shunt. Pediatr Cardiol 34:112–118
24. Photiadis J, Sinzobahamvya N, Haun C et al (2012) Does the shunt type determine mid-term outcome after Norwood operation? Eur J Cardio-Thorac Surg 42:209–216
25. Padalino MA, Castellani C, Toffoli S et al (2008) Pathological changes and myocardial remodelling related to the mode of shunting following surgical palliation for HLHS. Cardiol Young 18:415–422
26. Kutty S, Graney BA, Khoo NS et al (2012) Serial assessment of right ventricular volume and function in surgically palliated HLHS using real-time transthoracic 3D echocardiography. J Am Soc Echocardiogr 25:682–689
27. Piran S (2002) Heart failure and ventricular dysfunction in patients with single or systemic RV. Circulation 105:1189–1194