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ORIGINAL RESEARCH

Association of Digoxin With Preserved Echocardiographic Indices in the Interstage Period: A Possible Mechanism to Explain Improved Survival?

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BACKGROUND: For patients with hypoplastic left heart syndrome, digoxin has been associated with reduced interstage mortality after the Norwood operation, but the mechanism of this benefit remains unclear. Preservation of right ventricular (RV) echocardiographic indices has been associated with better outcomes in hypoplastic left heart syndrome. Therefore, we sought to determine whether digoxin use is associated with preservation of the RV indices in the interstage period.

METHODS AND RESULTS: We conducted a retrospective cohort study of prospectively collected data using the public use data set from the Pediatric Heart Network Single Ventricle Reconstruction trial, conducted in 15 North American centers between 2005 and 2008. We included all patients who survived the interstage period and had echocardiographic data post-Norwood and pre-Glenn operations. We used multivariable linear regression to compare changes in RV parameters, adjusting for relevant covariates. Of 289 patients, 94 received digoxin at discharge post-Norwood. There were no significant differences in baseline clinical characteristics or post-Norwood echocardiographic RV indices (RV end-diastolic volume indexed, RV end-systolic volume indexed, ejection fraction) in the digoxin versus no-digoxin groups. At the end of the interstage period and after adjustment for relevant covariates, patients on digoxin had better preserved RV indices compared with those not on digoxin for the ΔRV end-diastolic volume (11 versus 15 mL, P=0.026) and the ΔRV end-systolic volume (6 versus 9 mL, P=0.009) with the indexed ΔRV end-systolic volume (11 versus 20 mL/BSA$^{1.3}$, P=0.034). The change in the RV ejection fraction during the interstage period between the 2 groups did not meet statistical significance (–2 versus –5, P=0.056); however, the trend continued to be favorable for the digoxin group.

CONCLUSIONS: Digoxin use during the interstage period is associated with better preservation of the RV volume and tricuspid valve measurements leading to less adverse remodeling of the single ventricle. These findings suggest a possible mechanism of action explaining digoxin's survival benefit during the interstage period.

Key Words: congenital heart disease ■ digoxin ■ hypoplastic left heart syndrome ■ interstage ■ right ventricular echocardiography ■ right ventricular volume ■ single ventricle

Infants with hypoplastic left heart syndrome remain one of the most fragile populations with congenital heart disease. Despite improvement in operative and postoperative care, the interstage period after the Norwood (stage I palliation) and before the Glenn operation (stage II palliation) remains an opportunity to improve survival as mortality has been previously described as high as 10% to 15%.[1–6] Digoxin has been

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CLINICAL PERSPECTIVE

What Is New?

- Previous studies have shown that preservation of the right ventricular echocardiographic indices after a Norwood procedure for hypoplastic left heart is associated with improved survival during the interstage period.
- Other studies have independently shown that use of digoxin is associated with decreased risk of death during the interstage period, but the mechanism for its beneficial effect remained unknown.
- By using the public data set from the Pediatric Heart Network Single Ventricle Reconstruction trial, we demonstrate that infants treated with digoxin at discharge after the Norwood procedure have better preserved right ventricular and tricuspid valve echocardiographic characteristics compared with nontreated patients.

What Are the Clinical Implications?

- The clinical significance of these findings is that the use of digoxin during the interstage period is associated with preserved right ventricular and tricuspid valve characteristics, leading to less adverse remodeling of the single ventricle.
- These findings suggest a possible mechanism of action explaining digoxin's survival benefit during the interstage period.

Nonstandard Abbreviations and Acronyms

RVEDV	right ventricular end-diastolic volume
RVESV	right ventricular end-systolic volume

used for centuries to treat congestive heart failure and has been previously shown to statistically reduce interstage mortality. Oster et al[7] described that for patients not on digoxin interstage mortality was 12.3%, compared with 2.9% among those on digoxin, with an adjusted hazard ratio of 3.5 (95% CI, 1.1–11.7; P=0.04). Brown et al[8] found also that infants with no history of arrhythmia prescribed digoxin at hospital discharge post stage I palliation had a lower rate of interstage mortality in both retrospective cohort and propensity-score–adjusted logistic regression analysis. The mechanism of action, however, remains unknown.

Right ventricular (RV) morphology and function have been well demonstrated to be important factors in long-term outcomes in the population with hypoplastic left heart syndrome. Oster et al[9] reported that those with left ventricular morphology had better short-term outcomes following their initial congenital heart disease surgery and demonstrably better long-term transplant-free survival compared with those with systemic RV. The authors concluded after multivariable analysis that the ventricular morphology is a significant risk factor for long-term transplant-free mortality. The relative risk for later mortality (not immediately after the Norwood operation) has been described as ≈11 times greater if there is initial RV dysfunction.[10] Several studies are focused on serial assessment of specific echocardiographic indices of the RV size, shape, and function during the different stages of palliation and their prognostic value on long-term outcomes.[10–13] Preservation of RV echocardiographic indices such as RV end-systolic area, RV end-diastolic area, RV end-systolic volume (ESV), and ejection fraction (EF) have been shown to be associated with better outcomes in patients with hypoplastic left heart syndrome.[14]

The objective of our study was to determine whether digoxin use is associated with preservation of the RV indices post stage I palliation in infants with single ventricle congenital heart disease in a multicenter study using the database from the PHN/SVR (Pediatric Heart Network Single Ventricle Reconstruction) trial. We hypothesized that the use of digoxin would be associated with preservation of the RV indices.

METHODS

Study Design

We performed a retrospective cohort study using anonymized data and materials from the PHN/SVR trial public use data set (available at https://www.pediatricheartnetwork.org/datasets/?selectedStudy=438). In brief, the SVR trial enrolled infants from 2005 to 2008 with single ventricle congenital heart disease and a morphologically dominant right ventricle. The goal was to compare the outcomes for the Norwood procedure with the modified Blalock-Taussig shunt versus the right ventricle-to-pulmonary artery shunt. The patients were randomized to either of the 2 surgical treatment options and followed long term. Institutional review board approval and informed consent were obtained at participating institutions for the initial trial, and the public use data set contains no personally identifiable information.

For our study, the goal was to compare the echocardiographic findings in infants in the SVR trial who were discharged to home on digoxin to those discharged to home without digoxin. Interstage mortality was defined as death before stage II palliation. The inclusion criterion was any patient who had adequate echocardiographic data after the Norwood procedure and before stage II palliation. Patients whose date of death was very close to the mean age of the cohort

for having their Glenn operation were also included in the analysis. To avoid the potential confounder for mortality attributable to arrhythmia, which may be collinear with digoxin treatment, all infants with a history of arrhythmia during their Norwood hospitalization were excluded. In the SVR trial, arrhythmias that required medication or other treatment during the Norwood hospitalization were recorded; these included atrial fibrillation, atrial flutter, supraventricular tachycardia, junctional ectopic tachycardia, ventricular tachycardia, and second- or third-degree atrioventricular block.

Echocardiography

Core laboratories were used for interpretation of 2-dimensional and 3-dimensional echocardiograms and for genetic analysis (ApoE [apolipoprotein E] gene). There were 2 echocardiograms analyzed for each patient, the first one after the Norwood operation (median age that echo was obtained: day of life 20 with 25–75th age 14–28 days) and the second one closest to the date before the Glenn operation (median age that echo was obtained: day of life 120 with 25–75th age 94–148 days). Continuous echo parameters were summarized as mean and SDs or medians and 25th to 75th percentile for nonnormally distributed variables after the Norwood operation and before the Glenn as well as the change during this period (post-Norwood to pre-Glenn). Particularly, previously described in the literature,[12,13,15,16] attention was placed on RV size and shape with a focus on RVEDV (mL) and RVEDV (mL)/BSA$^{1.3}$, RVESV (mL) and RVESV (mL)/BSA$^{1.3}$, RV end-diastolic area (mm^2)/BSA$^{0.8}$, and RV eccentricity. The tricuspid valve regurgitation was assessed by measuring the change of the tricuspid valve annulus area and diameter as well as the regurgitant jet. The RV systolic function was assessed by measuring RV EF % and RV area change %.

Statistical Analysis

Descriptive statistics were calculated for all variables of interest and include means and SDs, medians (25th–75th percentile), or counts and percentages, when appropriate. Normality of continuous variables was assessed using the histogram, normal probability plots, and Anderson-Darling test for normality. Comparisons between groups were made using chi-square tests for categorical variables and when expected cell counts were <5, a Fisher's exact test was used in place of the chi-square test and comparisons between continuous variables were made using *t* tests or Wilcoxon rank-sum tests, as appropriate. Demographics and clinical characteristics (pre-Norwood, during Norwood hospitalization, and after discharge for Norwood) were compared between patients on digoxin at Norwood discharge to those not on digoxin at discharge. To account for site variation and potential confounding by shunt type (modified Blalock-Taussig shunt versus right ventricle-to-pulmonary artery shunt), discharge medication (angiotensin-converting enzyme inhibitor and/or diuretic) as well as age at pre-Glenn echocardiogram, an adjusted linear regression analysis was fitted via generalized estimating equation modeling to control for patients clustered within sites and treating shunt type (modified Blalock-Taussig shunt versus right ventricle-to-pulmonary artery shunt), discharge medication (angiotensin-converting enzyme inhibitor and/or diuretic) as well as age at pre-Glenn as a fixed effect. Effect size was calculated as the absolute difference in adjusted means divided by pooled SD post-Norwood (Cohen's d) to assess the clinical significance of the findings.

RESULTS

All patients enrolled in the PHN/SVR trial were eligible for enrollment. From the original 549 patients in the SVR trial, 330 met inclusion criteria for this study. Those who had a history of arrhythmia (n=149) during hospitalization for the Norwood procedure, those who did not survive to hospital discharge (n=60), and those who remained inpatient until stage II (n=10) were excluded. Additionally, there were 10 patients with insufficient pre-Glenn echocardiographic data and 31 patients who died during the interstage period (Figure 1).

Of the 289 remaining patients, 94 received digoxin at discharge post-Norwood. There were no statistically significant differences between the 2 groups with regard to demographic data or pre-Norwood and post-Norwood characteristics. However, those patients discharged home on digoxin were more likely to have a longer hospitalization post-Norwood operation and to be younger at the time of the Glenn procedure than those not on digoxin (Table 1).

In the post-Norwood echocardiograms, RV indices of EDV, ESV, and EF were not statistically different in the digoxin group compared with the no-digoxin group of patients. In the echocardiograms before the Glenn operation, the mean RVEDV for the patients on digoxin was 23.8±8.01 mL compared with 26.2±8.38 mL for the patients who were not on digoxin (P=0.045), the median RVESV was 13.31 (9.2, 16.5) mL and 14.29 (10.8, 17.8) mL respectively (P=0.031), and the mean RVEF was similar between the 2 groups (45±8.6, 44%±8.58%, P=0.419) (Table 2).

When the data were analyzed based on the change during interstage (Δ indicating change), accounting for site variation, shunt type (modified Blalock-Taussig shunt versus right ventricle-to-pulmonary artery shunt), age at pre-Glenn echocardiogram as

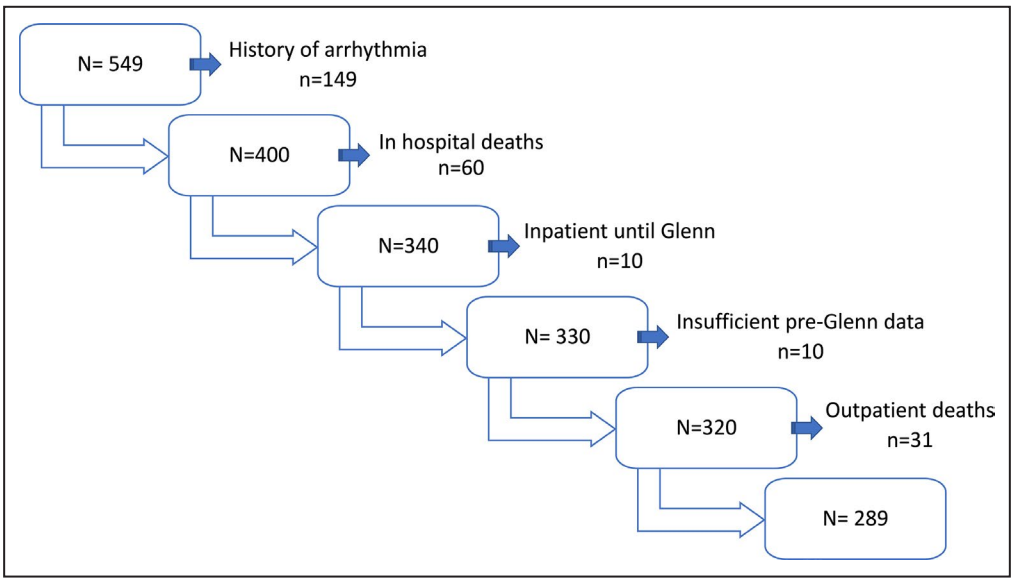

Figure 1. Graph of patient selection criteria.
All patients enrolled in the Pediatric Heart Network Single Ventricle Reconstruction Trial were eligible for enrollment. Those who had a history of arrhythmia during hospitalization for the Norwood procedure, who did not survive to hospital discharge, who remained in the hospital during interstage, who had insufficient pre-Glenn echocardiographic data, and who died as an outpatient during interstage were excluded from the study.

well as discharge medication usage (angiotensin-converting enzyme inhibitor and/or diuretic), those on digoxin had better preserved RV indices during the interstage period for ΔRVEDV (increase of 11.1 versus 14.5 mL, *P*=0.026), ΔRVESV (increase of 6.4 versus 9 mL, *P*=0.009), and indexed ΔRVESV=(10.6 versus 19.5 mL/BSA$^{1.3}$, *P*=0.034) (Table 3). There was, however, no statistical difference in the change of indexed ΔRVEDV between the 2 groups during interstage. The change in the RVEF during the interstage period between the 2 groups did not meet statistical significance (–2% versus –5%, *P*=0.056); however, there was a trend for preserved RV function on the group on digoxin. There was no difference between the 2 groups in terms of change of the RV area fraction or eccentricity. There was also no difference between the 2 groups in terms of change of the tissue Doppler characteristics during interstage (Table S1).

Additional analysis was performed focusing on the change of the tricuspid valve characteristics (Table 3). There was a trend toward larger change of the tricuspid valve annulus diameter *Z* score when measured anteroposterior and transverse on the group that did nott receive digoxin but without reaching statistical significance (group not on digoxin +0.22 versus group on digoxin –0.19, *P*=0.09 for the anteroposterior diameter z-score, and 0.43 versus 0.07, *P*=0.077 for the transverse diameter *Z* score respectively). The change of the tricuspid valve annulus area as well as the tricuspid valve annulus area *Z* score were better preserved on the group on digoxin (tricuspid valve annulus area: group on digoxin 55.8 versus 77.7 mm^2 for the group not on digoxin, *P*=0.017 and tricuspid valve annulus area *Z* score on the group on digoxin –0.31 versus 0.41 for the group not on digoxin, *P*=0.025). In addition, we calculated the effect size in units of SD (Cohen's d) and demonstrated that these findings were in favor of digoxin treatment with the effect size ranging consistently from small to moderate.

We summarized the findings of the most relevant echocardiographic indices related to preservation of the RV geometry and tricuspid valve function in a Forest plot to graphically display the direction and magnitude of changes between the digoxin and no-digoxin groups (Figure 2). Of importance, the directionality and effect size of RV indices with and without digoxin suggests a consistent small to moderate favorable effect of digoxin on all relevant indices even when not reaching statistical significance. We consider this a strong indicator supporting the protective role of digoxin in preserving the RV health in the stage I single ventricle physiology.

DISCUSSION

In this multicenter cohort study of children with single ventricle of RV morphology, the use of digoxin was associated with better preservation of the RV volume and the tricuspid valve annulus area during

Table 1. Patient and Center Characteristics at Norwood Stage by Digoxin Treatment Group

Variable	Total n=289	Digoxin n=94	No digoxin n=195	*P* value
Sex	289			0.959
Female		35 (37.2%)	72 (36.9%)	
Race	289			0.583
Under-represented racial groups		19 (20.2%)	45 (23.1%)	
White		75 (79.8%)	150 (76.9%)	
Ethnicity	286			0.933
Hispanic		19 (20.2%)	38 (19.8%)	
Mean birthweight, kg (SD)	289	3160 (0.49)	3155 (0.52)	0.942
Mean gestational age, wk (SD)	289	37.5 (6.1)	37.3 (6.6)	0.822
Median age at Norwood, d*	289	6 (4, 8)	6 (4, 8)	0.747
Aortic atresia	289	61 (64.9%)	122 (62.6%)	0.700
Norwood perfusion type	287			0.873
DHCA only		51 (54.8%)	112 (57.7%)	
RCP only or RCP/DHCA ≤10 min		25 (26.9%)	47 (24.2%)	
RCP/DHCA and DHCA >10 min		17 (18.3%)	35 (18.0%)	
Number of complications post-Norwood per patient*	289	2 (1, 4)	2 (1, 4)	0.878
Presence of syndrome or genetic anomaly	289	22 (30.1%)	40 (32.5%)	0.729
Shunt type at Norwood	289			0.679
Modified Blalock-Taussig shunt		40 (42.6%)	78 (40%)	
Right ventricle-to-pulmonary artery shunt		54 (57.4%)	117 (60%)	
Oral feeds at Norwood discharge	289			0.468
No		15 (16%)	38 (19.5%)	
Yes		79 (84%)	157 (80.5%)	
TR grade pre-Norwood	289			0.283
Mild/none		82 (87.2%)	178 (91.3%)	
Moderate/severe		12 (12.8%)	17 (8.7%)	
TR grade post-Norwood at time of discharge	289			0.376
Mild/none		73 (77.7%)	160 (82.1%)	
Moderate/severe		21 (22.3%)	35 (18%)	
Pre-Norwood ascending aorta diameter	283			0.552
<3 mm		43 (47.3%)	98 (51%)	
≥3 mm		48 (52.8%)	94 (49%)	
Mitral or aortic valve atresia at baseline	289	48 (51.1%)	106 (54.4%)	0.599
Mean O_2 sat in % at Norwood discharge (SD)	276	82.1 (4.7)	82.65 (4.5)	0.353
Post-Norwood length of stay, d*	289	26 (19, 39)	21 (15, 32)	0.005
Diuretics use at discharge post Norwood	289	74 (78.7%)	183 (93.9%)	0.001
Angiotensin-converting enzyme inhibitor use at discharge post-Norwood	289	37 (39.4%)	67 (34.4%)	0.407
Mean age at pre-Glenn echocardiogram, d (SD)	286	153.6 (54.5)	168.4 (43.3)	0.023
Mean center volume per year	289			0.109
Large ≥20 patients		77 (81.9%)	143 (73.3%)	
Small <20 patients		17 (18.1%)	52 (26.7%)	

All values represent means and SD are given within parenthesis, except values with a symbol of * that represent median (25th–75th percentile). DHCA indicates deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; and TR, tricuspid valve regurgitation.

the interstage period between the Norwood and the Glenn operation. These findings suggest that the use of digoxin is associated with favorable RV physiology during the interstage period. This is to our knowledge the first study that links the potential survival benefit of digoxin with echocardiographic RV changes in patients with single ventricle systemic RV during the interstage period.

Table 2. Echocardiographic Indices at Discharge Post-Norwood and Before Glenn

Variable	Post-Norwood				Pre-Glenn			
	Total n=289	Digoxin n=94	No Digoxin n=195	*P* value	Total n=289	Digoxin n=94	No Digoxin n=195	*P* value
Right ventricular (RV) size and function								
RVEDV, mL	233	12.4 (3.78)	12.3 (3.73)	0.759	205	23.8 (8.01)	26.2 (8.38)	0.045
RVEDV indexed, mL/BSA$^{1.3}$	233	90.1 (23.67)	90.6 (23.49)	0.872	205	108.4 (33.87)	114.9 (35.93)	0.208
RV end diastolic area indexed, mm^2/BSA$^{0.8}$	278	22.0 (5.01)	21.9 (4.68)	0.894	270	25.7 (6.66)	26.3 (6.18)	0.467
RVESV, mL*	233	6.63 (4.5, 8)	5.95 (4.8, 8)	0.505	205	13.31 (9.2, 16.5)	14.29 (10.8, 17.8)	0.031
RVESV indexed,* mL/BSA$^{1.3}$	233	47.07 (37.1, 60.9)	45.25 (37.5, 56.6)	0.601	205	57.91 (41.5, 72.6)	62.6 (47.8, 77.8)	0.180
RV cardiac index/BSA by volume assessment*	228	3.5 (3.0, 4.3)	3.7 (3.2, 4.4)	0.425	203	3.97 (3.2, 4.8)	3.94 (3.2, 4.8)	0.779
RV ejection fraction, %	233	47 (8.46)	48 (7.56)	0.717	205	45 (8.6)	44 (8.58)	0.419
RV area fraction, %	278	0.37 (0.08)	0.37 (0.07)	0.697	270	0.35 (0.08)	0.33 (0.08)	0.115
RV eccentricity	279	1.3 (0.33)	1.3 (0.33)	0.333	272	1.4 (0.37)	1.3 (0.33)	0.124
TV								
TV_AP diameter *Z* score	280	2.14 (1.56)	1.98 (1.63)	0.452	280	1.9 (1.75)	2.2 (1.88)	0.196
TV_transverse diameter *Z* score	283	2.09 (1.41)	1.88 (1.43)	0.249	286	2.2 (1.73)	2.3 (1.65)	0.524
TR proximal jet width AP, mm*	263	0 (0, 0)	0 (0, 0)	0.340	258	0 (0, 0)	0 (0, 0)	0.246
TR proximal jet width transverse, mm*	263	0 (0, 0)	0 (0, 0)	0.216	262	0 (0, 0)	0 (0, 0)	0.065
TV annulus area, mm^2	277	156.4 (44.26)	150.0 (47.23)	0.279	278	211.9 (69.93)	226.6 (70.35)	0.101
TVi annulus area, mm^2/BSA$^{1.3}$	277	7.2 (2.1)	7 (2.04)	0.285	278	6.8 (2.21)	7.1 (2.34)	0.256
TV annulus area *Z* score	277	3.6 (2.31)	3.3 (2.25)	0.289	278	3.3 (2.55)	3.7 (2.69)	0.247
TR proximal jet area, mm^2	30	9.4 (3.08)	7.4 (3.57)	0.137	42	14.5 (9.72)	13.3 (8.45)	0.714

All values represent means; SDs are given within parenthesis, except values with a symbol of * that represent median (25th–75th percentile). AP indicates anteroposterior; BSA, body surface area; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; TR, tricuspid regurgitation; and TV, tricuspid valve.

Although the potential benefit on interstage mortality from the use of digoxin has been previously reported, a mechanism for that effect remains unknown. Changes of the single RV echocardiographic indices of the single RV population were previously analyzed by Kim et al who reported that increased change of the RV indexed end-systolic area and end-diastolic area and dilatation were associated with adverse remodeling.[12] A study by Kutty et al[15] looked at patients with hypoplastic left heart syndrome at 4 time points from diagnosis to stage II palliation using real-time 3-dimensional echocardiography. Indexed RVESV was noted to increase throughout staged palliation and there was an increase in indexed RVEDV volume from pre-Norwood to post-Norwood. In addition, they found a trend toward decreasing EF throughout staged palliation, with significant decreases noted from pre-Norwood to post-Norwood and pre-Glenn to post-Glenn echocardiographic evaluations. These changes, however, were not associated with outcomes.[15] Frommelt et al[16] looked at the impact of shunt type on echocardiographic indices in children with single RV anomalies using the SVR trial data set. They concluded that at the 14-month age echocardiogram, a larger RV indexed ESV and EDV and end-systolic and end-diastolic areas, lower RV EF, 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. With the established RV anatomic changes noted to occur over time in the patient population with hypoplastic left heart syndrome and the association with adverse outcomes, our study revealed that patients who are prescribed digoxin had preserved RV indices from the post-Norwood to pre-Glenn time period, thus, offering a potential target for the favorable effects of digoxin on this fragile population.

Digoxin's protective effect on the RV remodeling is still to be investigated and there are several biologically plausible mechanisms to contemplate.[17] One of them is digoxin's well-known inotropic effect through inhibition of the Na, K-ATPase pump.[18] However, another possible benefit may come from its sympatholytic effect resulting in slowing the heart rate.[19,20] One can speculate that the drop of the heart rate allows for better

Table 3. Changes of Echocardiographic RV and Tricuspid Valve Variables Between Discharge Post-Norwood and Before Glenn procedure

Variable	Unadjusted				Adjusted*	
	n	Digoxin n=94	No Digoxin n=195	*P* value	*P* value	Effect size†
ΔRVEDV, mL	181	11.1 (7.51)	14.5 (8.76)	0.009	0.026	−0.33
ΔRVEDV indexed, mL/BSA$^{1.3}$	181	16.5 (32.29)	25.9 (37.83)	0.093	0.126	−0.24
ΔRV end-diastolic area indexed, mm^2/BSA$^{0.8}$	263	3.7 (6.84)	4.6 (6.48)	0.289	0.171	−0.17
ΔRVESV, mL	181	6.4 (5.21)	9 (6.18)	0.005	0.009	−0.39
ΔRVESV indexed, mL/BSA$^{1.3}$	181	10.6 (23.87)	19.5 (27.94)	0.032	0.034	−0.33
ΔRV ejection fraction, %	181	−2 (10.75)	−5 (10.90)	0.065	0.056	0.29
ΔRV area fraction, %	263	−0.02 (0.10)	−0.04 (0.09)	0.205	0.233	0.16
ΔRV eccentricity	265	0.1 (0.36)	0.1 (0.32)	0.274	0.273	0.15
ΔTV_AP diameter *Z* score	273	−0.19 (1.69)	0.22 (1.75)	0.069	0.090	−0.22
ΔTV_transverse diameter *Z* score	281	0.07 (1.82)	0.43 (1.80)	0.113	0.077	−0.22
ΔTR_AP proximal jet width, mm‡	239	0 (0, 0)	0 (0, 0)	0.255	0.165	
ΔTR_ transverse proximal jet width, mm‡	243	0 (0, 0)	0 (0, 0)	0.082	0.019	
ΔTV annulus area, mm^2	269	55.8 (62.82)	77.7 (66.57)	0.010	0.017	−0.30
ΔTVi annulus area, mm^2/BSA$^{1.3}$	269	−0.42 (2.19)	0.21 (2.33)	0.035	0.024	−0.29
ΔTV annulus area Z score	269	−0.31 (2.48)	0.41 (2.65)	0.034	0.025	−0.29

All values represent means and SDs are given within parenthesis, except values with a symbol of ‡ that represent median (25th–75th percentile). AP indicates anteroposterior; BSA, body surface area; RV, right ventricular; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; TR, tricuspid regurgitation; and TV, tricuspid valve.

*Adjusted for shunt type, discharge medication usage (angiotensin-converting enzyme inhibitor and/or diuretic), age at pre-Glenn echocardiogram and clustering of patients within centers.

†Effect size is expressed in SD units; effect size guideline: 0.20=small, 0.50=medium and 0.80 =large effect size.

coronary perfusion and that leads to less adverse remodeling over time.[17]

In conclusion, our study offers initial support that digoxin might be associated with preservation of the RV indices during interstage. Besides digoxin's hemodynamic effects, it has also antiarrhythmic effects and modulates the neurohormonal axis of heart failure; thus, digoxin's potential mechanism of action may be complex and multifactorial. Additional studies will be needed to explore the exact mechanism of action and whether digoxin may carry also longer term survival advantage beyond stage II palliation.

Study Limitations

There are several limitations to this study, including the usual limitations when using retrospective registry data, such as the inability to independently verify registry data and the inability to collect any missing data points. The participants were also not randomized to receive digoxin. In addition, there is no information collected in the registry on the indication for starting digoxin, the drug dosages used, and no data regarding actual patient adherence to giving the medication. However, if digoxin was prescribed to these children because they were felt to be in more-severe heart failure, one would expect their outcomes to be worse, not better and have worsening echocardiographic findings. There were also 31 patients who died during the interstage period and 10 patients who remained inpatient during interstage for whom we could not identify if they were on or not on digoxin and presumably were the sickest patients of this population and thus would benefit more.

CONCLUSIONS

In the PHN/SVR trial, infants with single right ventricle congenital heart disease who were prescribed digoxin upon discharge after the Norwood procedure had preserved RV volume and tricuspid valve regurgitation characteristics as measured by echocardiography during the interstage period, indicating a potential favorable hemodynamic effect on the RV's interstage physiology.

ARTICLE INFORMATION

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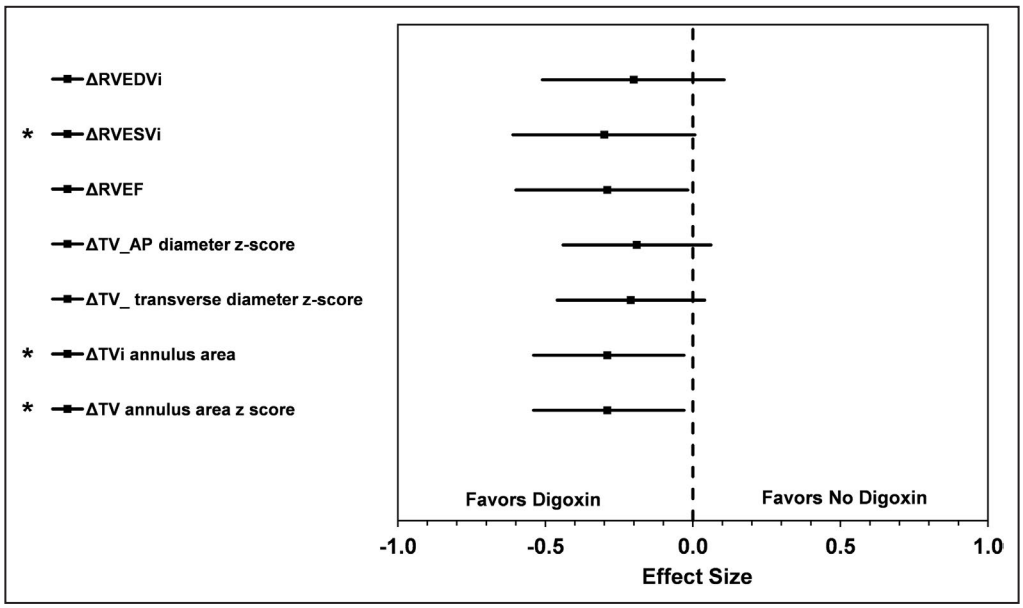

Figure 2. Forest plot of change on echocardiographic indices during interstage.
The vertical dashed line represents an effect size of zero, which is associated with equal effect for both groups. For each echocardiographic value displayed, the symbol depicts the estimate of the effect size and the line represents the 95% CI. CIs that extend across the 0.0 line indicate that the effect size is not statistically different than 0.0. Asterisks next to the values indicate statistically significant adjusted difference between the 2 groups in favor of the use of digoxin (to the left of the dashed line) or not (to the right of the dashed line). Δ indicates change; RVEDVi, right ventricle end-diastolic volume indexed; RVEF, RV ejection fraction; RVESVi, end-systolic volume indexed; TV_AP diameter *Z* score, tricuspid valve anteroposterior diameter *Z* score; TV_transverse diameter *Z* score, tricuspid valve transverse diameter *Z* score; and TVi annulus area, tricuspid valve annulus area indexed.

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Supplementary Material

Table S1

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Supplemental Material

Table S1. Changes of Tissue Doppler characteristics between discharge post-Norwood and pre-Glenn.

Variable	N	Unadjusted			Adjusted*	
		Digoxin N=94	No Digoxin N=195	P-Value	P-Value	Effect Size§
TD Tei index (z-score)	44	-1.1 (2.44)	-0.5 (2.27)	0.407	0.546	-0.18
TD MPI DTI calculation	44	-0.1 (0.32)	-0.1 (0.30)	0.392	0.546	-0.18
TD R-R interval (msec)¶	289	77.5 (0,129)	82 (28,140)	0.232	0.718	
TD Summation wave¶	289	0 (-1, 0)	0 (0,1)	0.068	0.115	
TD Peak atrial diastolic velocity (cm/sec) ¶	289	0 (-11.7,13)	0.3 (-1,11.8)	0.262	0.385	
TD Peak early diastolic velocity (cm/sec) ¶	289	1 (-4,4)	1 (-1.8,5)	0.661	0.606	
TD Peak systolic velocity (cm/sec) ¶	289	1 (-1,2)	1 (-0.4,3)	0.547	0.559	
TD Ejection time (msec)¶	289	0 (-8,35)	0 (0,198)	0.027	0.021	
TD Isovolumic contraction acceleration (cm/sec^2) ¶	289	0 (0,29)	0 (0,24)	0.658	0.776	
TD Onset of ICT to end of IRT (msec) ¶	289	27.5 (-12,89)	62 (3,101)	0.028	0.090	

All values represent means and standard deviations (SD) are given within parenthesis, except values with a symbol of ¶ that represent median (25th -75th percentile). TD, Tissue Doppler; MPI, myocardial performance index; ICT, isovolumic contraction time; IRT, isovolumic relaxation time.

*Adjusted for shunt type, discharge medication usage (ACE inhibitor and/or diuretic), age at pre-Glenn and clustering of patients within centers. §Effect size is expressed in SD units.