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ORIGINAL RESEARCH

PEDIATRIC CARDIOLOGY

Biventricular Repair in Borderline Left Hearts

Insights From Cardiac Magnetic Resonance Imaging

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ABSTRACT

BACKGROUND Cardiac magnetic resonance imaging (CMR) may augment 2-dimensional (2D) echocardiography in decision-making for biventricular repair in borderline hypoplastic left hearts.

OBJECTIVES This study evaluates: 1) the relationship between 2D echocardiography and CMR; 2) imaging variables affecting assignment to biventricular vs non-biventricular management; and 3) variables affecting transplant-free biventricular survival.

METHODS We reviewed clinical, echocardiographic, and CMR data in 67 infants, including CMR-determined ascending aortic (AAo) flow and comparable left ventricular end-diastolic volume indexed (LVEDVi) by 2D-echocardiography and CMR.

RESULTS Treatment assignment to biventricular repair was either direct (BV, n = 45) or with a bridging hybrid procedure (H1-BV, n = 12). Echocardiographic LVEDVi was <20 mL/m^2 in 83% of biventricular repair infants and underestimated CMR-LVEDVi by 16.8 mL/m^2. AAo flows had no/weak correlation with aortic and mitral valve *z*-scores or LVEDVi. AAo flows differed between BV, H1-BV, and single-ventricle groups (median): 2.1, 1.7, and 0.7 L/min/m^2, respectively. Important variables for treatment assignment were presence of endocardial fibroelastosis, AAo flow, and mitral valve *z*-score. Biventricular repair was achieved in 54. The median follow-up was 8.0 (0.1-16.4) years. Transplant-free biventricular survival was 96%, 82%, and 77% at 1, 5, and 10 years, respectively. Patients without aortic coarctation repair were at higher risk of death, transplantation, or single-ventricle conversion (HR: 54.3; 95% CI: 6.3-47.1; $P < 0.001$) during follow-up. AAo flow had a smaller nonlinear effect with hazard ratio increasing at lower flows.

CONCLUSIONS Historical 2D echocardiographic criteria would have precluded many patients from successful biventricular repair. AAo flow, an integrative index of left heart performance, was important in assigning patients to a biventricular circulation and affected survival. Biventricular survival was strongly associated with the need for aortic coarctation repair. (JACC Adv 2022;1:100066) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional
AAo = ascending aortic
AoV = aortic valve
b-HLH = borderline hypoplastic left heart
BV = biventricular repair group
CMR = cardiac magnetic resonance imaging
CoA = coarctation of the aorta
EFE = endocardial fibroelastosis
H1-BV = hybrid stage 1 bridging to biventricular repair group
LV = left ventricle
LVEDVi = left ventricular end-diastolic volume indexed
MV = mitral valve
SV = single ventricle

The management pathway at the extremes of the hypoplastic left heart spectrum is clear; however, in those with patent mitral and aortic valves (AoVs) and "borderline" hypoplasia of the left ventricle (LV), the initial decision-making process with regard to single-ventricle (SV) vs biventricular pathway is complex and challenging. Infants who achieve biventricular physiology may suffer with residual left heart pathology causing pulmonary hypertension.[1-6] In this regard, successful repair includes absence of life-threatening pulmonary hypertension.

Cardiovascular imaging during this critical assessment seeks to quantify functionality of hypoplastic ± stenotic left heart structures, often occurring at multiple levels. Contemporary decision-making, which recognizes the "growth" potential of these structures, is made with increased understanding of pathophysiology, for example, atrial septal defect sizing, and in the context of a growing armamentarium of cardiac procedural options, including fetal interventions, staging procedures such as the hybrid stage 1 (H1) (arterial duct stenting and bilateral pulmonary artery banding), endocardial fibroelastosis (EFE) resection, and novel mitral valve (MV) replacement surgery.[1,3,4,7-10]

Two-dimensional (2D) echocardiographic assessment has historically been the main determinant in decision-making. Echocardiographic parameters to support pursuit of a biventricular strategy have included left ventricular end-diastolic volume indexed (LVEDVi) ≥20 mL/m^2, MV z-score >−2, AoV/root z-score >−2, absence of EFE, and presence of an apex-forming LV.[4,5,11] Cardiac magnetic resonance imaging (CMR) is increasingly being utilized as it provides additional parameters such as ascending aortic (AAo) flow and superior 3-dimensional quantification of ventricular volume.[6,12]

Our institution began a protocol in the year 2003 to perform CMR in infants with borderline hypoplastic left heart (b-HLH) in whom the management decision for SV or biventricular circulation was uncertain. Our hypothesis was that CMR had the potential to improve the quantification of cardiac output based on blood flow parameters and 3-dimensional ventricular volumes. The initial experience demonstrated a preoperative mean AAo flow of 1.63 ± 0.57 L/min/m^2 in early biventricular repair survivors.[12] In this study, our objectives were: 1) to study the relationship between CMR and 2D echocardiographic left heart parameters, including CMR-determined AAo flow; 2) to identify preoperative cardiac variables that influenced assignment to a biventricular vs non-biventricular management pathway; and 3) to identify variables that affected transplant-free biventricular survival.

MATERIAL AND METHODS

PATIENT POPULATION. This retrospective study was approved by the institutional ethics review board. The indication to perform CMR was concern for pursuing a biventricular strategy based on echocardiographic imaging. Selection of the study population began with the search of our CMR database to identify all infants between January 2003 and December 2015 with the diagnoses of borderline LV, aortic stenosis, and coarctation of the aorta (CoA). In order to capture the spectrum of disease, b-HLH was defined retrospectively as presence of 2 or more of the following:

- LVEDVi by 2D echocardiography of <20 mL/m^2
- Non-apex-forming LV
- EFE
- AoV or MV diameter z-score of <−2
- Valvular and/or subvalvular LV outflow tract or mitral inflow obstruction

Exclusions included: 1) only AoV or MV diameter z-score <−2 with associated obstruction, that is, isolated valvular hypoplasia with stenosis; 2) valvular atresia; 3) discordant ventriculoarterial connection; 4) atrioventricular septal defects; and 5) isolated aortic arch obstruction with adequate size AoV, MV, and LV.

Infants were triaged to 5 possible treatment pathways: 1) direct biventricular circulation (BV); 2) H1-bridging for intended biventricular circulation (H1-BV); 3) SV circulation by either Norwood or H1 procedures; 4) H1-bridging for heart transplantation; and 5) no cardiac treatment. In infants who underwent H1 procedure as the first intervention, information regarding the intended pathway was extracted from cardiosurgical conference summaries. Infants underwent clinically required procedures based on their intended type of circulation physiology. These procedures (postnatal and fetal) included interventions on any cardiac valve, aortic arch, atrial septum, LV outflow tract, EFE resection, and ventricular septal defect closure. Our institution only utilized the H1 and not the Norwood procedure for bridging to potential biventricular repair.[2,3]

DATA COLLECTION. Clinical, 2D echocardiographic, CMR, cardiac catheterization, and catheter-based and surgical procedural data were reviewed. Clinical data included patient demographics and characteristics

and the outcomes of survival, need for transplantation, and death.

The initial preoperative and last available follow-up 2D echocardiographic data were retrospectively reviewed by one pediatric cardiologist (S.-L.K.) who was blinded to the CMR data. MV and AoV annuli were measured in the 4-chamber and parasternal long-axis views, respectively. LVEDVi was measured by Simpson's rule in the apical 4- ± 2-chamber views. Valvular function was noted.[13] Measurements were normalized for body surface area as *z*-scores.[11]

LV EFE was defined as brightness of the endocardial wall or papillary muscle compared to the right ventricle endocardium with or without a globular LV geometry and categorized as per Congenital Heart Surgeon Society definition.[4]

Hemodynamic data were obtained from 2D echocardiography and cardiac catheterization. Right ventricular systolic pressure was measured by tricuspid regurgitation velocity jet plus right atrial pressure (assumed as 5 mmHg). Mean pulmonary artery pressure was calculated as peak pulmonary regurgitation velocity plus right atrial pressure. An interventricular septal curvature position being flat was interpreted as the right ventricular pressure being at least half the systolic blood pressure. Pulmonary hypertension was defined as a direct or calculated mean pulmonary artery pressure ≥25 mmHg or echocardiographic evidence of right ventricular pressure ≥$^1/_2$ systolic blood pressure.

The CMR protocol is outlined in the Supplemental Appendix.[6] CMR data of interest were AAo flow, ventricular volumes, and presence of EFE. This was extracted from the clinical reports which were used for clinical decision-making and interpreted by 3 experienced congenital heart imaging specialists. In brief, the AAo flow was calculated by through-plane phase-contrast velocity mapping of the ascending aorta at the level of the right pulmonary artery. LV volumetry was based on short-axis cine imaging using a segmented spoiled gradient refocused echo sequence. EFE was diagnosed by late gadolinium enhancement. The comprehensive echocardiographic and CMR data acquired are listed in Supplemental Table 1.

DATA ANALYSIS. Continuous variables were characterized using median, minimum, and maximum, and categorical variables were summarized using frequency. For continuous variables, between-group differences were evaluated using a Kruskal-Wallis test followed by Dunn pairwise test. Between-group difference in categorical variables were assessed by Pearson chi-square test or Fisher exact test. A Bonferroni correction was used for multiple comparisons.

Three main primary outcomes were assessed: 1) differences between LVEDVi measured by CMR and echocardiography; 2) treatment pathway assignment of patients; and 3) survival from birth that was free of transplantation or conversion to the SV pathway.

To assess the difference in LVEDVi measured by echocardiography or CMR, we first visualized paired data for all patients using a scatter plot and evaluated the differences by a paired *t*-test. Next, we quantified the association between echocardiography and CMR LVEDVi by Spearman rank correlation coefficient. The scatter plot demonstrated a nonlinear relationship between echocardiography and CMR LVEDVi, which was modeled using restricted cubic splines with 4 interior knots at fixed quantiles (package *Hmisc*[13]). Finally, we applied Bland-Altman analysis to assess the echocardiography-CMR agreement.

The treatment pathways in the order BV, H1-BV, SV form an ordinal scale of most-to-least desirable clinical outcome. Ordinal logistic regression was used to explore our treatment pathway assignments using only variables that were available at the time of the decision. Four standard clinical variables (presence of EFE, MV *z*-score, AoV *z*-score, and LVEDVi measured by CMR) and LV cardiac output (AAo flow measured by CMR) were used in our model.

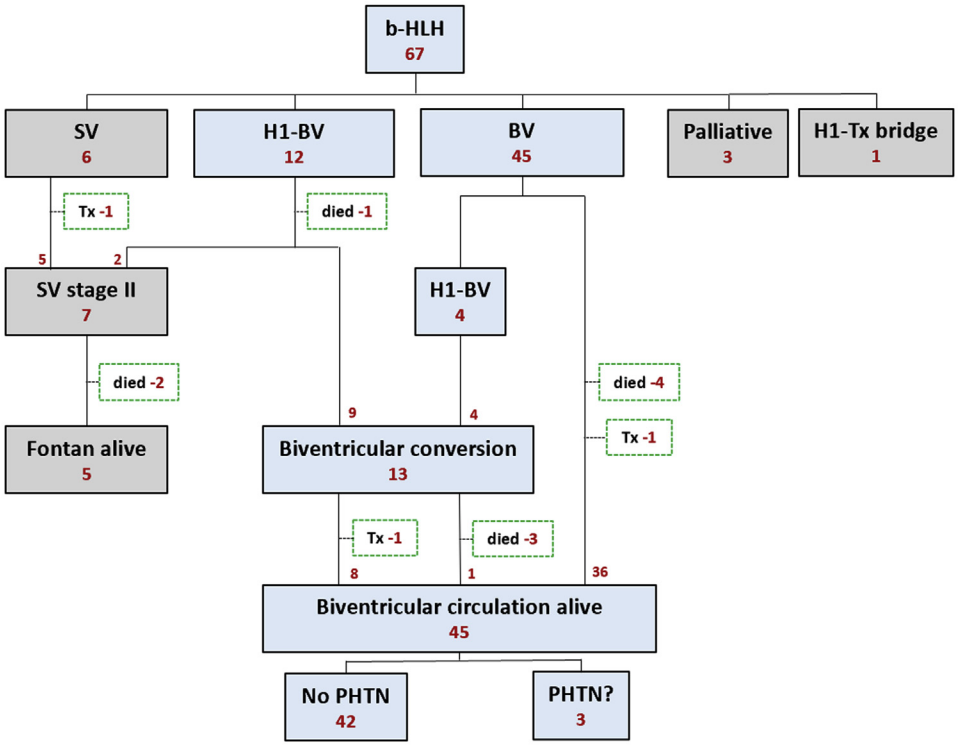
Freedom from death, transplantation, or conversion to a SV circulation was estimated using Kaplan-Meier survival method among the patients receiving BV or H1-BV management. Pointwise 95% confidence intervals (CIs) for transplant-free biventricular survival for subgroups were estimated using nonparametric bootstrap, for example, for patients on the BV and H1-BV pathway and for those with pulmonary hypertension. The estimated freedom and 95% CI at 1, 5, and 10 years were reported.

Univariate survival analysis by Cox regression for 5 preoperative and 5 postoperative variables is in Supplemental Table 2. Multivariate survival analysis by Cox regression used 2 variables: need for coarctation repair and AAo flow, a continuous variable which was modeled with penalized splines to permit a nonlinear effect (package *survival*). The proportional hazards assumption in Cox regression was assessed by confirming that the Schoenfeld residuals were independent with respect to time by a score test and graphically. Analysis was performed in R-4.20[14] with packages rms and Hmisc[15].

RESULTS

The CMR database identified 67 patients with b-HLH. The median (range) weight and age at presentation were 3.3 (1.7-4.6) kg and 1 (0-32) days, respectively.

FIGURE 1 Clinical Outcomes



B-HLH = borderline hypoplastic left heart; BV = biventricular; H1-BV = hybrid stage 1 with intended biventricular repair; H1-Tx = hybrid stage 1 bridging to transplant; PHTN = pulmonary hypertension; SV = single ventricle; Tx = heart transplantation.

Seven neonates were premature at 28 to 36 weeks' gestation. Prostaglandin E1 infusion was initiated in 91%.

Infants underwent the following initial management pathways: BV (n = 45), H1-BV (n = 12), and SV palliation (n = 6). One infant underwent H1-Tx and 3 infants received palliative care for noncardiac reasons. The baseline imaging data of these 4 infants were utilized for CMR and 2D echocardiographic data comparison but were excluded from follow-up analyses.

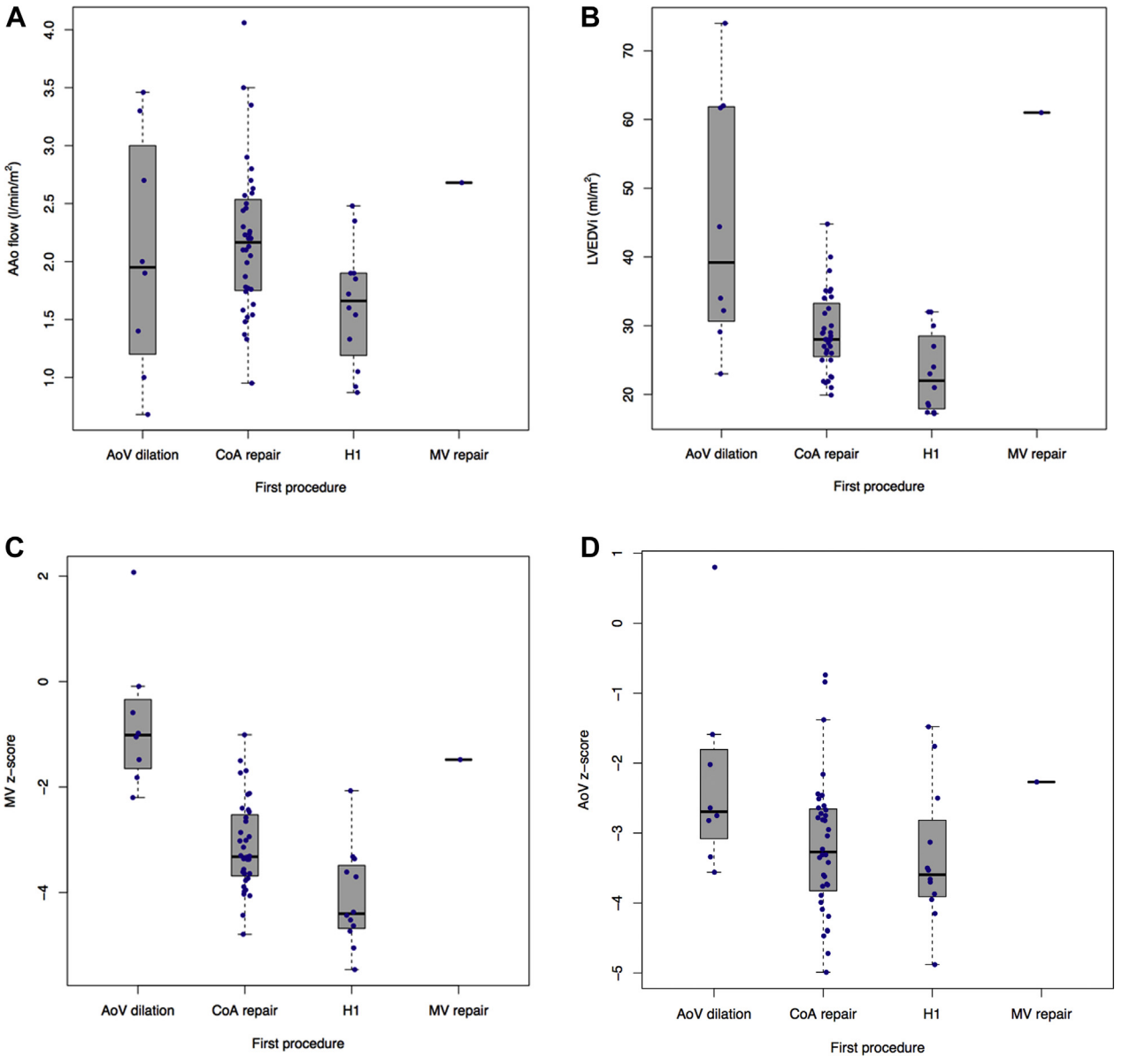
The clinical outcomes of all patients are outlined in Figure 1. The median age at CMR was 4 (1,165) days, 91% being <30 days. The first procedure was performed at a median 6 (2-35) days in all but one patient who had the CMR on day 26, then MV surgery as the only procedure at 3 years of age. CMR was performed before the first procedure in 89% and otherwise after the H1-procedure (n = 4) and/or after AoV balloon dilation (n = 4).

Procedures for the BV and H1-BV groups are listed in Supplemental Table 3. The 3 fetuses who underwent AoV balloon dilation were assigned to the BV group. First procedures in the BV group were CoA repair (n = 36), AoV dilation (n = 8), and MV surgery (n = 1) (Figure 2). CoA repair was the only procedure required in 56% of BV patients (n = 25) and only additional procedure in 42% of H1-BV (n = 5) patients. Twelve additional patients had CoA repair plus additional procedures (MV surgery (n = 6), AoV intervention (n = 5)). Fourteen (25%) patients underwent MV operations. There were 22 AoV/LV outflow tract procedures in BV patients (n = 13). Moderate to severe EFE was observed in 12 patients (BV [n = 9], SV [n = 3]). EFE resection (n = 5) was performed in 4 BV patients.

Two H1-BV infants were switched to SV pathway following intraoperative judgment of MV inadequacy during intended biventricular repair. Four BV infants had initial AoV balloon dilation but subsequently underwent a H1 procedure to allow for further left heart development and intervention. All subsequently had H1 takedown and conversion to biventricular circulation occurred at a median of 5.9 (4.9-11.1) months.

Biventricular circulation was ultimately achieved in 54 infants, 95% of the initial BV and H1-BV groups.

FIGURE 2 **First Procedures for BV and H1-BV Groups**

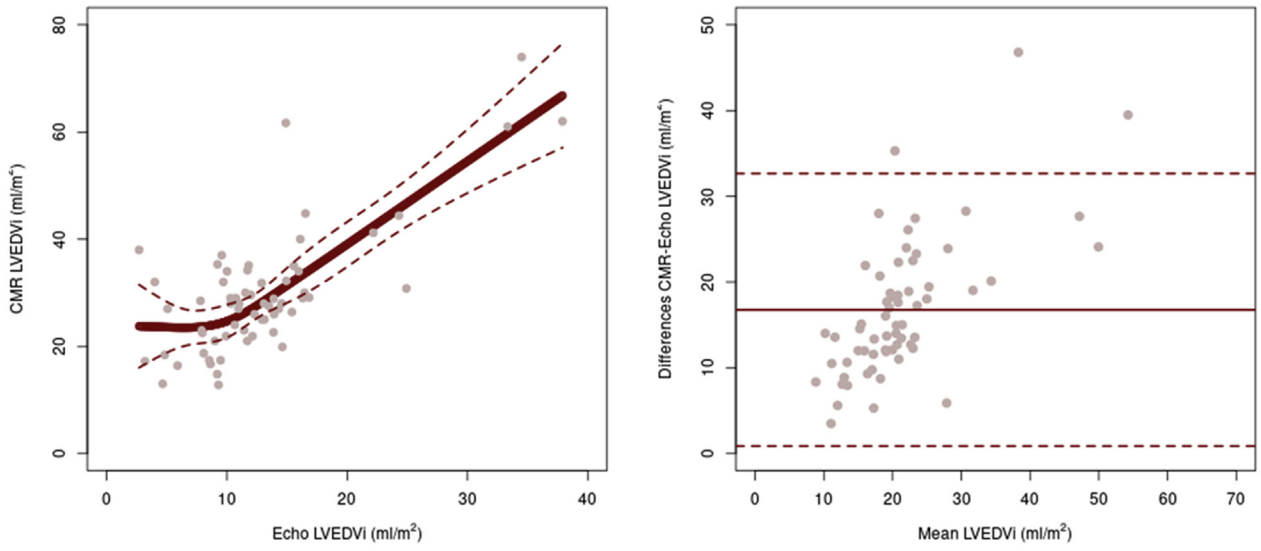


First procedures for BV group were CoA repair (n = 36), AoV dilation (n = 8), MV repair (n = 1), and H1-procedure for H1-BV group (n = 12). H1-BV infants had significantly lower ascending aortic flow **(A)**, smaller CMR-LVEDVi **(B)**, smaller MV *z*-score **(C)**, and no difference in AoV *z*-score **(D)** compared with BV infants. AAo = ascending aortic flow; AoV = aortic valve dilation; CoA = coarctation of aorta; H1-BV = hybrid 1 procedure staging for biventricular repair; LVEDVi = left ventricular end-diastolic volume indexed; MV = mitral valve.

Follow-up data were reviewed up to December 2020. At last follow-up (median: 8.0 [0.1-16.4] years), 45 (83%) of these patients were alive without heart transplantation, of which 42 had no evidence of pulmonary hypertension. The pulmonary hypertension status was unknown in 3 patients followed at outside institutions. Their median follow-up was 3.5 (3.4-12.2) years.

COMPARISON OF 2D ECHOCARDIOGRAPHY AND CMR. Preoperative cardiovascular imaging parameters are shown in Supplemental Table 1. Sixty-one infants had 2D echocardiograms and CMR performed

FIGURE 3 Comparison Between Echocardiographic and CMR-Derived LVEDVi



The relationship between CMR-LVEDVi and echo-LVEDVi fitted by regression splines **(left)**. Bland-Altman agreement plot with mean difference of 16.8 ± 8.0 mL/m^2. Lines indicate 95% limits of agreement (1.1-32.5) **(right)**. CMR = cardiac magnetic resonance imaging; echo = echocardiography; LVEDVi = left ventricular end-diastolic volume indexed.

<2 weeks apart (median: 2 [1-13] days) with no intervening cardiac procedures. LVEDVi (mL/m^2) of the overall cohort was 11.8 (interquartile range: 9.3-14.6) by 2D echocardiography and 28 (IQR: 23-34) by CMR. Two-dimensional echocardiographic measurements were consistent with its CMR counterpart as their correlation was high (Spearman r = 0.74; 95% CI: 0.61-0.84, $P < 0.0001$), but CMR measurements were significantly larger (group mean difference: 16.8, 95% CI: 14.7-18.8, $P < 0.0001$) (**Figure 3**). There was no significant difference in CMR-LVEDVi between the LV apex-forming (median: 28.4 [14.8-74.0] mL/m^2) and non-apex-forming groups (median: 28 [12.8-344.8] mL/m^2) ($P = 0.15$).

The association of AAo flow with other variables available at the time of treatment pathway assignment, as assessed by the Spearman rank correlation coefficient, was weak: CMR-LVEDVi (coefficient: 0.40, 95% CI: 0.17-0.59, $P = 0.0012$), AoV *z*-score (coefficient: −0.055, 95% CI: −0.30 to 0.20, $P = 0.6679$), MV *z*-score (coefficient: 0.21, 95% CI: −0.04 to 0.44, $P = 0.0918$), EFE (coefficient: −0.14, 95% CI: −0.37 to 0.11, $P = 0.2815$) (Supplemental Figure 1).

EFE was observed in 13 (19%) baseline echocardiograms. Only 15 CMRs were performed with late gadolinium enhancement sequencing; EFE was present in 7, concordant with echocardiography.

CHARACTERISTICS BY ASSIGNED TREATMENT PATHWAY. **Table 1** and the **Central Illustration** bottom left image presents the preoperative variables by intended management pathway. The AAo flow (median [range] L/min/m^2) was highest in the BV group (2.1 [0.7-3.5]) compared to the H1-BV (1.7 [0.9-2.5]) and SV (0.7 [0.2-1.3]) groups (BV vs SV, $P < 0.001$). EFE was more common in those triaged directly to SV (50%) compared to the BV (20%) and H1-BV groups (0%) (Supplemental Figure 2). The SV group did not differ from the BV or H1-BV groups in terms of CMR-LVEDVi, MV, or AoV *z*-scores (**Table 1**). The H1-BV in comparison to BV infants had smaller MV *z*-score and lower AAo flow but no difference in AoV *z*-score (**Table 1**, **Figure 2**).

The BV group had larger median LVEDVi by CMR and 2D echocardiography compared with the H1-BV group (**Table 1**, **Figure 2B**). In the BV group, all patients had LVEDVi ≥20 mL/m^2 by CMR, while by 2D echocardiography, 82% were <20 mL/m^2, with the smallest being 5.1 mL/m^2. In the H1-BV group, the LVEDVi was <20 mL/m^2 in 42% by CMR and 100% by 2D echocardiography (Supplemental Figure 2).

The ordinal logistic regression model fitted the data well (**Table 2**) (C-statistic: 0.876, likelihood ratio χ^2: 38.22, $P < 0.0001$), and the results suggested the 3 most important variables associated with the assigned treatment pathway were the presence of

TABLE 1 Preoperative Variables by Intended Management Pathway

	BV (n = 45)	H1-BV (n = 12)	SV (n = 6)	*P* Value
Birth weight (kg)	3.4 (2.4 to 4.6)	2.8 (2.4 to 3.7)	3.4 (3.0 to 4.0)	0.09
Preoperative CMR parameters				
LVEDVi (mL/m^2)	29[a] (20 to 74)	22[a] (17 to 32)	27 (13 to 44)	0.02[a]
Ascending aortic flow (L/min/m^2)	2.1[a] (0.7 to 3.5) n = 41	1.7 (0.9 to 2.5)	0.7[a] (0.2 to 1.3)	<0.001[a]
LVEF (%)	58 (29 to 83) n = 43	59 (42 to 81)	45 (23 to 64)	0.24
Preoperative echocardiogram				
LVEDVi (mL/m^2)	13.1[a] (5.1 to 37.9)	9.7[a] (3.2 to 16.5)	9.2 (4.7 to 22.2)	0.016[a]
LVEDd *z*-score	−3.3 (−5.7 to 3.3)	−3.8 (−6.3 to −2.2)	−3.3 (−6.1 to −1.2)	0.14
MV diameter (mm)	7.0 (4.8 to 13)	5.1 (4 to 8.5)	7.0 (4.9 to 7.3)	
MV z-score	−3[a] (−4.8 to 2.1)	−4.4[a] (−5.5 to −2.1)	−3.1 (−4.5 to −2.7)	0.001[a]
AoV diameter (mm)	4.8 (3.6 to 8.1)	4.4 (3.2 to 5.6)	4.9 (4.7 to 5.3)	
AoV *z*-score	−3 (−4.9 to 0.8)	−3.6 (−4.9 to −1.5)	−2.9 (−3.6 to −2.4)	0.44
LV non-apex-forming	21 (47%)	10 (83%)	5 (83%)	0.23
TR—moderate to severe	10 (22%)	0	0	0.58
EFE present	9 (20%)	0	3 (50%)	0.08

Values are median (range) or n (%). [a]Statistically significant between groups.

AoV = aortic valve; BV = direct biventricular repair; CMR = cardiac magnetic resonance; H1-BV = hybrid stage 1 with intended biventricular repair; EFE = endocardial fibroelastosis; LV = left ventricle; LVEDd = left ventricular end-diastolic dimension; LVEDVi = left ventricular end-diastolic volume indexed; LVEF = left ventricular ejection fraction; MV = mitral valve; SV = single-ventricle repair; TR = tricuspid regurgitation.

EFE which decreased the odds of triage to BV and higher values of AAo flow and MV *z*-score, both of which increased the odds of BV assignment (**Table 2**).

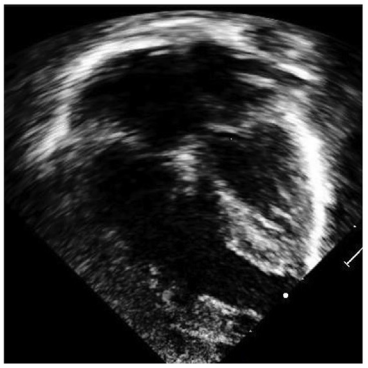
TRANSPLANT-FREE BIVENTRICULAR SURVIVAL IN BV AND H1-BV GROUPS. In the 57 patients with intended biventricular repair (BV and H1-BV groups), freedom from death, transplant, or SV conversion was 96% (95% CI: 91%-100%) at 1 year, 82% (95% CI: 71%-91%) at 5 years, and 77% (95% CI: 65%-88%) at 10 years. Outcomes including death, heart transplantation, conversion to SV palliation, and pulmonary hypertension are listed in Supplemental Table 4. Ten patients died at a median of 1.6 (0.1-7.6) years, with the most common dominant lesion being AoV stenosis ± MV pathology requiring intervention (n = 6). Two patients with predominant MV pathology underwent heart transplantation.

In retrospect, the need for an aortic coarctation repair identified patients with better transplant-free biventricular survival ($P < 0.001$, **Central Illustration** bottom right image). A subset of these patients only required CoA repair (n = 25) or bridging with an H1-BV procedure and CoA repair (n = 5) and had no biventricular survival failures during the study period. However, these patients were not identifiable prospectively: there was no difference in AAo flow, CMR-LVEDVi, AoV, or MV *z*-scores compared with the other patients (Supplemental Figure 3). Excluding the isolated CoA repair patients, survival for the rest (n = 32) was 91% (95% CI: 81-100%), 68% (95% CI: 52-84%), and 60% (95% CI: 42-78%) at 1, 5, and 10 years, respectively.

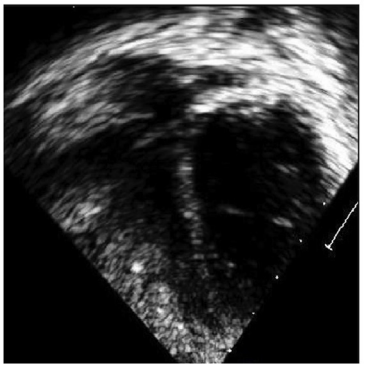
Given the limited number of patients with the composite outcome (n = 12), we only included 2 variables that we deemed clinically important in the multivariable Cox regression model (**Table 3**). The impact of a CoA repair is discussed previously. Patients without aortic coarctation repair were at higher risk of death, transplantation, or SV conversion (hazard ratio: 54.3; 95% CI: 6.3-471.1; $P < 0.001$) during follow-up. AAo flow was included as its measurement is a novel feature of this study and was found to be important in assignment to treatment pathways. Its impact on transplant-free biventricular survival was evaluated. Exploratory analysis of AAo flow had suggested a nonlinear effect on hazard, and this was included in the multivariate analysis by modeling AAo flow with penalized splines (**Figure 4**). This shows an increase in log hazard ratio for AAo flow <1.5 L/min/m^2, whereas at higher flows up to ~3.5 L/min/m^2, its effect was relatively constant and had only a small impact (Supplemental Figure 4). A decrease in AAo flow from 2.0 to 1.0 L/min/m^2 increased the hazard ratio by 3.2 (95% CI: 1.1-9.6). There were few patients with AAo flow >3.5 L/min/m^2, and this resulted in considerable uncertainty of its impact in that range.

PULMONARY HYPERTENSION OUTCOMES. Pulmonary hypertension was present initially in 10 (18.5%) patients after biventricular management. Four patients who had EFE underwent AoV intervention ± MV surgery ± EFE resection died with persistent pulmonary hypertension. The remaining patients had resolution of pulmonary hypertension

CENTRAL ILLUSTRATION **Cardiac Magnetic Resonance Imaging in Borderline Hypoplastic Left Hearts**

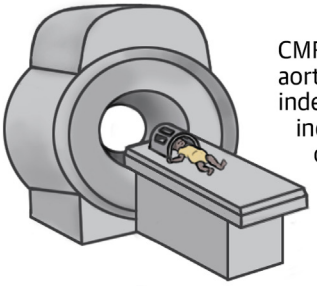


Which hypoplastic left hearts will have successful biventricular repair?



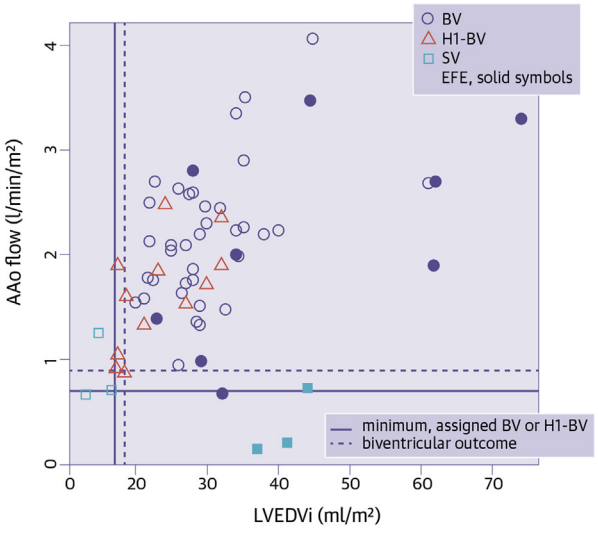
CMR (n=67)

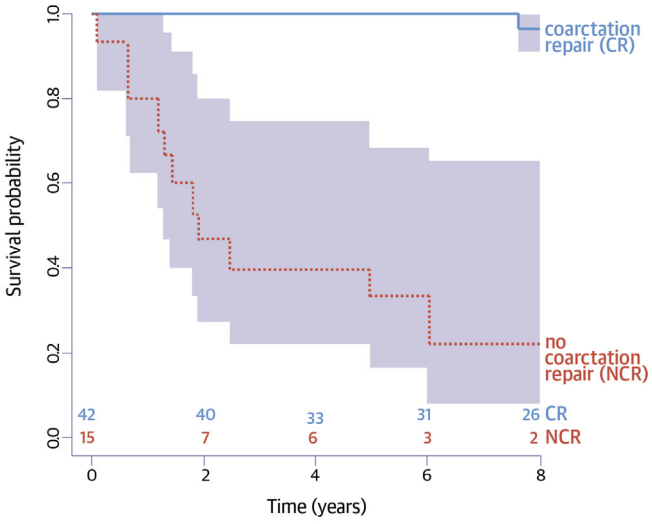
Biventricular repair (n=54)



CMR-derived ascending aortic flow is an integrative index of left heart performance independent of the size of left heart structures

Assignment to biventricular repair (n=57)





Kang S-L, et al. JACC Adv. 2022;1(3):100066.

Scatterplot of ascending aortic flow and CMR-LVEDVi of BV, H1-BV, and SV groups, each group further distinguished by presence/absence of endocardial fibroelastosis. Solid lines represent the smallest value based on assignment to either BV or H1-BV groups; broken lines represent the smallest value based on achieving eventual biventricular circulation. Kaplan-Meier survival curve demonstrating freedom from death, heart transplantation, and single-ventricle palliation in patients who had coarctation of aorta repair vs all others ($P < 0.001$). AAo = ascending aortic flow; BV = biventricular group; CMR = cardiac magnetic resonance imaging; EFE = endocardial fibroelastosis; H1-BV = hybrid 1 staging for intended biventricular repair; LVEDVi = left ventricular end-diastolic volume indexed by cardiac magnetic resonance imaging; SV = single ventricle.

TABLE 2 Assignment to Treatment Pathways: Proportional Odds Logistic Regression Model

	Odds Ratio	95% CI	*P* Value
CMR AAo flow (1/min/m^2)	2.05	3.41 to 0.90	0.001
EFE present	−2.86	−0.61 to −5.30	0.014
MV *z*-score	0.95	1.79 to 0.22	0.012
AoV *z*-score	−0.41	−0.26 to 1.09	0.23
CMR LVEDVi (mL/m^2)	0.02	−0.06 to 0.12	0.59

AAo = ascending aortic flow; AoV = aortic valve; CMR = cardiac magnetic resonance imaging; EFE = endocardial fibroelastosis; LVEDVi = left ventricular end-diastolic volume indexed; MV = mitral valve.

TABLE 3 Cox Proportional Hazards Model for Transplant-Free and Single-Ventricle Pathway Conversion Free Survival

	Hazard Ratio	95% CI	*P* Value
CoA repair not required	54.32	6.26-471.11	0.0003
AAo flow (linear component)	See Figure 4		0.20
AAo flow (nonlinear component)			0.33

Likelihood ratio test = 37.88, 4.99*df*, *P* = 4e-07.
AAo = ascending aortic flow; CoA = aortic coarctation.

after heart transplantation (n = 2) and following further MV and AoV procedures (n = 4). No patient with resolved pulmonary hypertension reverted to a hypertensive state.

Transplant-free biventricular survival for BV and H1-BV patients without pulmonary hypertension at any time was 94.4% (95% CI: 87.0%-100%) at 1 year, 81.1% (95% CI: 69.6%-90.7%) at 5 years, and 76.2% (95% CI: 63.4%-87.8%) at 10 years. In this group, the smallest LVEDVi (H1-BV infant) was 18.4 mL/m^2 by CMR, 4.8 mL/m^2 by 2D echocardiography, the lower limit for MV diameter was 4.8 mm (*z*-score −5.2) and AoV diameter 3.2 mm (*z*-score: −4.9), and lowest AAo flow was 0.9 L/min/m^2.

DISCUSSION

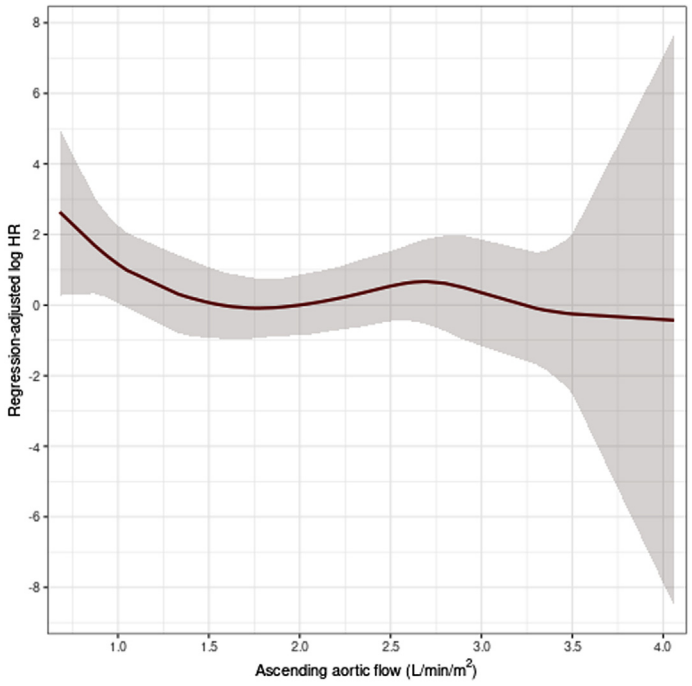
Based on combined CMR and echocardiographic imaging data, a biventricular strategy was pursued in 90% of our cohort (BV or H1-BV groups) with transplant-free and SV conversion-free survivals of 96%, 82%, and 77% at 1, 5, and 10 years, respectively. This is comparable to published outcomes of b-HLH with attainment of biventricular circulation, ranging from 73% to 90%, despite lower echocardiographic left ventricular end-diastolic dimension, MV, and AoV *z*-scores in our cohort compared to these studies.[1,3,9,12] This study also incorporates the absence of pulmonary hypertension as a criterion of success not reported in other studies.

This study suggests modifications and alternatives to historical imaging parameters utilized in decision-making of b-HLH for potential biventricular circulation. Significant underestimation of LVEDVi by 2D echocardiography compared with CMR was observed (group mean difference: 16.8 ± 8.1 mL/m^2). Factors limiting the accuracy of LV volume estimation by 2D echocardiography include geometrical assumptions and poor endocardial definition; thus, CMR-LVEDVi represents the gold standard.[6,16] The 2D echocardiographic criterion of LVEDVi ≥20 mL/m^2 would have precluded 83% of this cohort from biventricular repair. A non-apex-forming LV did not identify LVs with lower CMR-LVEDVi. In the BV without pulmonary hypertension group, the smallest LVEDVi by CMR was 18.4 mL/m^2 and 4.8 mL/m^2 by 2D echocardiography.

CMR-determined AAo flow integrated both anatomy and function of multilevel diseased left hearts. It provided unique information and had no/minor correlation with other left heart parameters such as MV or AoV *z*-scores or CMR-LVEDVi. In our cohort, the BV without pulmonary hypertension group had 1.5× AAo flow at baseline compared to BV and H1-BV patients with unsuccessful outcomes. In our institution's early experience, the mean AAo flow was 1.63 ± 0.57 in biventricular survivors and as low as 1.0 L/min/m^2 in one survivor.[6] In comparison, Li et al[17] have reported a mean of 1.8 ± 0.6 L/min/m^2 for Norwood survivors. Cardiac output (AAo flow) is a continuous variable, and while 2.0 L/min/m^2 is acceptable, 1.0 L/min/m^2 is low and of clinical concern. Despite our limited sample size, in this 1.0 to 2.0 L/min/m^2 range, there appears to be subsequent worse survival as manifest in our Kaplan-Meier curves and an increase in hazard of failure at AAo flows <1.5 L/min/m^2. Rather than regarding 1.5 L/min/m^2 as a threshold, it is moving down the range of AAo flow from 2.0 to 1.0 L/min/m^2 that should be regarded as increasing the hazard of biventricular failure by a ratio of 3.2, based on our multivariate analysis.

The BV and BV without pulmonary hypertension patients were heavily skewed toward either CoA as the first or only cardiac intervention. Excellent isolated CoA repair outcomes in patients with left heart hypoplasia has been reported by others.[18] In this study, we were not aware at the time of assignment if CoA repair would be the only procedure required as these patients did not have significantly different parameters of left heart

FIGURE 4 Log Hazard Ratio vs Ascending Aortic Flow for the Multivariate Cox Regression Model



The hazard rises approximately at flows <1.5 L/min/m^2. Between 1.5 and 3.5 L/min/m^2, the log hazard ratio is relatively constant and low, but at higher flows, there are few patients in this study and hence large uncertainty.

pathology compared with the other patients. This study confirmed 100% transplant-free biventricular survival in this subgroup but observed 17 (40%) patients with CoA repair required additional procedures, including 5 H1-BV procedures. The beneficial impact of the need for CoA repair on biventricular survival in b-HLH, even when the isolated CoA patients are excluded, is intriguing as additional procedures included 6 MV operations and 5 AoV interventions, which are both worrisome co-lesions but neither deleterious by our survival analyses.[4,11]. Our therapies for b-HLH promote left heart growth which is constrained by LV interstitial fibrosis (overt or microscopic). Severe CoA produces little LV fibrosis or myocyte disarray during fetal life and infancy compared with other obstructive lesions such as severe aortic stenosis.[19,20] Then if b-HLH is accompanied by CoA, any additional left heart lesions and the extent of LV fibrosis must be relatively mild, otherwise hypoplastic left heart syndrome would occur. The b-HLH hearts with limited fibrosis may have more growth potential once obstructive lesions have been relieved. As such, it appears prudent to identify these patients with aortic coarctation either in isolation or with associated lesions with potential for excellent long-term outcomes.

We summarize our approach: 1) decisions based on LV volume should use CMR-derived values. 2) The hazard of failure of a biventricular circulation increases as CMR-derived AAo flow decreases from 2.0 to 1.0 L/min/m^2, but this should be interpreted in the context of residual obstructive lesions and LV dysfunction. 3) CoA requiring treatment encourages us to pursue biventricular repair. In contrast, we are more cautious if significant aortic stenosis is present as the myocardium may be damaged. 4) EFE remains difficult to evaluate. Not all LVs with bright endocardium are stiff and invasive assessment of filling pressure may be required. EFE resection is feasible, but long-term outcomes for each patient remain uncertain. 5) Delay MV surgery for as long as possible. This remains true in general terms, but the increasing use of MELODY valves in the mitral position gives additional flexibility.[10]

STUDY LIMITATIONS. Prospectively choosing biventricular vs SV strategies for b-HLH infants is challenging. Small patient numbers and the sheer number of possible treatment sequences limited our statistical analyses. For example, 6 of 10 deaths occurred in patients who had AoV intervention, but this clinical observation did not prevail in our statistical analysis. The lack of simple criteria for biventricular repair is inherent to the complexity of left heart pathology in the b-HLH entity. In this regard, we emphasize this is not a comparative study between SV and biventricular strategies as these same patients may have survived SV management. However, we hope this series which integrates CMR-derived data and an expanded range of cardiac procedures will encourage others to collect and pool similar information to overcome the heterogeneity and establish effective management guidelines.

CONCLUSIONS

CMR-derived left heart assessment expands on historical 2D echocardiographic criteria to pursue biventricular repair. AAo flow, a functional parameter that integrates left heart performance, is a useful tool for assigning patients to a biventricular pathway. Transplant-free biventricular survival without pulmonary hypertension was improved by the dominant lesion being CoA and by higher AAo flows.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Assignment of borderline hypoplastic left heart infants to biventricular vs single-ventricle strategies is complex. Historically, decision-making has relied on 2-dimensional echocardiography which has limitations. Cardiac magnetic resonance imaging provides accurate ventricular volumes and measures of cardiac output.

TRANSLATIONAL OUTLOOK: Cardiac magnetic resonance imaging and expanded cardiac procedures offer new considerations and may expand the number borderline hypoplastic left heart infants deemed suitable for biventricular repair.

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KEY WORDS borderline left heart, left ventricle hypoplasia, magnetic resonance imaging

APPENDIX For supplemental text, tables, and figures, please see the online version of this paper.