Tricuspid Regurgitation In Hypoplastic Left Heart Syndrome: Mechanistic Insights
From Three Dimensional Echocardiography And Relationship With Outcomes

Kutty et al: Three-Dimensional Echocardiography in Hypoplastic Left Heart

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Abstract

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

Methods and Results—Infants were prospectively studied with 3DE and 2DE pre-stage 1, and followed-up for the end-points of TR, TV surgery, transplantation or death. From pre-stage 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 measured. TR was assessed pre-stage 1 and at latest follow up. Of 70 patients, 62 (88.6%) had ≤mild TR; 8 (11.4%) had ≥moderate TR pre-stage 1. Pre-stage 1 tethering volume correlated to leaflet area (r=0.736; p<0.001), annulus area (r=0.651; p<0.001), right ventricular (RV) 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 TR (group A), 24 (34.3%) had ≥moderate TR (group B). Pre-stage 1 3DE showed greater TV tethering volume and flatter annulus in group B. Survival was better in group A.

Conclusion—Increased TV tethering volume and flatter bending angle pre-stage 1 palliation is associated with TV failure at medium-term follow-up. Increased pre-stage 1 tethering is related to having larger TV annulus, larger leaflet area, larger RV size and reduced systolic function. TR progression results in increased TV intervention and decreased survival.

Key Words: tricuspid valve, right ventricle, hypoplastic left heart syndrome, three-dimensional echocardiography, pediatric cardiology, adult congenital heart disease
Tricuspid regurgitation (TR) is associated with morbidity and mortality in children with hypoplastic left heart syndrome (HLHS). Cross-sectional studies using two-dimensional echocardiography (2DE), three dimensional echocardiography (3DE), and intraoperative surgical inspection of the tricuspid valve (TV) after stage 1 palliation have suggested multiple etiological factors for TR in HLHS. These include annular and ventricular dilation, leaflet prolapse and tethering, leaflet dysplasia, papillary muscle displacement and right ventricular (RV) dyssynchrony.

Real time 3DE has emerged as a clinically useful tool for anatomic and functional assessment of atrioventricular valves before and after surgical repair. Several studies have shown the added value of 3DE over 2DE in the evaluation of mitral valve disease. In pediatric subjects, real-time transthoracic 3DE generates optimal images of the TV. 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 papillary muscle (PM) angles. 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.

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 prior to stage 1, and its potential implications on TR and RV function at follow up. The relevance of pre-stage 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 prior to 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 prior to 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 extracardiac malformations were present. Institutional Review Board approvals were obtained from both institutions and informed consent was obtained from parents of all recruited patients.

Prior to 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 a right ventricle–to–pulmonary artery conduit (Sano shunt) as the provision 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 was
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 prior to stage 1 palliation and at follow-up on iE33 (Philips Medical Systems, Andover, MA) or Vivid 7 (GE Medical Systems, Milwaukee, Wisconsin) ultrasound systems with electrocardiogram tracing. Prior to stage 1 palliation and at latest follow-up, the following 2DE measurements were included: (1) RV fractional area change (FAC), (2) RV diastolic area, (3) left ventricular (LV) diastolic area, (4) RV sphericity index, and (5) degree of TR. Right ventricular areas were measured from the apical 4-chamber view by tracing the RV endocardium in systole and diastole, and percentage FAC calculated as (end-diastolic area - end-systolic area)/end-diastolic area X 100. Sphericity index was measured at end-diastole from the apical 4-chamber view, with the long-axis dimension measured from the midpoint 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. Left ventricular 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.

Tricuspid regurgitation was assessed with 2DE prior to stage 1 palliation and at most recent follow up (prior to 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 mid-portion 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**

The iE33 ultrasound system and matrix X7-2 transthoracic transducer (Philips Medical Systems, Andover, MA) were used for image acquisition prior to stage 1 palliation. Images were acquired during an expiratory breath-hold if the patient was ventilated, or free breathing if not ventilated. Multi-beat acquisitions (with electrocardiogram gating to merge pyramidal scans obtained over 4 or 7 heart beats) were used to maximize frame rate in all patients. Multiple full-volume datasets were acquired in the apical window using the high–frame rate mode and the smallest sector format was used to acquire an image optimized for spatial and temporal resolution. Care was taken to minimize stitch artifacts by avoiding significant respiratory changes and by reducing transducer movement during image acquisition. Analysis was performed only on the 3D dataset without stitch artifact from respiratory movement.

**3DE quantification**

The raw 3DE datasets were transferred from the ultrasound system to an offline system for analysis (TomTec Inc., Unterschleissheim, Germany) as described previously. In brief, one experienced observer (TC) 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 were counted and mid-systole was defined as the midpoint. Twelve radial planes were obtained (every 15 degrees) around the center of the TV annulus and the annulus was delineated at the leaflet hinge-points in mid-systole. To delineate the three-dimensional surface of the leaflets, 9 radial planes (20
degrees between each) were obtained around the center point of the TV annulus. In mid-systole, 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 papillary muscle was triangulated from three planes that were centered on the TV annulus at three 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 three TV annular points such that the PM tip and base were each marked by three 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.\textsuperscript{4,11} Briefly, by using the extracted x, y, and z spatial coordinates, the software defined two 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 1 panels A and C, for two 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 two sample cases are shown in Figure 1 panels A and C, 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 1 panels B and D, 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 two 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 1.4 Briefly, the annulus was divided into anterior and posterior sections, as defined by the bending points, identified in the figure near the mid-septum. The annular points in each of these sections were fit with a plane (nonnegative least-squares), from which 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.

**Statistics**

Continuous variables are presented as median (range) or mean ± standard deviation 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.4 Comparisons of outcomes (mortality or transplant) among patients grouped by categorical variables such as gender, morphologic type, and tricuspid regurgitation were compared using Fisher’s exact test for 2X2 tables, and the Freeman-Halton extension of Fisher’s exact test for 2X3 tables. Intra-observer
and inter-observer 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 standard deviation 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. Prior to stage 1 palliation, 62 patients (88.6%) had ≤mild TR; 8 patients (11.4%) had ≥moderate TR. At latest follow-up, 46 (65.7%) patients had ≤mild TR (group A), 24 (34.3%) had ≥moderate TR (Group B). The 2DE characteristics at pre-stage 1 palliation and at latest follow-up compared between groups A and B are shown in Table 1. At pre-stage 1, the right ventricular FAC, 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 two groups in 2DE RV parameters.

The morphology, surgical history and outcomes are shown in Table 2. The pre-stage 1 palliation 3DE data for all patients and comparisons between groups A and B are shown in Table 3. Low pre-stage 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 pre-stage 1 3DE parameters (TV leaflet and annular areas, bending and papillary muscle angles) were not found to have a statistically significant relationship with survival. While greater tethering volume (p=0.009) and bending angle (p=0.022) was demonstrated in group B compared to group A, there were no statistically significant differences in leaflet area, annulus area, or papillary muscle angle between the groups. Pre-stage 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 FAC (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 very 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 (vs. 0 in group A; p=0.005) and 6 progressing to transplantation (vs. 2 in group A, p=0.038). Twelve of 46 patients in group A (26%) died, as compared to 13 of 24 (54%) from group B (p=0.027). The Bland-Altman analysis showed good intra-observer and inter-observer 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, prior to 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.

Tricuspid valve failure in HLHS

Normal TV function requires coordinated action of multiple components: annulus, leaflets, subvalvar apparatus (chordae and papillary muscles) as well as normal RA and RV function. Abnormalities in any of these components may result in abnormal function. Pediatric data on TV function is 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 morphologic 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. Tricuspid regurgitation 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, while those with TV prolapse had a more dilated annulus, smaller septal leaflet size, and were older.

Tethering and tricuspid valve 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 prior to any surgical intervention, demonstrated by the very 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, while intrinsic myocardial ischemia due 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 prior to 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

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with increased RV size and reduced RV function would further support an alternative explanation of congenital TV tethering in HLHS, as compared to current concepts in functional TV incompetence.

The lack of significant prolapse volumes in our very young cohort, despite previous data that prolapse is an important mechanism of TR in HLHS in older patients,\textsuperscript{4} 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 AV valves are able to adapt to stresses by increasing leaflet length and thickness as demonstrated in both human and animal studies.\textsuperscript{25-27} Leaflet tethering, RV dilation and dysfunction likely influence this adaptation in HLHS. Although tethering forces influence leaflets to compensate and expand, as demonstrated by \textit{in vitro} studies,\textsuperscript{28} our data suggest that too much early tethering is clinically unfavorable. Tricuspid valve 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 towards 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 due to a change in the septal position.\textsuperscript{29} 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 sub-valve apparatus may also affect TV function.

**Clinical implications**

Tricuspid regurgitation 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. Tricuspid valve repair has been reported in up to 25% of early survivors. However, there are limited technical options for repair and the commonly employed techniques do not directly address leaflet tethering. Though 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 papillary muscle 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 (prior to 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. Right ventricular 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 mid-systole therefore dynamic
changes in annulus and leaflets were not assessed. Patients were recruited from two institutions with potential differences in pre-operative and post-operative 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 tricuspid valve 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 tricuspid valve function in the neonatal period for risk stratification of HLHS warrants further investigation.

Acknowledgements

The authors are grateful to the patients who participated in this study. We also appreciate the assistance of the echocardiography laboratory staff at both participating institutions.

Disclosures

None
References


Table 1. 2DE measurements compared between groups – Pre-stage 1 and at latest follow-up

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<th>Group A (n=46)</th>
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<td>≥ Mod TR</td>
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<td>(cm²/m²)</td>
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<td>Indexed TV annulus</td>
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<td>diameter (cm/m²)</td>
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<tr>
<td>FAC (%)</td>
<td>37.8±7.7</td>
<td>34.5±8.8</td>
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<tr>
<td>Indexed RV end-</td>
<td>29.5±18.9</td>
<td>26.3±7.8</td>
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<tr>
<td>diastolic area (cm²/m²)</td>
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<tr>
<td>RV sphericity index</td>
<td>0.65±0.17</td>
<td>0.69±0.15</td>
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<td><strong>At latest follow-up</strong></td>
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<td>FAC (%)</td>
<td>36.8±8.2</td>
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<td>Indexed RV end-</td>
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<td>RV sphericity index</td>
<td>0.67±0.22</td>
<td>0.73±0.20</td>
<td>0.62</td>
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FAC=Fractional area change; RV=right ventricle; LV=Left ventricle, TV=Tricuspid valve, TR=Tricuspid regurgitation
Table 2. Morphology, Surgical history and Outcomes compared between groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
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<td></td>
<td>Mitral stenosis-aortic atresia</td>
<td>7</td>
<td>5</td>
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<td></td>
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<tr>
<td>Norwood-Sano</td>
<td>N</td>
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<td>22</td>
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<td>Age at Norwood-Sano (days)</td>
<td>9.0 (4.0-40.0)</td>
<td>12.0 (7.0-38.0)</td>
<td>0.174</td>
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<tr>
<td>Glenn</td>
<td>N</td>
<td>36</td>
<td>9</td>
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<tr>
<td>Age at Glenn (months)</td>
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<td>5.4 (4.2-9.4)</td>
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<td>Fontan</td>
<td>N</td>
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<tr>
<td>Age at Fontan (months)</td>
<td>36.1 (28.9-49.3)</td>
<td>31.3 (28.8-41.3)</td>
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<tr>
<td>TV surgery</td>
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<tr>
<td>Age at TV surgery (months)</td>
<td>——</td>
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<td>10.1 (8.4-14.1)</td>
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<td>5</td>
</tr>
</tbody>
</table>

Data shown as numbers or median (ranges)
Table 3. Pre-stage 1 3DE measurements compared between groups

<table>
<thead>
<tr>
<th>Pre-stage 1 3DE variable</th>
<th>Group A (n=46)</th>
<th>Group B (n=24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaflet area/BSA (cm²/m²)</td>
<td>8.0±3.4</td>
<td>8.9±2.8</td>
<td>0.23</td>
</tr>
<tr>
<td>Annulus area/BSA (cm²/m²)</td>
<td>7.2±3.2</td>
<td>7.8±2.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Tethering volume/BSA (mL/m²)</td>
<td>0.54±0.40</td>
<td>0.86±0.60</td>
<td>0.009</td>
</tr>
<tr>
<td>Prolapse volume/BSA (mL/m²)</td>
<td>0.024±0.05</td>
<td>0.043±0.12</td>
<td>0.897</td>
</tr>
<tr>
<td>Bending angle</td>
<td>150.3±9.2</td>
<td>155.6±8.9</td>
<td>0.022</td>
</tr>
<tr>
<td>Papillary muscle angle</td>
<td>74.7±17.9</td>
<td>76.6±17.3</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1: Derivation of three-dimensional model of the tricuspid valve components for characterization of morphology.

This figure demonstrates the methodology used to quantify the targeted tricuspid valve parameters. Panels A and B shows the tricuspid valve in a subject with a smaller tethering volume, and panels C and D a large tethering volume. The raw leaflet coordinates from the 9 radial planes, and best-fit annulus from the 12 radial planes, are shown in the left panels. Also shown in the left panels is a best-fit annular surface, which defines the surface of zero tether or prolapse. The corresponding right panels show the best-fit leaflet surface and the annular plane, which intersect at the annulus. For measurement of bending angle (panel E), the annulus was divided into anterior and posterior sections as defined by the bending points, identified in the figure near the mid-septum. 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.

Figure 2. Medium term survival in patients with low and high tricuspid valve tethering volumes pre-stage 1.

Figure 3. Correlations of pre-stage 1 tethering volume with tricuspid valve leaflet and annulus areas are stronger than those with right ventricular end diastolic area and fractional area change.

Figure 4. Bland-Altman plots of intra-observer agreements for quantitative tricuspid valve measurements on three-dimensional echocardiography

Figure 5. Bland-Altman plots of inter-observer agreements for quantitative tricuspid valve measurements on three-dimensional echocardiography
Cumulative Survival (%)

Follow-up (months)

Low Indexed Tethering Volume

High Indexed Tethering Volume

Number at risk

Low Indexed Tethering Volume

41
25
18
9
0

High Indexed Tethering Volume

29
13
9
0
0

p=0.0423
Tricuspid Regurgitation In Hypoplastic Left Heart Syndrome: Mechanistic Insights On Tricuspid Valve Tethering And Relationship With Outcomes
Shelby Kutty, Timothy Colen, Richard B. Thompson, Edythe Tham, Ling Li, Chodchanok Vijarnsorn, Amanda Polak, Dongnan T. Truong, David A. Danford, Jeffrey Smallhorn and Nee Scze Khoo

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