Tricuspid Regurgitation in Hypoplastic Left Heart Syndrome
Mechanistic Insights From 3-Dimensional Echocardiography and Relationship With Outcomes

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Background—Our purpose was to test the following hypotheses: (1) patients with hypoplastic left heart syndrome who develop significant tricuspid regurgitation (TR) or require tricuspid valve (TV) surgery in the medium term have detectable TV abnormalities by 3-dimensional echocardiography (3DE) prestage 1 palliation and (2) TR is associated with reduced survival and increased TV intervention.

Methods and Results—Infants were prospectively studied with 3DE and 2DE prestage 1 and followed up for the end points of TR, TV surgery, transplantation, or death. From prestage 1 3DE, spatial coordinates of TV annulus and leaflets were extracted; annulus size, leaflet area, prolapse volume, tethering volume, bending angle, and papillary muscle angle were measured. TR was assessed prestage 1 and at latest follow-up. Of 70 patients, 62 (88.6%) had mild or less TR and 8 (11.4%) had moderate or greater TR prestage 1. Prestage 1 tethering volume correlated to leaflet area (r=0.736; P<0.001), annulus area (r=0.651; P<0.001), right ventricular end-diastolic area (r=0.347; P=0.003), fractional area change (r=−0.387; P<0.001), and TR grade (r=0.447; P<0.001). At follow-up, 46 (65.7%) had mild or less TR (group A) and 24 (34.3%) had moderate or greater TR (group B). Prestage 1 3DE showed greater TV tethering volume and flatter annulus in group B. Survival was better in group A.

Conclusions—Increased TV tethering volume and flatter bending angle prestage 1 palliation is associated with TV failure at medium-term follow-up. Increased prestage 1 tethering is related to having larger TV annulus, larger leaflet area, larger right ventricular size, and reduced systolic function. TR progression results in increased TV intervention and decreased survival. (Circ Cardiovasc Imaging. 2014;7:765-772.)

Key Words: echocardiography, three-dimensional ■ heart ventricles ■ hypoplastic left heart syndrome ■ pediatric cardiology ■ tricuspid valve

Tricuspid regurgitation (TR) is associated with morbidity and mortality in children with hypoplastic left heart syndrome (HLHS).1-3 Cross-sectional studies using 2-dimensional echocardiography (2DE), 3-dimensional echocardiography (3DE), and intraoperative surgical inspection of the tricuspid valve (TV) after stage 1 palliation have suggested multiple causative factors for TR in HLHS. These include annular and ventricular dilation, leaflet prolapse and tethering, leaflet dysplasia, papillary muscle (PM) displacement, and right ventricular (RV) dyssynchrony.4,6 Real-time 3DE has emerged as a clinically useful tool for anatomic and functional assessment of atrioventricular valves before and after surgical repair.7,8 Several studies have shown the added value of 3DE over 2DE in the evaluation of mitral valve disease.5,9-16 In pediatric subjects, real-time transthoracic 3DE generates optimal images of the TV.4,9-10 Quantitative 3DE permits evaluation of the spatial relationships between the TV annulus, leaflets, and the supporting apparatus by measurement of tethering and prolapse volumes, leaflet and annular areas, and PM angles.4,11 We have reported the use of quantitative 3DE to assess mechanisms of TR and demonstrated that this technique is able to detect areas of TV tethering and prolapse in HLHS.4

Previous studies have evaluated mechanisms for TR in HLHS at or beyond the time of the second-stage palliation; however, there is a paucity of literature on TV function before...
stage 1 and its potential implications on TR and RV function at follow-up. The relevance of prestage 1 TR in the management of HLHS is unknown because there are no longitudinal studies on evolution of TV function over time. After our initial reports on the use of 3DE in the assessment of HLHS, we established a prospective, longitudinal, bi-institutional study since 2007 to serially examine TV function using 2DE and 3DE. Our primary hypothesis was that patients who develop significant TR at any stage have functional abnormalities of the TV before stage 1 palliation. Accordingly, the specific aims of the present study were to (1) prospectively derive parameters for quantitative assessment of the TV by real-time 3DE before stage 1 palliation and (2) correlate the severity of TR at follow-up with medium-term outcomes in patients with HLHS.

Methods

Patient Population
This was a prospective study of patients with classic HLHS born at the Stollery Children’s Hospital, University of Alberta and the Children’s Hospital and Medical Center, University of Nebraska Medical Center from January 2007. Variants of HLHS such as heterotaxy or unbalanced atrioventricular septal defect were excluded. Patients were also excluded if their gestational age was <35 weeks or if extracardiac malformations were present. Institutional review board approvals were obtained from both institutions, and informed consent was obtained from parents of all recruited patients.

Before stage 1 palliation, all patients were cared for in a neonatal intensive care unit on prostaglandin E1. The physicians responsible for clinical care determined the requirement for ventilation or inotropic support. Patient demographics and acid-base status at the time of echocardiogram were recorded. Patients underwent stage 1 palliation with an RV-to-pulmonary artery conduit (Sano shunt) as the proviso for pulmonary blood flow. Elective bidirectional cavopulmonary anastomosis was performed between 4 and 6 months of age on the basis of the treating cardiologist’s clinical assessment, including level of urgency for single ventricular unloading, trends in arterial oxygenation, and somatic growth. Data were assessed via review of surgical database and clinical records for outcomes including the occurrence and timing of TV repair, further palliative surgery, cardiac transplant, or death.

Two-Dimensional Echocardiography
Standard 2DE was obtained before stage 1 palliation and at follow-up on iE33 (Philips Medical Systems, Andover, MA) or Vivid 7 (GE Medical Systems, Milwaukee, WI) ultrasound systems with ECG tracing. Before stage 1 palliation and at latest follow-up, the following 2DE measurements were included: (1) RV fractional area change, (2) RV diastolic area, (3) left ventricular (LV) diastolic area, (4) RV sphericity index, and (5) degree of TR. RV areas were measured from the apical 4-chamber view by tracing the RV endocardium in systole and diastole, and percentage fractional area change was calculated as (end-diastolic area−end-systolic area)/end-diastolic area. Sphericity index was measured at end-diastole from the apical 4-chamber view, with the long-axis dimension measured from the midportion of the TV annulus to the RV apex and the short-axis dimension measured from the free wall to the septum perpendicular to the long-axis dimension at its midpoint. LV size was measured as LV area at end-diastole from the apical 4-chamber view. Ventricular sizes were indexed to body surface area calculated using the Haycock formula.

TR was assessed with 2DE before stage 1 palliation and at most recent follow-up (before TV surgery, cardiac transplantation, death, or conclusion of the study) by qualitative grading. The severity of TR was graded as follows: trivial (narrow single jet), mild (multiple narrow jets), moderate (wide jet reaching midportion of the right atrium), and severe (wide jet reaching the back wall of the right atrium). The TR grades at latest follow-up were grouped as mild or less (group A) and moderate or greater (group B) for analysis.

Three-Dimensional Echocardiography

Quantification

The raw 3DE data sets were transferred from the ultrasound system to an offline system for analysis (TomTec Inc, Unterschleissheim, Germany) as described previously. In brief, one experienced observer (T.C.) performed all analyses in a blinded fashion. End-diastole was defined as the frame after TV closure, and end-systole was defined as the frame before TV opening. The number of frames between end-diastole and end-systole was counted, and midsystole was defined as the midpoint. Twelve radial planes were obtained (every 15°) around the center of the TV annulus, and the annulus was delineated at the leaflet hinge points in midsystole. To delineate the 3D surface of the leaflets, 9 radial planes (20° between each) were obtained around the center point of the TV annulus. In midsystole, 9 coordinate points were placed along the leaflet from annulus to annulus on each plane. To mark the anterior PM, the tip and base of the anterior PM was triangulated from 3 planes that were centered on the TV annulus at 3 equidistant points. From each point in turn, the plane was rotated manually until the tip of the PM was identified and a marker was placed. From the same annular point, the base of the PM was marked using the same technique. This was performed from 3 TV annular points such that the PM tip and base were each marked by 3 markers.

All points were converted into spatial coordinates (x, y, and z) and exported into Matlab (MathWorks Inc, Natick, MA) for analysis. This proprietary software was used to develop 3D models of the TV and its apparatus for analysis as described previously. Briefly, by using the extracted x, y, and z spatial coordinates, the software defined 2 separate surfaces, one surface that is fit to the TV leaflets and one that is fit to the annulus. The coordinate system was rotated and translated so that the origin (0, 0, 0) is at the center of the annulus and the z axis is perpendicular to the best-fit plane to the annulus, as shown in Figure 1A and 1C, for 2 representative subjects. In this new frame of reference, the leaflet and annular surfaces were defined by z-coordinates over a uniformly spaced x−y grid, with points every 1.0 mm. The best-fit annular surfaces for 2 sample cases are shown in Figure 1A and 1C, showing the uniformly spaced mesh grid that defines a smooth surface passing through all annular points. A similar surface was defined for the leaflet points, shown in Figure 1B and 1D, with a solid texture to highlight the volume contained by the leaflet. The volume was calculated as the sum of elemental rectangular volumes defined in the x−y dimension by the uniformly spaced grid and in the z-dimension (the vertical dimension in Figure 1) by the 2 surfaces at each of the x−y coordinates. The tethering volume was defined as the volume between the surfaces below the annulus (toward the RV), and the prolapse volume was the volume between the surfaces above the annulus (toward the right atrium). The leaflet and annular areas were calculated as the areas of these respective
surfaces, where the annulus defines the intersection of the surfaces. The annular bending angle was measured using a previously reported method, illustrated in Figure 1. Briefly, the annulus was divided into anterior and posterior sections, as defined by the bending points, identified in the figure near the midseptum. The annular points in each of these sections were fit with a plane (non-negative least squares), from which the bending angle was measured as the angle between the normal lines for each plane.

Statistics
Continuous variables are presented as median (range) or mean±SD as appropriate. Comparisons of normally distributed continuous variables between groups were made using Student t test. Comparisons of non-normally distributed variables were made using Mann–Whitney U test. Total count and percentages are reported for categorical variables. Pearson product–moment correlation coefficients were used to determine the strength of the relationship between continuous variables. Abnormal TV tethering was defined as a tethering volume of >0.69 mL/m² per our previous work. Comparisons of outcomes (mortality or transplant) among patients grouped by categorical variables such as sex, morphological type, and TR were compared using Fisher exact test for 2×2 tables, and the Freeman–Halton extension of Fisher exact test for 2×3 tables. Intraobserver and interobserver agreements for 20 repeated quantitative 3DE measurements were determined using Bland–Altman analysis to identify possible bias (mean divergence) and the limits of agreement (2 SD of the divergence). The level of statistical significance was set at \( P < 0.05 \). Analysis was performed using commercially available statistical software (SPSS version 19.0, SPSS Inc., Chicago, IL and MedCalc version 13.0.2, Ostend, Belgium).

Results
The study cohort consisted of 70 infants with HLHS. Forty-five patients completed bidirectional cavopulmonary anastomosis at a mean age of 5.8±1.5 months, and 20 patients have undergone Fontan completion at a mean age of 34.6±5.8 months. Seven patients required TV surgery, 8 have undergone cardiac transplantation for deteriorating RV function, and there were 25 deaths. Before stage 1 palliation, 62 patients (88.6%) had mild or less TR and 8 patients (11.4%) had moderate or greater TR. At latest follow-up, 46 (65.7%) patients moderate or greater TR (group A) and 24 (34.3%) had mild or less TR (group B). The 2DE characteristics at prestage 1 palliation and at latest follow-up compared between groups.

Figure 1. Derivation of 3-dimensional model of the tricuspid valve components for characterization of morphology. This figure demonstrates the methodology used to quantify the targeted tricuspid valve parameters. Tricuspid valve in a subject with (A and B) a smaller tethering volume and (C and D) a large tethering volume. Left, The raw leaflet coordinates from the 9 radial planes, and best-fit annulus from the 12 radial planes, are shown. Also shown is a best-fit annular surface, which defines the surface of zero tether or prolapse. Right, The corresponding panels show the best-fit leaflet surface and the annular plane, which intersect at the annulus. For measurement of bending angle (E), the annulus was divided into anterior and posterior sections as defined by the bending points, identified in the figure near the midseptum. The annular points in each section were fit with a plane, and the bending angle was measured as the angle between the normal lines for each plane. The line of the PM was defined as the best-fit line between the points identifying the tip and the base of the anterior PM. The angle of this line to the annular plane was then measured.
A and B are shown in Table 1. At prestage 1, the RV fractional area change, RV end-diastolic area, or RV sphericity index in group B were no different to group A. There was a trend toward smaller LV end-diastolic area in group B. At latest follow-up, there was no difference between the 2 groups in 2DE RV parameters.

The morphology, surgical history, and outcomes are shown in Table 2. The prestage 1 palliation 3DE data for all patients and comparisons between groups A and B are shown in Table 3. Low prestage 1 tethering volume conferred significant survival benefit over those patients with high tethering volume (Figure 2). Survival to 53 months in the low-indexed tethering volume group was 72% and in the high-indexed tethering volume group was 41% (P=0.042). Other prestage 1 3DE parameters (TV leaflet and annular areas, bending, and PM angles) were not found to have a statistically significant relationship with survival.

Although greater tethering volume (P=0.009) and bending angle (P=0.022) was demonstrated in group B compared with group A, there were no statistically significant differences in leaflet area, annulus area, or PM angle between the groups. Prestage 1 tethering volume correlated to leaflet area (r=0.74; P<0.001), annulus area (r=0.65; P<0.001), RV end-diastolic area (r=0.35; P=0.003), and fractional area change (r=−0.39; P<0.001) as shown in Figure 3. Tethering volume also correlated significantly with TR grade at follow-up (r=0.45; P<0.001). The TV prolapse volumes were small in all patients with no statistically significant difference between the groups.

All patients in group B had significant morbidity with 7 requiring TV surgery (versus 0 in group A; P=0.005) and 6 progressing to transplantation (versus 2 in group A; P=0.038). Twelve of 46 patients in group A (26%) died, as compared with 13 of 24 (54%) from group B (P=0.027). The Bland–Altman analysis showed good intraobserver and interobserver agreements for quantitative 3DE measurements as represented in Figures 4 and 5.

**Discussion**

The main finding of the present study is that TV failure at medium-term follow-up in HLHS is associated with a larger tethering volume and bending angle (flatter annulus) in the first weeks of life, before any surgical intervention. This larger tethering volume is related to larger TV annulus area, total TV
leaflet size, and, to a lesser extent, larger RV size and reduced RV systolic function. Previous studies in HLHS have shown a trend toward increased risk of mortality with greater degrees of preoperative TR. The present study confirms that progression of TR results in increased TV intervention and decreased survival. Furthermore, our findings suggest that TV tethering soon after birth may be an important precursor for early and intermediate TV failure in HLHS. We speculate that this early tethering manifests mostly from in utero developmental variations in TV and RV structural components.

**TV Failure in HLHS**

Normal TV function requires coordinated action of multiple components: annulus, leaflets, subvalvular apparatus (chordae and PMs), as well as normal right atrial and RV function. Abnormalities in any of these components may result in abnormal function. Pediatric data on TV function are limited, especially for the TV in a systemic circulation. In adults with congenitally corrected transposition, a morphologically abnormal TV predicts the development of TR, and significant TR precedes RV dysfunction. In contrast to the mitral valve, the morphological TV (with its variable PM morphology and PM attachments to the interventricular septum) is likely to be less suited to function as a systemic atrioventricular valve. The TV in HLHS is even more vulnerable as it is exposed to various volume and pressure load stresses. TR in turn may cause significant volume loading during staged palliation, leading to dilatation, geometry changes, and dysfunction of the systemic RV. RV dilatation from volume overloading may further progress TR. Multiple observational studies have shown that TR is an important contributor to RV failure and has a negative impact on medium and long-term outcomes.

Our group has previously demonstrated a role for interventricular septal position, hence LV function, in maintaining an elliptical TV annulus shape. In conjunction with RV free wall motion during systolic contraction, the annulus shape is important for maintaining TV leaflet coaptation in normal biventricular hearts. In a cross-sectional study of HLHS, this mechanism was found to be disturbed in those with significant TR. In addition, the TV annulus was flatter, a geometry known to increase leaflet stress, and the anterior PM was more laterally displaced. Using 3DE, our group then demonstrated that TR in HLHS is associated with 2 distinct mechanisms of failure: tethering or prolapse of the TV leaflets. Those with TV tethering had a flattened annulus (increased bending angle) and a more laterally displaced anterior PM, whereas those with TV prolapse had a more dilated annulus, smaller septal leaflet size, and were older.

**Tethering and TV Failure**

Tethering is an important risk factor for atrioventricular valve regurgitation. Tethering is known to be associated with PM position and ventricular size and is possibly an adaptation to ischemia. In our cohort of neonatal HLHS, some degree of tethering was almost universally present before any surgical intervention, demonstrated by the small prolapse volume measured. This finding would suggest that early HLHS tethering is unlikely to be secondary to an ischemic insult related to the
cardiopulmonary bypass, whereas intrinsic myocardial ischemia attributable to reduced coronary perfusion remains possible. The tethering volume instead was moderately associated with increased TV annulus size and TV leaflet area in a cohort that had little TR before first-stage surgery, hence the usual pathophysiology of annulus dilation and subsequent increased atrial surface leaflet area from tethering and reducing coaptation area, was not the likely explanation. This coupled with a weak association with increased RV size and reduced RV function would further support an alternative explanation of congenital TV tethering in HLHS, as compared with current concepts in functional TV incompetence. The lack of significant prolapse volumes in our young cohort, despite previous data that prolapse is an important mechanism of TR in HLHS in older patients, lends support to the concept that TR associated with leaflet prolapse evolves, rather than being a congenital abnormality in this condition. Leaflet growth is likely an important factor for maintaining normal leaflet coaptation. The atrioventricular valves are able to adapt to stresses by increasing leaflet length and thickness as demonstrated in both human and animal studies. Leaflet tethering, RV dilation, and dysfunction likely influence this adaptation in HLHS. Although tethering forces influence leaflets to compensate and expand, as demonstrated by in vitro studies, our data suggest that too much early tethering is clinically unfavorable. TV failure may represent an inability of TV reserve to adequately compensate for the increased demand of greater congenital leaflet tethering and the rapid annular dilation that accompanies volume and pressure loading stressors after stage 1 palliation. This hypothesis should be tested in future longitudinal 3DE studies assessing the effects of early tethering and subsequent TV leaflet size.

Although there was no statistically significant difference in indexed LV area between groups, there was a trend toward smaller LV areas in group B. Septal position is likely an important contributor to normal TV function, especially affecting the septal leaflet. It has been demonstrated in the systemic RV of congenitally corrected transposition of the great arteries that increasing LV pressure reduces TR, possibly attributable to a change in the septal position. A pathological study suggested that septal leaflet support apparatus differed in HLHS patients with smaller LV (mitral atresia/aortic atresia). This pathological series did not have clinical correlates to identify which patient group had significant TR; however, it is possible that structural differences in subvalvular apparatus may also affect TV function.

**Clinical Implications**

TR is an important risk factor for morbidity and mortality in HLHS. Understanding the predictors and evolution of TR may improve the understanding of TV and RV failure in HLHS. TV repair has been reported in ≤25% of early survivors. However, there are limited technical options for repair, and the commonly used techniques do not directly address leaflet tethering. Although volume unloading with the cavopulmonary shunt results in RV remodeling, its impact on TR is minimal. The need for innovative new surgical approaches to this complex valve is pressing. The pursuit of understanding the
TV unit (annulus function, leaflet function, chordae and PM function, interactions with atrial and ventricular function) and its adaptive reserve may prove valuable for surgical teams in the development of surgical approaches that address the functional abnormalities.

**Study Limitations**

This study assessed TV function using quantitative 3DE at a single time point (before stage 1 intervention), so the evolution of TR was not studied by 3DE. Comparison with quantitative 3DE measurements at follow-up was not performed and is a recognized limitation of this study. RV function was assessed using only 2DE parameters. TR at follow-up was graded qualitatively because there are no widely accepted guidelines to grade TR in children. Functional parameters were measured only at midsystole therefore dynamic changes in annulus and leaflets were not assessed. Patients were recruited from 2 institutions with potential differences in preoperative and postoperative strategies, although both institutions used Norwood procedure with the Sano modification as the initial palliation. Finally, the cohort does not represent the entire spectrum of patients with palliated HLHS, in part because of the exclusion of patients with variants of HLHS.

**Conclusions**

Quantitative 3DE indices of increased TV tethering volume and a flatter annulus early in life are associated with valve failure at medium-term follow-up of HLHS. Having low TV tethering volume before stage 1 palliation is associated with improved survival. The potential of 3DE quantitated TV function in the neonatal period for risk stratification of HLHS warrants further investigation.

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**Disclosures**

None.

**References**


Tricuspid valve regurgitation is associated with significant morbidity and mortality in patients with hypoplastic left heart syndrome. In the present study, we prospectively investigated parameters for quantitative assessment of the tricuspid valve by real-time 3-dimensional echocardiography before stage 1 palliation and correlated the severity of tricuspid regurgitation with clinical and echocardiographic outcomes. Three-dimensional echocardiography indices of increased tricuspid valve tethering volume and greater bending angle (flutter annulus) before stage 1 were associated with tricuspid valve failure at medium-term follow-up. Increased prestage 1 tethering volume was related to having larger valve annulus, larger leaflet area, larger right ventricular size, and reduced right ventricular systolic function. Progressive regurgitation resulted in increased tricuspid valve intervention and decreased survival. Further investigation into the mechanistic aspects of tricuspid regurgitation may prove valuable for the development of surgical approaches to address functional abnormalities of the tricuspid valve in this lesion.
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