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Echocardiographic parameters associated with biventricular circulation and right ventricular growth following right ventricular decompression in patients with pulmonary atresia and intact ventricular septum: Results from a multicenter study

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Abstract

Background: In patients with pulmonary atresia, intact ventricular septum (PA/IVS) following right ventricular (RV) decompression, RV size and morphology drive clinical outcome. Our objectives were to (1) identify baseline and postdecompression echocardiographic parameters associated with 2V circulation, (2) identify echocardiographic parameters associated with RV growth and (3) describe changes in measures of RV size and changes in RV loading conditions.

Methods: We performed a retrospective analysis of patients who underwent RV decompression for PA/IVS at four centers. We analyzed echocardiograms at baseline, postdecompression, and at follow up (closest to 1-year or prior to Glenn circulation).

Results: Eighty-one patients were included. At last follow-up, 70 (86%) patients had 2V circulations, 7 (9%) had 1.5 ventricle circulations, and 4 (5%) had single ventricle circulations. Follow-up echocardiograms were available in 43 (53%) patients. The majority of patients had improved RV systolic function, less tricuspid regurgitation (TR), and more left-to-right atrial shunting at a median of 350 days after decompression. Multivariable analysis demonstrated that larger baseline tricuspid valve (TV) *z*-score ($P = .017$), ≥ moderate baseline TR ($P = .045$) and smaller baseline RV area ($P < .001$) were associated with larger increases in RV area. Baseline RV area ≥6 cm^2/m^2 had 93% sensitivity and 80% specificity for identifying patients who ultimately achieved 2V circulation. All patients with RV area ≥8 cm^2/m^2 at follow up achieved 2V circulation. This finding was confirmed in a validation cohort from a separate center ($N = 25$). Factors associated with achieving RV area ≥8 cm^2/m^2 included larger TV *z*-score ($P = .004$), ≥ moderate baseline TR ($P = .031$), and ≥ moderate postdecompression pulmonary regurgitation ($P = .002$).

Conclusions: Patients with PA/IVS and smaller TV annuli are at risk for poor RV growth. Volume-loading conditions signal increased capacity for growth sufficient for 2V circulation.

KEYWORDS
catheter-based intervention, congenital heart disease, pediatric echocardiography, pulmonary atresia intact ventricular septum

1 | INTRODUCTION

Outcomes for patients with pulmonary atresia and intact ventricular septum (PA/IVS) vary substantially, depending largely on whether patients are candidates for biventricular (2V) repair.[1] Patients who undergo single ventricular palliation have lower long-term survival and increased risk for clinical morbidities including heart failure symptoms, arrhythmia, protein losing enteropathy, and need for repeat cardiac surgery.[2] Patients are at times selected to undergo one and one-half ventricular repairs (1.5V), in which there is prograde flow through the right heart and a significant right to left shunt—typically in the form of a superior cavopulmonary anastomosis (Glenn operation). Although patients with 1.5V circulation have improved survival compared to single ventricle patients, they continue to suffer arrhythmia, decreased exercise tolerance, and are at risk for conversion to single ventricle circulation.[3-5] In those without right ventricular (RV) dependent coronary circulation, RV cavity volume, RV morphology and tricuspid annular dimension largely dictate decision-making and ultimate circulation. The capacity for postnatal RV growth in this population is widely disparate, and factors which contribute to RV growth in this population are poorly understood.[6]

Baseline echocardiographic characteristics and clinical outcomes in PA/IVS have been studied extensively. In a large multicenter cohort, our group recently demonstrated that mild or no baseline TR was a significant risk factor for failing to achieve a 2V outcome.[7] Other risk factors suggested for failing to achieve a 2V outcome include smaller tricuspid valve (TV), smaller RV area, mild or no baseline tricuspid regurgitation (TR), and lack of left to right atrial septal flow.[1,7-10] Postdecompression echocardiographic parameters associated with achieving a 2V outcome have not been extensively studied. Furthermore, criteria for promoting a patient to a 2V circulation vary across centers.[11,12] The characteristics of RVs which are ultimately sufficient for 2V repair are not clearly understood. For these reasons, we chose to perform a multicenter, retrospective study to evaluate RV growth in patients with PA/IVS who undergo RV decompression. Specifically, our objectives were: (1) to identify baseline and postdecompression echocardiographic parameters associated with 2V circulation, (2) identify echocardiographic parameters associated with RV growth and (3) to describe changes in measures of RV size and changes in RV loading conditions.

2 | METHODS

We performed a case control study to assess echocardiographic parameters associated with achievement of a 2V circulation and with RV growth. This was a post hoc analysis of a previously performed study of clinical outcomes in patients with PA/IVS who underwent RV decompression in the neonatal period.[7] The patient population consisted of all infants with PA/IVS who underwent RV decompression at less than 30 days of age between January 1, 2005 and May 1, 2015 at four large pediatric centers (Children's Healthcare of Atlanta, Children's Hospital of Philadelphia, Cincinnati Children's Hospital Medical Center, and Texas Children's Hospital). These four participating centers comprise the Congenital Catheterization Research Collaborative (CCRC). Institutional Review Board approval was obtained at all centers. Patients were included if they: (1) were diagnosed at initial postnatal echocardiogram as having PA-IVS, (2) were deemed candidates for RV decompression, either surgically or via transcatheter methods, (3) underwent intervention within the first 30 days of life, and (4) underwent a postdecompression echocardiogram. Patients who were identified on cardiac catheterization to have RV dependent coronary circulation were not included, as they were not candidates for RV decompression. During the study period, RV dependent coronary circulation was defined as the presence of RV coronary connections in addition to proximal coronary artery stenosis or atresia. Patients were excluded if (1) prograde or retrograde flow was noted across the pulmonary valve (ie, critical pulmonic stenosis) on preintervention echocardiogram, or (2) were clearly noted to have Ebstein's anomaly of the TV. Data were collected using the web-based REDCap database, and Children's Healthcare of Atlanta functioned as the data coordinating center for the study. Patients with genetic anomalies were included in the study. Although patient enrollment was based upon volume of each participating center during the study period, we performed power calculations to ensure adequate sample size.

De-identified echocardiograms were analyzed by faculty members in pediatric echocardiography from each center (SAM, RS, DJG, LR). Echocardiograms were analyzed at three time points: baseline (preintervention), postdecompression (first postintervention echocardiogram) and at follow-up (closest to 1-year postdecompression, or last echocardiogram prior to Glenn operation, whichever is earlier). TV annular dimension and RV area were measured during diastole on the baseline and follow-up echocardiogram (Figure 1). Because we did not expect an immediate change in RV size or TV annular dimension, these measurements were not repeated on the postdecompression echocardiogram. *z*-Scores for the TV were calculated using the Detroit *z*-score package.[13] RV area was indexed to body surface area (BSA) calculated using the Haycock formula.[14] At each time point, echocardiograms were qualitatively assessed for RV systolic function, degree of TR, degree of pulmonary regurgitation (PR), and presence and direction of atrial level shunt. TR and PR were graded based upon adult standards adapted to pediatric use.[15] The following were taken into account when grading TR: vena contracta,

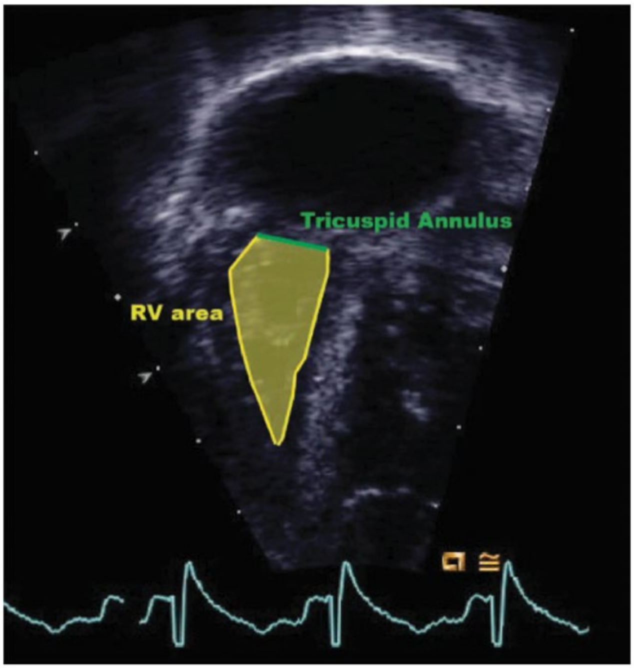

FIGURE 1 The tricuspid valve annulus (green) and right ventricular (RV) area (yellow) were measured in the 4-chamber view as depicted [Colour figure can be viewed at wileyonlinelibrary.com]

number of jets, and jet area. When grading PR, the following were considered: vena contracta, jet area, deceleration time, and presence or absence of flow reversal in the branch pulmonary arteries. When possible, regurgitation was assessed in more than one view. TV inflow duration indexed to the cardiac cycle length was measured and the presence of monophasic tricuspid valve inflow assessed on the baseline echocardiogram when possible. Inflow duration was measured as previously reported, and indexed to the cardiac cycle.[16,17] All 2D measurements and codification were performed based upon published standards, and methods of measurement were agreed upon by all four echocardiogram reviewers.[18] Regular web-based teleconferences were held during which example studies were reviewed in an attempt to generate "core laboratory" standards without necessitating the use of a single echocardiographic core laboratory. Interobserver reliability testing was performed for measurement of TV annulus diameter and TR grade as part of the initial study, and demonstrated excellent agreement between observers for both measures.[7]

The primary end point was the achievement of 2V circulation. Patients were considered to have 2V circulation if they satisfied the following criteria: (1) presence of antegrade pulmonary blood flow through a patent RV outflow tract, (2) had not undergone any cavopulmonary anastomosis (ie Glenn or Fontan operation) and (3) had no atrial septal defect (ASD) shunt, had an ASD with exclusive left-to-right shunt, or had an ASD and bidirectional shunt with a systemic saturation ≥92%. In cases without a Glenn operation in which the ASD could not be visualized, the systemic saturation had to be ≥92% to be considered as having achieved 2V circulation. For this outcome, cases were defined as those who achieved a 2V circulation, while those who achieved a 1.5V or single ventricle circulation were controls. Patients who initially underwent a systemic to pulmonary shunt or ductus arteriosus stent without subsequent stent or shunt intervention beyond 30 days from RV decompression and met the above criteria were included in the 2V group. Subjects were defined as having 1.5V circulation if they had antegrade flow through the tricuspid and pulmonary valves in combination with a Glenn operation or patients without a Glenn operation but bidirectional shunt across an atrial septal defect and saturations <92% at latest follow-up.

Because baseline echocardiographic parameters associated with achieving a 2V circulation had been previously reported in our initial study,[7] we did not repeat these analyses. We did generate an receiver operating characteristic (ROC) curve of baseline RV area and achievement of 2V circulation as this had not been previously performed. One secondary endpoint was RV growth as measured by change in RV area from baseline to the follow up echocardiogram on a continuous scale. Only patients with outpatient follow up echocardiograms were included in this analysis. Backwards stepwise linear regression was employed to create a model which best fit change in RV area. The following parameters were initially included in the model: baseline TV *z*-score, degree of baseline TR, baseline RV area, postdecompression pulmonary insufficiency, and postdecompression atrial level shunt direction.

In order to provide a clinically meaningful threshold for RV size, ROC curve analysis was used to identify a cut-point which best discriminated achievement of a 2V circulation. Subjects who achieved this cutoff value were defined as cases while those that did not were defined as controls. We then applied ROC curves obtained in the initial cohort to a validation cohort. Validation cohort subjects were recruited from a non CCRC member site—Lucile Packard Children's Hospital Stanford (LPCH)—and were not included in the original cohort. Univariate statistics were used to identify parameters associated with achieving an RV area greater than this threshold.

Based on the proportion of patients with baseline TR and 2V or <2V circulation in our initial study, desired power of 0.80, and $\alpha = .05$ we estimated a sample size of 39 would be necessary to study dichotomous end points (2V circulation or achievement of a particular RV area). In order to identify an expected correlation of $r = 0.5$ between a continuous predictor variable and change in RV area, a sample size of 29 would be necessary. As echocardiographic data did not follow a normal distribution, nonparametric analyses were used and data were reported as median and interquartile range (IQR). In comparing echocardiographic measures across the three time points, paired analyses were used. Continuous variables were compared using Wilcoxon rank-sum (2 groups) and Friedman's analysis (>2 groups); categorical variables were compared using McNemar's (2 groups) and Cochran's Q (>2 groups) tests. To compare baseline and postdecompression echocardiographic parameters to measures of RV growth, continuous variables were compared using Spearman correlation and categorical variables using the Mann–Whitney U test. IBM SPSS Statistics for Macintosh, Version 23.0 (IBM, Armonk, New York) was used for all analyses.

3 | RESULTS

Over the study period, 103 neonates underwent RV decompression for PA-IVS. Patient characteristics, procedural details and outcomes were previously reported.[7] In brief, there were two procedural deaths. An additional two who underwent decompression also had the diagnosis of Ebstein's anomaly and were excluded. Of the remaining 99 subjects, 81 (82%) had postdecompression echocardiograms available for review and comprised the study population. Five (6%) patients had identified genetic abnormalities. Ten (12%) patients had right ventricular coronary connections. Four (5%) underwent initial surgical decompression, while 77 (95%) underwent initial catheter-based decompression. Of those who underwent initial catheter-based decompression, radiofrequency perforation was performed in 53 (69%) while wire perforation was performed in 24 (32%). Surgical systemic to pulmonary artery shunt or stenting of the ductus arteriosus was performed in 37 (46%) of patients. Median follow-up time was 2.6 years (1.0-8.7). During the follow-up period, there were no mortalities, and 1 patient had a heart transplant. Seventy (86%) patients had 2V circulation, 7 (9%) had 1.5V circulation, and 4 (5%) had single ventricle circulation (Table 1). Glenn operations were performed at median 369 (298, 428) days of age. Follow up echocardiograms were available in 43 of 81 (53%) patients. Those without echocardiographic follow up had a median baseline RV area of 12.1 (9.2, 16.0) cm^2/m^2 compared to 8.3 (6.1, 12.5) cm^2/m^2 in those with echocardiographic follow-up (P = .011). Between those with and without echocardiographic follow-up, there was no significant difference in median TV z-score (−0.64 (−1.78, −0.12) vs −1.31 (−2.25, −0.22), P = .515), % with ≥ moderate baseline TR (24% vs 40%, P = .113), and % with 2V circulation (12% vs 16%, P = .411). Median age at follow-up echocardiogram was 347 (284, 422) days in the 2V group and 355 (160, 371) in the <2V group (P = .963). The oxygen saturation at last clinical follow-up was 97 (93, 99) in the 2V group and 90 (85, 96) in the <2V group (P = .006). Baseline echocardiographic images were sufficient to measure inflow duration in 28 of 43 (65%) patients and evaluate for E/A fusion in 18 of 43 (42%) cases. The validation cohort was comprised of patients who underwent RV decompression during the study period at LPCH. Of 31 patients who underwent decompression, 25 (81%) had sufficient follow up for inclusion in the study.

3.1 | Changes in echocardiographic parameters with RV decompression

Echocardiographic parameters at baseline, postdecompression, and at follow-up are provided in Table 2. From the baseline to postdecompression and follow-up echocardiogram, there was a serial decrease in the percentage of subjects with ≥ moderate RV systolic dysfunction (P < .001) and in the percentage of subjects with ≥ moderate TR (P < .001). Compared to the baseline echocardiogram, the postdecompression and follow-up echocardiogram also demonstrated lower median TR velocity (P < .001). For the cohort as a whole, there were no significant differences between median baseline and follow up measures of TV z-score and indexed RV area. The median (IQR) change in indexed RV area was 0.84 cm^2/m^2 (−2.6, 5.3), and in TV z-score was 0.48 (−0.59, 1.2). Compared to the initial postdecompression echocardiogram, more patients at follow up had bidirectional and left-to-right shunt flow across the atrial septum, and fewer patients had right-to-left shunt flow across the atrial septum.

TABLE 1 Postdecompression echocardiographic parameters associated with two ventricle circulation

	Two ventricle	Single or 1.5 ventricle	
	(N = 70)	(N = 11)	*P* value
RV function			.685
Normal/mildly depressed	56 (81.2%)	8 (72.7%)	
Moderately/severely depressed	13 (18.8%)	3 (27.3%)	
TR severity			.006
None/mild	37 (53.6%)	11 (100.0%)	
Moderate/severe	32 (46.4%)	0 (0.0%)	
PDA			1.00
Present	63 (90.0%)	10 (90.9%)	
Absent	7 (10.0%)	1 (9.1%)	
PV velocity (m/s)	2.1 (1.7, 2.8)	1.5 (1.4, 1.5)	.002
PR severity			
None/mild	7 (10.0%)	2 (18.2%)	.602
Moderate/severe	63 (90.0%)	9 (81.8%)	

Data presented as *N* (%) and median (25th-75th IQR) where applicable. Abbreviations: PDA, patent ductus arteriosus; PR, pulmonary regurgitation; PV, pulmonary valve; RV, right ventricle; TR, tricuspid regurgitation.

TABLE 2 Comparison of echocardiographic parameters at baseline, postdecompression, and follow-up

	Baseline	Postdecompression	Follow-up	*P* value
Age (days)	3 (2, 4)	6 (3,9)	351 (277, 405)	N/A
RV systolic dysfunction				
None/mild	10 (23.3%)	36 (83.7%)	42 (97.7%)	<.001
Moderate/severe	33 (76.7%)	7 (16.4%)	1 (2.3%)	
TR severity				
None/mild	17 (39.5%)	29 (67.4%)	36 (83.7%)	<.001
Moderate/severe	26 (60.5%)	14 (32.6%)	7 (16.4%)	
TR velocity (m/s)	5.0 (4.7, 5.4)	3.1 (2.8, 3.6)	3.2 (2.4, 3.5)	<.001
TV *z*-score	−0.64 (−1.78, −0.12)	N/A	−0.30 (−1.93, 0.38)	.331
PV velocity (m/s)	N/A	1.98 (1.54, 2.50)	1.83 (1.50, 3.28)	.937
PV regurgitation severity				
None/mild	N/A	6 (14.0%)	9 (20.9%)	.388
Moderate/severe	N/A	37 (86.0%)	34 (79.1%)	
RV area/BSA (cm^2/m^2)	12.1 (9.2, 16.0)	N/A	14.3 (8.3, 18.3)	.449
ASD flow				
Right to left	43 (100%)	25 (58.1%)	8 (18.6%)	<.001
Left to right	N/A	0 (0.0%)	5 (11.6%)	
Bidirectional	N/A	14 (32.6%)	17 (39.5%)	
No atrial level shunt	N/A	0 (0.0%)	4 (9.3%)	
Not visualized	N/A	4 (9.3%)	9 (21%)	

Data presented as *N* (%) and median (25^{th}-75^{th} IQR) where applicable.
P values refer to comparisons of all 3 categories when present.
N = 43 for all groups. Abbreviations: ASD, atrial septal defect; BSA, body surface area; PV, pulmonary valve; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve.

3.2 | RV area and 2V circulation

Baseline RV area demonstrated ability to discriminate patients who ultimately achieved 2V circulation in the initial cohort with an area under the curve (AUC) = 0.88 (95% CI = 0.71, 1.00) (Figure 2A). Baseline RV area ≥ 6 cm^2/m^2 had 93% sensitivity, 80% specificity and odds ratio of 50.4 (95% CI = 8.4, 304.0) for discriminating patients who achieved 2V circulation. In the validation cohort, baseline RV area also demonstrated discriminatory ability with an AUC = 0.86 (95% CI = 0.70, 1.00) (Figure 2C). RV area ≥6 cm^2/m^2 had 89% sensitivity, 71% specificity and odds ratio of 21.2 (95% CI = 2.36, 191.60) for discriminating patients who achieved 2V circulation. Postdecompression echocardiographic parameters associated with achieving a 2V circulation are listed in Table 1. Higher pulmonary valve velocity and the presence of ≥ moderate TR were associated with 2V circulation. No patient with ≥ moderate postdecompression TR failed to achieve a 2V circulation.

Logistic regression demonstrated that RV area at follow-up was also significantly associated with 2V vs <2V circulation (OR = 2.15, 95% CI = 1.10, 4.23). This measure demonstrated good discriminatory ability with an AUC = 0.96 (95% CI = 0.90, 1.00) (Figure 2B). RV area ≥8 cm^2/m^2 had 87% sensitivity and 100% specificity for discriminating patients who achieved 2V circulation with an odds ratio of 67.0 (95% CI = 3.2, 1389.9). In the validation cohort, follow up RV area also demonstrated ability to discriminate between patients who achieved a 2V circulation with AUC = 0.99 (95% CI = 0.96, 1.00) (Figure 2D). RV area ≥ 8 cm^2/m^2 had 95% sensitivity and 83% specificity for identifying patients achieved 2V circulation with an odds ratio of 90.0 (95% CI = 4.7, 1708.5).

All 33 patients with follow up RV area ≥8 cm^2/m^2 achieved a 2V circulation, compared to 5 of 10 patients with follow-up RV area <8 cm^2/m^2 (Figure 3). Factors associated with achieving an RV volume ≥8 cm^2/m^2 included baseline TV annulus *z*-score, baseline TR, and postdecompression PR (Table 3). The association between larger baseline RV area and achieving a follow up RV area ≥8 cm^2/m^2 approached statistical significance. Of the three patients with baseline TV *z*-score > −2 who did not achieve an RV area ≥8 cm^2/m^2, all three had mild or no baseline TR, and two of the three had mild or no postdecompression PR. Of the three patients with baseline TV *z*-score < −2 who achieved an RV area ≥8 cm^2/m^2 at follow up, 2 of the 3 had ≥ moderate baseline TR, and all 3 had ≥ moderate postdecompression PR.

3.3 | Factors associated with RV growth

Echocardiographic measures associated with changes in RV size are provided in Table 4. Smaller baseline RV area and TV *z*-score correlated with larger changes in each of these measures. Patients with

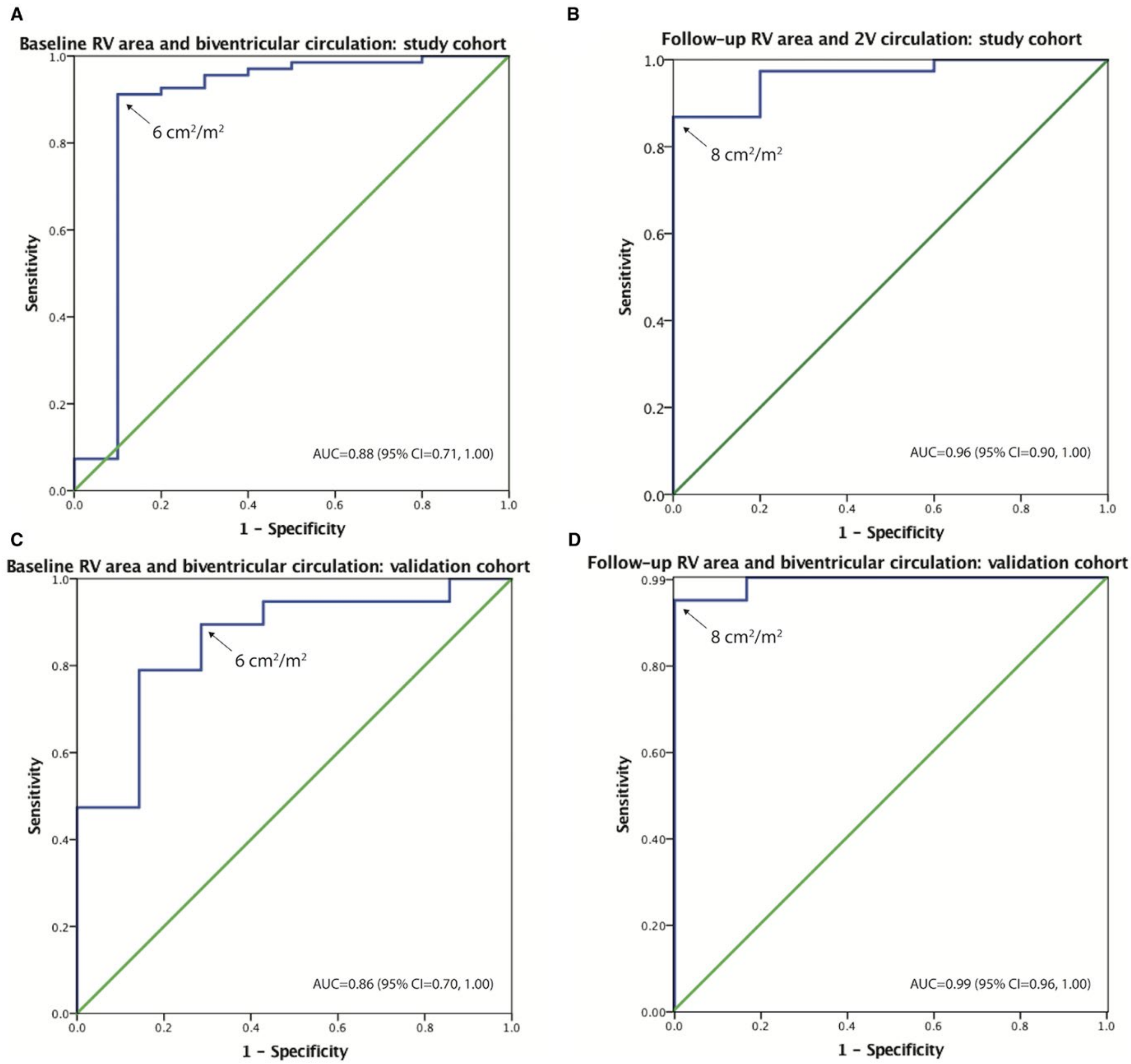

FIGURE 2 These ROC curves displays the ability of RV area obtained at baseline (A) and at follow-up (B) to discriminate the likelihood of achieving a biventricular (2V) circulation. The discriminatory abilities of RV area at baseline and follow up were then validated in separate cohort (C and D). Abbreviations: ROC, receiver operating characteristic; RV, right ventricle [Colour figure can be viewed at wileyonlinelibrary.com]

≥ moderate baseline TR had larger increases in RV area compared to those with no or mild TR (Figure 4). There were no significant association with tricuspid inflow duration or TV inflow pattern and degree of change in TV *z*-score or RV area. There was a trend toward larger change in RV area in patients with biphasic TV inflow pattern ($P = .064$). Postdecompression TR was not associated with changes in TV *z*-score or RV area. Bidirectional atrial level shunt (as compared with exclusive right to left shunt) postdecompression was associated with larger increase in RV area, although this finding did not reach significance. Longer follow up time was not associated with change in RV area ($R = 0.24$, $P = .16$). Among 43 patients with follow-up echocardiograms, 26 (60%) underwent radiofrequency perforation, while 13 (30%) underwent wire perforation. Systemic to pulmonary artery shunt or ductus arteriosus stent was performed in 37 (46%) patients. Nineteen (44%) underwent repeat RV decompression. Patients who underwent radiofrequency perforation had median change in RV area 0.84 (−2.89, 5.85) cm^2/m^2, and median change in TV *z*-score 0.57 (−0.08, 1.41) compared to −0.36 (−2.54, 2.72) and 0.46 (−1.17, 1.10) in those who underwent wire perforation ($P = .478$, .273, respectively). Patients who underwent surgical systemic to pulmonary artery shunt or ductus arteriosus stent had median change in RV area 2.17 (−1.26, 5.68) and median change in

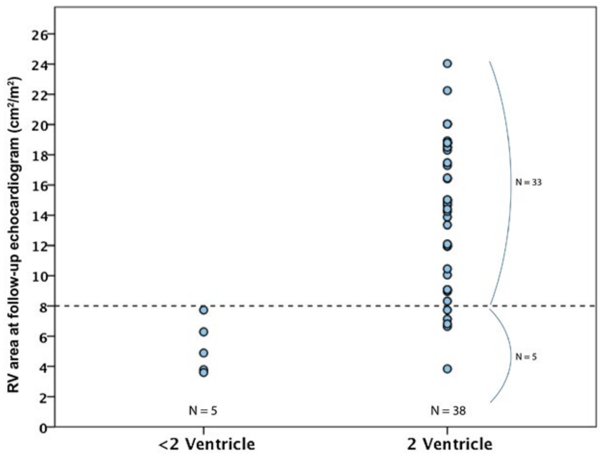

FIGURE 3 This scatter plot depicts RV area at follow up in subjects with 2V and <2V circulations. The dashed line represents RV area of 8 cm^2/m^2. All 33 patients with RV area ≥8 cm^2/m^2 achieved a 2V circulation, compared to 5 of 10 patients with RV area <8 cm^2/m^2. Abbreviation: RV, right ventricle [Colour figure can be viewed at wileyonlinelibrary.com]

TV *z*-score 0.56 (−0.21, 1.83) compared to −1.11 (−7.39, 4.65) and 0.29 (−1.15, 0.73) in those did not undergo systemic to pulmonary artery shunt or ductal stent (*P* = .118, .275, respectively). Patients who underwent repeat RV decompression had median change in RV area −0.36 (−2.59, 5.40) and median change in TV *z*-score 0.46 (−0.92, 0.66) compared to 1.66 (−2.66, 5.46) and 0.55 (−0.32, 1.79) in those did not undergo repeat RV decompression (*P* = .695, .278, respectively).

The multivariable linear regression model with best fit for the continuous outcome change in RV area included the following parameters: baseline TV *z*-score, baseline ≥ moderate TR, baseline RV area, and ≥ moderate postdecompression PR with an R^2 of 0.72. Results of this multivariable analysis are provided in Table 5.

4 | DISCUSSION

In this multicenter, retrospective analysis of patients with PA/IVS who underwent RV decompression, we found that baseline RV area ≥6 cm^2/m^2 had high discriminative value in identifying patients who achieved 2V circulation. Postdecompression parameters associated with achieving a 2V circulation included ≥ moderate postdecompression TR and higher pulmonary valve velocity. All patients with RV area ≥8 cm^2/m^2 at follow up had 2V circulation. Moderate or greater baseline TR and ≥ moderate postdecompression PR were associated with achieving an RV area of ≥8 cm^2/m^2. Preintervention parameters associated with greater RV growth included larger TV annulus *z*-score, smaller RV area, and ≥ moderate TR. At follow up, the majority of subjects exhibited improved RV systolic function, reduced TR and more left to right shunting at the atrial septum.

TABLE 3 Factors associated with achieving RV end diastolic area ≥8 cm/m^2

	RV end diastolic area ≥8 cm^2/m^2 (N = 33)	RV end diastolic area <8 cm^2/m^2 (N = 10)	*P* value
Baseline echocardiogram			
TV annulus size (*z*-score)	−0.500 (−1.15, −0.11)	−2.44 (−4.78, -0.87)	.004
TR severity			.031
None/mild	10	7	
Moderate/severe	23	3	
RV area (cm^2/m^2)	12.4 (10.2, 14.8)	7.4 (4.7, 15.9)	.064
Postdecompression echocardiogram			
TR Severity			.287
None/mild	21	8	
Moderate/severe	12	2	
ASD flow (N=39)			.205
Right to left	17	8	
Bidirectional	12	2	
PV velocity (m/s)	2.04 (1.59, 2.80)	1.89 (1.53, 2.00)	.313
PR Severity			.020
None/mild	2	4	
Moderate/severe	31	6	

Data presented as *N* (%) and median (25^{th}-75^{th} IQR) where applicable.
N = 43 unless otherwise specified. Abbreviations: PR, pulmonary regurgitation; PV, pulmonary valve; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve.

TABLE 4 Factors associated with measures of RV growth

	Change in TV annulus (z-score)	P value	Change in RV Area (cm^2/m^2)	P value
Baseline echocardiogram				
TV annulus size (z-score)	r = −0.342	.022	r = 0.130	.413
TR severity				
None/mild	−0.32 (−1.16, 0.66)	.462	−1.24 (−6.05, 2.05)	.048
Moderate/severe	0.50 (−0.13, 1.79)		1.76 (−2.46, 5.67)	
RV area (cm^2/m^2)	r = −0.156	.318	r = −0.425	.005
TV inflow duration ratio (N = 28)	r = −0.151	.435	r = −0.278	.152
TV inflow pattern				
Biphasic (N = 10)	0.48 (−0.06, 1.17)	.330	1.35 (−1.53, 6.75)	.064
Monophasic (N = 8)	0.21 (−1.21, 1.47)		−0.53 (−17.26, 3.94)	
Postdecompression echocardiogram				
TR Severity				
None/mild	0.53 (−0.54, 1.63)	.374	0.84 (−1.90, 4.77)	.968
Moderate/severe	0.29 (−0.60, 0.62)		1.23 (−5.62, 5.56)	
ASD flow (N = 39)				
Right to left	0.53 (−0.80, 1.81)	.475	−0.66 (−2.69, 3.65)	.210
Bidirectional	0.23 (−0.38, 0.82)		2.5 (−4.77, 6.50)	
PR severity				
None/mild	0.12 (−1.13, 0.66)	.684	−1.92 (−2.58, 2.68)	.449
Moderate/severe	0.48 (−0.32, 1.23)		1.53 (−2.46, 5.40)	

Data presented are Spearman correlation coefficient (r) and median (25th-75th IQR) where applicable.
Changes in TV annulus z-score and RV area refer to changes from baseline to follow-up echocardiogram.
N = 43 unless otherwise specified. Abbreviations: ASD, atrial septal defect; PR, pulmonary regurgitation; RV, right ventricle; TR, tricuspid regurgitation; TV, tricuspid valve.

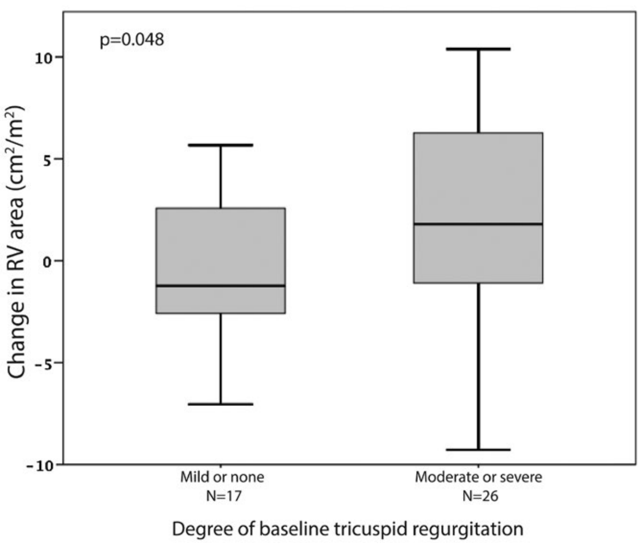

FIGURE 4 These box and whisker plots depict the change in right ventricular area from baseline to follow up in subjects with mild or no tricuspid regurgitation and those with ≥ moderate tricuspid regurgitation

Clinical and echocardiographic predictors of 2V circulation in infants with PA/IVS who have undergone RV decompression have been extensively described.[7,10,12,19-21] The primary end points in these studies are frequently survival and the achievement of a 2V circulation. While the achievement of a 2V circulation is a clinically relevant outcome measure, electing to promote a particular patient down a 2V or single ventricular pathway can be a subjective decision, influenced heavily by institutional practice.[11,12] RV size is one of a few important factors which influence the choice of ultimate surgical strategy. Furthermore, there is substantial variation between patients promoted down either pathway. Within <2V patients, those with 1.5V circulation tend to have improved survival relative to single ventricle patients. Within 2V patients, there is considerable variation in exercise capacity due in part to RV size.[22] For these reasons, we chose to study RV growth in this population.

The capacity for RV growth in this population is fascinating. While some reports suggest that this capacity is limited to growth proportional to somatic growth,[23,24] others suggest that there is capacity for growth beyond the matching of somatic growth, in even the smallest of RVs.[25-27] However, anatomic and physiologic factors associated with RV growth have not been extensively investigated. Markers of RV growth which have been studied in this population include change in TV z-score[6,20] and right ventricular end diastolic volume as measured by planimetry of RV angiograms.[6] We believe RV area to be an intuitive and easily reproducible measure, ideally suited

TABLE 5 Multivariable linear regression analysis of change in right ventrical area (cm^2/m^2)

	ß coefficient	Standard error	*t*-value	*P* value
Baseline tricuspid valve annulus (*z*-score)	1.07	0.43	2.50	.017
Baseline ≥ moderate tricuspid regurgitation	3.11	1.50	2.07	.045
Baseline RV area (cm^2/m^2)	−0.91	0.10	−9.25	<.001
Postdecompression ≥ moderate pulmonary regurgitation	3.02	2.01	1.50	.141

R^2 for model = 0.72.
N = 43.

for this clinical context. In the present study, we found that higher degree of baseline TR severity was associated with larger increase in RV area. In our initial report of clinical outcomes in this cohort, higher degree of TR severity was associated with 2V circulation.[7] In reports of fetuses with PA/IVS, higher degree of TR has been associated with larger RV size and eventual 2V circulation.[28,29] Taken together, these studies suggest that during the period of rapid cardiac growth and development present in prenatal and early postnatal life, volume loading may stimulate increases in RV volume. However, this relationship is not entirely straightforward. More compliant RVs should be more accommodating of increased volume load and subsequently have more RV growth. While we found no relationship between tricuspid valve inflow duration and RV growth, the association between biphasic tricuspid valve inflow and increased change in RV area approached significance. Since atrial level shunting reflects ventricular compliance, patients with more compliant RVs should have bidirectional as opposed to exclusively right to left flow. Our finding of less right to left flow from the postintervention study to the follow up study likely represents improved RV compliance. However, we found no association between measures of RV growth and the direction of postintervention atrial septal flow. Furthermore, although increased baseline TR was associated with RV growth, TR severity lessened after decompression, and postdecompression TR was not associated with a greater degree of RV growth. In the setting of PA/IVS, greater baseline TR severity may simply be a marker of more favorable RV myocardial mechanics, which in turn relate to improved ventricular growth over time. RV growth in this population is a complex process, and is difficult to predict. It appears that the parameters most helpful in predicting growth sufficient for 2V circulation are baseline TV size, RV size, and degree of TR. TV inflow pattern may also be helpful. Postdecompression PR appears to be a consequence of successful decompression, promoting more effective forward flow, and may also contribute to RV growth. Although ventricular compliance likely plays a role, the direction of atrial septal flow and TV inflow duration do not appear to be helpful in predicting RV growth.

While many anatomic factors typically influence clinical outcome in this population, one of the most important is the size of the RV. Based on the ROC curve analysis described in the present study, an indexed RV area of 8 cm^2/m^2 at follow up appears to be a useful cut-point to allow for the accurate discrimination of those patients who will be able to manage with a 2V circulation. Larger baseline TV *z*-score, ≥ moderate baseline TR and ≥ moderate postdecompression PR were associated with the achievement of this cut-point. In those with TV *z*-scores < −2, baseline TR and postintervention PR may be particularly important. While the association between larger baseline RV area and follow up RV area ≥8 cm^2/m^2 approached significance, smaller baseline area was associated with a higher degree of RV growth. While these findings may appear inconsistent, they are easily resolved. While larger baseline RV size is beneficial, even those with small RV cavities have the potential for RV growth. Historical studies have suggested that subjects with baseline TV *z*-score < −3 are unable to achieve a 2V outcome, and this led to the practice of eliminating these patients from consideration for 2V repair.[25,30] However, more complex algorithm—including TV *z*-score, RV area, and degree of baseline TR—is likely necessary to decide whether or not RV decompression could potentially facilitate a 2V outcome.

There are important limitations to this study. While this is a relatively large cohort of patients from multiple institutions, data collection was not prospective. We only included patients chosen for RV decompression. This resulted in a relatively small number of patients who did not achieve a biventricular circulation. This would also exclude patients with very small RV size or TV annular dimension, as these patients who not have undergone RV decompression. Efforts were made to standardize follow up time, in that the echocardiogram closest to 1 year of age was recorded. In patients who underwent a Glenn operation, the most recent echocardiogram prior to the Glenn was utilized. Despite this, follow-up time was similar between patients with 2V and <2V circulation, as most patients in this cohort who underwent a Glenn operation did so close to or slightly beyond one year of age. Furthermore, change in RV area indexed to body surface area was unrelated to follow up time. RV area measured in a single plane may miss important aspects of RV size. In particular, the RV outflow tract is not visualized in this view. This may account for the minority of cases in which RV area did not accurately discriminate between 2V and <2V circulation. Quantitative measurements were made by four different observers at four institutions. However, efforts were taken to ensure sufficient agreement between observers, which was demonstrated to be excellent when tested.[7] RV dysfunction, TR and PR grading criteria were explicitly defined. Despite these efforts, assessment of these parameters remains qualitative. Other grading criteria or quantitative techniques (such as measuring regurgitant fraction) may reveal a closer relationship between PR and RV growth. Follow-up echocardiograms were only available for review in 43 (53%) patients in the study cohort. While patients with and without follow up echocardiograms were similar in reference to baseline TV *z*-score and ultimate 2V circulation, subjects without follow up echocardiograms had larger RV area at baseline. This introduces selection bias into the analyses of RV growth, as those with larger RVs at baseline are less likely to exhibit substantial increases in RV size relative to body surface area. To address this limitation, we confirmed the finding that follow-up RV area ≥8 cm^2/m^2 effectively discriminated patients with 2V and <2V circulation in a validation cohort. Our findings reflect associations between echocardiographic variables and measures of RV growth and do not imply the presence of a causal relationship. Specifically, while ≥ moderate baseline TR was associated with larger change in RV area, the mechanism of this association warrants further investigation. The assessments of TV inflow duration and pattern are further limited as a large portion of echocardiograms lacked the images to perform these assessments. These—and other—RV diastolic parameters should be investigated in future studies as indicators of potential RV growth.

5 | CONCLUSIONS

In this multicenter, retrospective study, we found that in infants born with PA/IVS who have undergone RV decompression there are multiple factors associated with RV growth and ultimate 2V outcome. Baseline RV area ≥6 cm^2/m^2 has good discriminatory value in identifying patients who ultimately achieve 2V circulation. Larger TV annulus *z*-score, and ≥ moderate baseline TR are associated with improved RV growth. RV area at follow up ≥8 cm^2/m^2 appears to be sufficient for a 2V circulation. Larger baseline RV area, ≥ moderate baseline TR and ≥ moderate postdecompression PR were associated with achieving this threshold RV area of ≥8 cm^2/m^2. In subjects with TV *z*-score < −2, TR and PR appear to be particularly important markers of potential RV growth.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Shiraz A. Maskatia, MD is the primary author. He designed the concept, Interpretated data analysis, Drafting article, Statistics, and Data collection.

Christopher J. Petit, MD. He designed the concept, Interpretated the data, Critical revision of article, Approval of article, and Data collection.

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