Surgical Palliation Strategy Does Not Affect Interstage Ventricular Dysfunction or Atrioventricular Valve Regurgitation in Children With Hypoplastic Left Heart Syndrome and Variants

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Background—All 3 palliation strategies, Norwood, Sano, and Hybrid, currently used for hypoplastic left heart syndrome pose a risk of myocardial injury at different times and through different mechanisms. We sought to compare these strategies to understand longitudinal differences in interstage ventricular dysfunction and their subsequent impact on transplant-free survival and atrioventricular valve regurgitation (AVVR) as well as the relationship between adverse events and ventricular function.

Methods and Results—Serial echocardiographic reports and clinical data were reviewed for 138 children with hypoplastic left heart syndrome who underwent stage I surgical palliation (Sano: 11; Norwood: 73; Hybrid: 54) between 2004 and 2011. Stage II palliation was achieved in 92 (67%) patients (Sano: 7; Norwood: 51; Hybrid: 34). Interstage transplant-free survival, ventricular dysfunction, and AVVR were equivalent among palliation strategies. Patients with preserved ventricular function had a higher rate of transplant-free survival and freedom from AVVR, regardless of palliation strategy. Patients who had cardiac arrest, cardiopulmonary resuscitation, or extracorporeal membrane oxygenation (adverse events) experienced more transient and persistent ventricular dysfunction compared to those without adverse events. Surgical palliation strategies were not identified as risk factors for ventricular dysfunction or AVVR.

Conclusions—Surgical palliation strategy does not affect mortality, interstage ventricular function, or interstage AVVR in children with hypoplastic left heart syndrome. Therefore, the different timing and mechanisms of myocardial injury among palliation strategies do not affect outcomes. Ventricular dysfunction adversely affects transplant-free survival and atrioventricular valve function. Adverse events are associated with the development of ventricular dysfunction. To improve outcomes, interstage treatment should focus on the preservation of ventricular function.

Key Words: Hybrid ■ hypoplastic left heart syndrome ■ Norwood ■ Sano ■ single ventricle ■ ventricular function

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in-hospital survival after stage I palliation for infants with hypoplastic left heart syndrome (HLHS) and its variants has dramatically improved during the past decade with refinements in surgical techniques and perioperative management. Nonetheless, interstage death and the need for heart transplantation between stage I and stage II palliation is still significant, resulting in 1-year transplant-free survival of ≈70%. Recent surgical modifications, namely the Sano procedure with a right ventricle–pulmonary artery conduit and the Hybrid procedure, have failed to show substantial survival advantages over the standard Norwood strategy. Multiple anatomic and physiologic risk factors for interstage death have been identified, including arrhythmia, ventricular dysfunction, and atrioventricular valve regurgitation (AVVR).

All surgical palliation strategies for HLHS were primarily designed to improve stage I survival, and therefore the impact of stage I surgical palliation strategies on ventricular function is poorly understood. Currently, all 3 major palliation strategies result in a volume-overloaded state in the systemic single ventricle until conversion to cavopulmonary physiology. The degree of volume overload, as measured by the pulmonary-to-systemic flow ratio, is generally comparable among the palliation groups. Cardiopulastic cardiac arrest and deep hypothermic circulatory arrest (DHCA) at stage I Norwood...
and Sano palliation cause varying degrees of ischemic and inflammatory injury to the neonatal myocardium that may or may not be reversible. The ventriculotomy may increase the risk of ventricular dysfunction in patients undergoing the Sano procedure. A potential advantage of the Hybrid stage I procedure is the avoidance of myocardial insult in the neonatal period. Nonetheless, the ascending aorta and coronary circulation are predominantly perfused retrogradely through the isthmus until stage II palliation, posing an ongoing risk of myocardial ischemia. Furthermore, comprehensive stage II palliation requires long cardioplegic cardiac arrest.

Few studies have focused on ventricular function after stage I palliation. Most of the studies that examined ventricular function were performed with a cross-sectional approach. Thus, longitudinal data comparing ventricular function for all 3 surgical palliation strategies does not exist. We hypothesized that the different timing and mechanisms of potential myocardial insult in the 3 surgical palliation strategies may have an impact on the incidence of ventricular dysfunction and subsequent clinical outcomes. Our secondary hypothesis was that adverse events, such as cardiac arrest or requirement of extracorporeal membrane oxygenation (ECMO), may have further negative effects on ventricular function. In this study, we sought to define the impact of surgical palliation strategy and adverse events on transplant-free survival, ventricular function, and AVVR.

**Methods**

All children undergoing staged single-ventricle palliation at the Hospital for Sick Children between 2004 and 2011 were reviewed. Research ethics board approval was obtained. During the study period, a total of 138 children underwent stage I single-ventricle palliation with Norwood (n=73), Sano (n=11), or Hybrid (n=54). Patients who underwent hybrid palliation as a salvage or rescue procedure were excluded. Certain patients had normal ventricular function at birth but were triaged to primary transplantation. Six (4%) of these patients underwent stage I hybrid procedure as an indication for bridge to transplantation and were included in the hybrid group. Perioperative profiles are shown for stage I (Table 1) and stage II (Table 2) palliation.

**Surgical Techniques**

The surgical techniques for Norwood, Sano, and Hybrid palliation have been previously described. Briefly, the Norwood procedure was performed using standard surgical techniques, including aortic arch reconstruction, atrial septectomy, and placement of a modified

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Table 1. Stage I Perioperative Profile

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sano (n=11)</th>
<th>Norwood (n=73)</th>
<th>Hybrid (n=54)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, d</td>
<td>6.0 (4.0–10.5)</td>
<td>7.0 (5.0–9.0)</td>
<td>7.0 (5.0–12.5)</td>
<td>0.663</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>3.0 (2.9–3.5)</td>
<td>3.5 (3.1–3.8)</td>
<td>3.3 (2.8–3.7)</td>
<td>0.159</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>0.21 (0.20–0.23)</td>
<td>0.23 (0.21–0.25)</td>
<td>0.23 (0.20–0.25)</td>
<td>0.381</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis, mitral stenosis</td>
<td>3 (27%)</td>
<td>13 (18%)</td>
<td>16 (30%)</td>
<td>0.280</td>
</tr>
<tr>
<td>Aortic stenosis, mitral atresia</td>
<td>...</td>
<td>5 (7%)</td>
<td>5 (9%)</td>
<td>0.548</td>
</tr>
<tr>
<td>Aortic atresia, mitral stenosis</td>
<td>5 (45%)</td>
<td>18 (25%)</td>
<td>9 (17%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Aortic atresia, mitral atresia</td>
<td>3 (27%)</td>
<td>13 (18%)</td>
<td>12 (22%)</td>
<td>0.693</td>
</tr>
<tr>
<td>Unbalanced AVSD</td>
<td>...</td>
<td>2 (3%)</td>
<td>4 (7%)</td>
<td>0.338</td>
</tr>
<tr>
<td>Double inlet LV, TGA</td>
<td>...</td>
<td>20 (27%)</td>
<td>6 (11%)</td>
<td>0.017†</td>
</tr>
<tr>
<td>Other</td>
<td>...</td>
<td>2 (3%)</td>
<td>2 (4%)</td>
<td>0.795</td>
</tr>
<tr>
<td>Preoperative data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular dysfunction</td>
<td>0 (0%)</td>
<td>4 (5%)</td>
<td>4 (7%)</td>
<td>0.623</td>
</tr>
<tr>
<td>Atrioventricular valve regurgitation</td>
<td>0 (0%)</td>
<td>2 (3%)</td>
<td>4 (7%)</td>
<td>0.338</td>
</tr>
<tr>
<td>Intraoperative data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary Bypass time, min</td>
<td>115 (112–122)</td>
<td>114 (101–156)</td>
<td>...</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Aortic cross-clamp time, min</td>
<td>75 (63–100)</td>
<td>59 (50–68)</td>
<td>...</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Deep hypothermic circulatory arrest, min</td>
<td>26 (20–32)</td>
<td>11 (5–25)</td>
<td>...</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>Regional cerebral perfusion, min</td>
<td>41 (34–57)</td>
<td>36 (24–45)</td>
<td>...</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Postoperative data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation time, d</td>
<td>7 (6–10)</td>
<td>10 (7–14)</td>
<td>4 (2–6)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Intensive care unit time, d</td>
<td>12 (9–13)</td>
<td>14 (10–19)</td>
<td>7 (4–10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital time, d</td>
<td>29 (22–38)</td>
<td>24 (14–37)</td>
<td>16 (11–23)</td>
<td>&lt;0.001‡</td>
</tr>
</tbody>
</table>

AVSD indicates atrioventricular septal defect; LV, left ventricle; TGA, transposition of the great arteries; NS, not significant; and S, significant.

*Post hoc tests (PHT) conducted if P<0.05. PHT significance set at P<0.016.
†PHT—Norwood vs Sano: NS; Norwood vs Hybrid: NS; Sano vs Hybrid: NS.
‡PHT—Norwood vs Sano: NS; Norwood vs Hybrid: S; Sano vs Hybrid: S.
§PHT—Norwood vs Sano: S; Norwood vs Hybrid: S; Sano vs Hybrid: S.
IPHT—Norwood vs Sano: NS; Norwood vs Hybrid: S; Sano vs Hybrid: NS.
A VVR were compared among the 3 surgical palliation strategies.

Outcome Assessment

Freedom from death/transplant, ventricular dysfunction, and AVVR were compared among the 3 surgical palliation strategies.

Statistical Analysis

Continuous data are presented as median (interquartile range). Discrete data are presented as frequency (percentage). The level of statistical significance was set at $P \leq 0.05$. Differences between the groups were analyzed with the Kruskal–Wallis $\chi^2$ test. Post hoc tests were conducted as necessary. End points were freedom from death or transplantation, freedom from moderate/severe ventricular dysfunction, freedom from moderate/severe AVVR, and freedom from adverse events. Simple group comparisons were made with the log-rank test and displayed using the Kaplan–Meier method. The analysis was repeated excluding the variant subgroup with dominant left heart morphology. Univariable predictors for ventricular dysfunction and AVVR were explored with Cox regression. Variables that were significant at $P \leq 0.05$ were included in a stepwise multivariable Cox regression model. Statistical analysis was performed using SPSS 17.0 software (IBM Corporation, Armonk, NY) and SAS 9.2 software (SAS Institute Inc, Cary, NC).

Table 2. Stage II Perioperative Profile

<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>Sano (n=7)</th>
<th>Norwood (n=51)</th>
<th>Hybrid (n=34)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td>4.8 (4.1–5.5)</td>
<td>6.0 (4.8–6.7)</td>
<td>6.3 (5.4–6.5)</td>
<td>0.060</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>6.8 (5.9–7.4)</td>
<td>6.5 (5.7–7.0)</td>
<td>6.2 (5.5–7.4)</td>
<td>0.889</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>0.38 (0.35–0.44)</td>
<td>0.37 (0.34–0.40)</td>
<td>0.36 (0.33–0.41)</td>
<td>0.759</td>
</tr>
</tbody>
</table>

Preoperative catheterization data

<table>
<thead>
<tr>
<th>Ventricular end-diastolic pressure, mm Hg</th>
<th>Sano (n=7)</th>
<th>Norwood (n=51)</th>
<th>Hybrid (n=34)</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right pulmonary artery pressure, mm Hg</td>
<td>9 (6–11)</td>
<td>8 (6–9)</td>
<td>7 (5–8)</td>
<td>0.254</td>
</tr>
<tr>
<td>Left pulmonary artery pressure, mm Hg</td>
<td>11 (8–12)</td>
<td>14 (12–16)</td>
<td>11 (9–15)</td>
<td>0.034†</td>
</tr>
<tr>
<td>Arterial saturations</td>
<td>69 (68–73)</td>
<td>75 (72–79)</td>
<td>77 (74–84)</td>
<td>0.049</td>
</tr>
<tr>
<td>Mixed venous saturations</td>
<td>55 (53–57)</td>
<td>58 (50–61)</td>
<td>58 (52–62)</td>
<td>0.632</td>
</tr>
</tbody>
</table>

Preoperative echocardiographic data

| Ventricular dysfunction                   | 0 (0%) | 2 (4%) | 1 (3%) | 0.853     |
| Atrioventricular valve regurgitation      | 1 (14%) | 8 (16%) | 2 (6%) | 0.386     |

Intraoperative data

| Cardiopulmonary bypass time, min          | 99 (69–138) | 89 (62–132) | 202 (171–259) | <0.001‡ |
| Aortic cross-clamp time, min              | 0 (0–58) | 0 (0–43) | 127 (89–153) | <0.001‡ |
| Deep hypothermic circulatory arrest, min  | 0 (0–12) | ... | 29 (20–41) | <0.001‡ |
| Regional cerebral perfusion, min          | ... | ... | 53 (26–74) | <0.001‡ |

Postoperative data

| Intubation time, d                        | 1 (0–8) | 1 (0–5) | 4 (1–11) | 0.055     |
| Intensive care unit time, d              | 7 (3–15) | 4 (2–7) | 7 (3–15) | 0.043§    |
| Hospital time, d                         | 11 (9–33) | 9 (6–14) | 16 (10–28) | 0.004§    |

NS indicates not significant; and S, significant.

*Post hoc tests (PHT) conducted if $P < 0.05$. PHT significance set at $P < 0.016$.
†PHT—Norwood vs Sano: NS; Norwood vs Hybrid: S; Sano vs Hybrid: NS.
‡PHT—Norwood vs Sano: NS; Norwood vs Hybrid: S; Sano vs Hybrid: S.
§PHT—Norwood vs Sano: NS; Norwood vs Hybrid: S; Sano vs Hybrid: NS.

Blalock–Taussig shunt or Sano shunt under DHCA with selective cerebral perfusion and cardiopulmonary cardiac arrest. Stage II bidirectional cavopulmonary shunt was performed under mild hypothermic cardiopulmonary bypass without cardiopulmonary cardiac arrest unless an additional intracardiac procedure was required. Bilateral branch pulmonary arteries were routinely reconstructed with a pericardial patch. For the Hybrid stage I procedure, bilateral pulmonary artery banding with a 3.5-mm polytetrafluoroethylene graft and ductal stent placement were achieved without cardiopulmonary bypass and cardiac arrest. For the stage II procedure, aortic arch reconstruction, D’Vries–Kaye–Stansel (DKS) anastomosis, bilateral pulmonary artery plasty, and creation of a bidirectional cavopulmonary shunt were performed under cardiopulmonary cardiac arrest and DHCA with regional cerebral perfusion. Given the difference in physiology and impact of ventricular function on outcomes, the analysis was divided into 2 interstage phases: the period between stage I and stage II and the period between stage II and Fontan. Cardiac arrest, requirement of cardiopulmonary resuscitation (CPR), and ECMO were defined as adverse events. Each palliation group was divided into groups: patients with ventricular dysfunction or no dysfunction and patients with adverse events or no adverse events. The impact of ventricular function and adverse events on primary end points was then analyzed.

Assessment of Ventricular and Atrioventricular Valve Function

All echocardiographic reports throughout the staged palliation process were reviewed for each patient. Qualitative assessments of ventricular function and degree of AVVR were based on techniques that have been previously described. Ventricular function was graded as 0 (normal), 1 (mildly reduced), 2 (moderately reduced), and 3 (severely reduced). The degree of AVVR was graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Ventricular dysfunction was divided into 2 categories: transient (ventricular function subsequently improved) and persistent (no subsequent improvement). Given the difference in physiology and impact of ventricular function on outcomes, the analysis was divided into 2 interstage phases: the period between stage I and stage II and the period between stage II and Fontan. Cardiac arrest, requirement of cardiopulmonary resuscitation (CPR), and ECMO were defined as adverse events. Each palliation group was divided into groups: patients with ventricular dysfunction or no dysfunction and patients with adverse events or no adverse events. The impact of ventricular function and adverse events on primary end points was then analyzed.

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Results

Interstage Outcomes Between Stage I and Stage II Palliation

Perioperative Data and Clinical Outcomes

Patient demographics, diagnoses, and preoperative data were comparable among the groups, except that the Norwood group had more morphologically left ventricles ($P=0.017$). The Sano group had longer aortic cross-clamp time ($P=0.010$) and deep hypothermic circulatory arrest time ($P=0.006$) compared with the Norwood group. Given the nature of Hybrid palliation, all intraoperative variables were different between the Hybrid group and both Norwood and Sano groups ($P<0.001$; Table 1). The Hybrid group had a shorter length of intensive care unit stay ($P=0.001$) and hospital stay ($P<0.001$) compared with the Norwood group. Between stage I and II palliation, there were 42 (30%) deaths or transplants (Sano: 3; Norwood: 20; Hybrid: 19). Transplant-free survival was comparable between the groups 6 months (Sano: 72.7%; Norwood: 69.7%; Hybrid: 64.8%) and 1 year (Sano: 62.3%; Norwood: 65.2%; Hybrid: 56.7%) after stage I ($P=0.669$; Figure 1).

After stage I palliation, there were 56 adverse events (cardiac arrest/CPR: 29; ECMO: 27) in 35 patients: 7 events (cardiac arrest/CPR: 3; ECMO: 4) in 5 Sano patients, 30 events (cardiac arrest/CPR: 18; ECMO: 12) in 19 Norwood patients, and 19 events (cardiac arrest/CPR: 8; ECMO: 11) in 11 Hybrid patients. Freedom from adverse events at 3 months (Sano: 72.7%; Norwood: 77.7%; Hybrid: 80.6%) and 6 months (Sano: 38.8%; Norwood: 72.9%; Hybrid: 76.7%) after stage I palliation was similar ($P=0.122$). Of the 138 patients who underwent stage I palliation, 92 (67%) patients (Sano: 7; Norwood: 51; Hybrid: 34) achieved stage II palliation and 4 (3%) were awaiting stage II palliation.

Ventricular Function and AVVR

There was no difference in pre-stage I ventricular dysfunction among the groups ($P=0.623$; Table 1). A total of 39 (28%) patients (Sano: 2; Norwood: 22; Hybrid: 15) developed moderate/severe ventricular dysfunction between stage I and stage II, including 15 (11%) patients (Sano: 1; Norwood: 9; Hybrid 5) who developed ventricular dysfunction immediately after stage I palliation. Of the 39 patients, 15 (39%; Sano: 0; Norwood: 8; Hybrid: 7) had persistent dysfunction, whereas 24 (61%; Sano: 2; Norwood: 14; Hybrid: 8) had transient dysfunction. Freedom from moderate/severe ventricular dysfunction was comparable among the groups at 3 months (Sano: 90.9%; Norwood: 72.2%; Hybrid: 81.0%) and 6 months (Sano: 68.2%; Norwood: 66.8%; Hybrid: 70.6%) after stage I palliation ($P=0.726$; Figure 2).

Freedom from moderate/severe AVVR was comparable among groups at 3 months (Sano: 77.8%; Norwood: 70.2%; Hybrid: 70.6%) and 6 months (Sano: 64.8%; Norwood: 64.5%; Hybrid: 63.4%) after stage I palliation ($P=0.872$). Freedom from moderate/severe AVVR in patients with early postoperative ventricular dysfunction was significantly lower at 3 months after stage I palliation, regardless of surgical palliation strategy ($P=0.004$).

Ventricular Function and Transplant-Free Survival

Freedom from death or transplantation for the whole cohort was significantly lower at 3 months (preserved function: 83.7%; dysfunction: 46.7%) and 6 months (preserved function: 73.1%; dysfunction: 26.7%) in the group that developed ventricular dysfunction in the early postoperative period after stage I palliation ($P<0.001$). Similarly, freedom from death or transplantation was lower at 3 and 6 months in patients with any interstage ventricular dysfunction, regardless of palliation strategy ($P=0.001$; Figure 3A).

Adverse Events and Ventricular Function

Of the 35 patients who had adverse events, 12 (34%; Sano: 3; Norwood: 8; Hybrid: 1) never developed ventricular dysfunction, 9 (26%; Sano: 0; Norwood: 7; Hybrid: 2) had ventricular dysfunction before the adverse event, and 14 (40%; Sano: 2; Norwood: 4; Hybrid: 8) developed ventricular dysfunction at or after the adverse event. Freedom from moderate/severe ventricular dysfunction was significantly lower in patients who had adverse events at 3 and 6 months after stage I palliation, regardless of palliation strategy ($P<0.001$; Figure 3B).

Figure 1. Transplant-free survival after stage I palliation stratified by surgical palliation strategy.

Figure 2. Freedom from moderate or severe ventricular dysfunction after stage I palliation stratified by surgical palliation strategy.
Relative to those without adverse events, patients with adverse events experienced more transient dysfunction (34% versus 12%; \(P=0.002\)) and more persistent dysfunction (29% versus 5%; \(P<0.001\)).

**Right-Dominant Morphology Subgroup Analysis**
The results did not change significantly when the analysis was repeated excluding patients with dominant left heart morphology.

**Risk Factor Analysis**
Adverse events \((P<0.001)\) were a predictor for the development of ventricular dysfunction. Surgical palliation strategies were not significant risk factors in univariable analysis (Sano: \(P=0.533\); Norwood: \(P=0.515\); Hybrid: \(P=0.750\)). Risk factors for AVVR included adverse events \((P=0.033)\) and the diagnosis of HLHS (compared with variants; \(P=0.024\)). Surgical palliation strategies were not significant predictors in univariable analysis (Sano: \(P=0.776\); Norwood: \(P=0.749\); Hybrid: \(P=0.625\)).

**Interstage Outcomes Between Stage II Palliation and Fontan Completion**

**Perioperative Data and Clinical Outcomes**
Patient demographics and pre-stage II catheterization data were similar between the groups (Table 2). There was significantly more ischemic time in the Hybrid group compared with both the Norwood and Sano groups (all intraoperative variables; \(P<0.001\)). The Hybrid group had significantly longer intensive care unit \((P=0.012)\) and hospital stay \((P=0.001)\) compared with the Norwood group. Of the 92 patients who reached stage II palliation, 49 (53%; Sano: 4; Norwood: 29; Hybrid: 16) achieved Fontan completion and 30 (33%) were awaiting Fontan completion. Between stage II and Fontan, there were 13 deaths or transplants (Sano: 2; Norwood: 7; Hybrid: 4).

After stage II palliation, there were 21 adverse events (cardiac arrest/CPR: 14; ECMO: 7) in 15 patients: 4 events (cardiac arrest/CPR: 3; ECMO: 1) in 4 Sano patients, 10 events (cardiac arrest/CPR: 7; ECMO: 3) in 6 Norwood patients, and 7 events (cardiac arrest/CPR: 4; ECMO: 3) in 5 Hybrid patients. Freedom from adverse events at 1 year (Sano: 57.1%; Norwood: 87.4%; Hybrid: 84.4%) after stage II palliation was lower in the Sano group compared with the Norwood/Hybrid groups \((P=0.008)\).

**Ventricular Function and AVVR**
There was no difference in pre-stage II ventricular dysfunction among the groups \((P=0.853;\) Table 2). A total of 26 (28%; Sano: 2; Norwood: 13; Hybrid: 11) patients developed moderate/severe ventricular dysfunction between stage II and Fontan, including 16 (17%; Sano: 0; Norwood: 8; Hybrid: 8) patients who developed ventricular dysfunction immediately after stage II palliation. Of these 26 patients, 6 (23%; Sano: 1; Norwood: 4; Hybrid: 1) had persistent dysfunction and 20 (77%; Sano: 1; Norwood: 9; Hybrid: 10) had transient dysfunction. Freedom from moderate/severe ventricular dysfunction was comparable among the groups at 1 year (Sano: 85.7%; Norwood: 75.9%; Hybrid: 69.9%) and 3 years (Sano: N/A; Norwood: 72.8%; Hybrid: 65.2%) after stage II \((P=0.700;\) Figure 4).

Freedom from moderate/severe AVVR was equivalent at 1 year (Sano: 83.3%; Norwood: 72.3%; Hybrid: 75.1%) and 3 years (Sano: N/A; Norwood: 72.3%; Hybrid: 66.8%) after stage II palliation \((P=0.714)\). However, freedom from moderate/severe AVVR was significantly lower at 1 year after stage II palliation in patients with early postoperative ventricular dysfunction, regardless of palliation strategy \((P<0.001)\).

**Ventricular Function and Transplant-Free Survival**
Freedom from death or transplantation was lower at 3 months (preserved function: 95.9%; dysfunction: 57.8%) and 6 months (preserved function: 95.9%; dysfunction: 50.6%) in the group that developed ventricular dysfunction in the early postoperative period after stage II palliation \((P<0.001)\). Similarly, freedom from death or transplantation was lower at 3 and 6 months in patients with any interstage ventricular dysfunction, regardless of palliation strategy \((P<0.001;\) Figure 5A).
Adverse Events and Ventricular Function

Of the 15 patients who had an adverse event, 6 (40%; Sano: 2; Norwood: 3; Hybrid: 1) never developed poor ventricular function, 5 (33%; Sano: 0; Norwood: 2; Hybrid: 3) developed ventricular dysfunction before the adverse event, 2 (13%; Sano: 1; Norwood: 1; Hybrid: 0) developed ventricular dysfunction at or after the adverse event, and 2 (13%) patients had incomplete resuscitation records. Freedom from moderate/severe ventricular dysfunction was significantly reduced in patients who had adverse events at 6 months and 1 year after stage II palliation, regardless of palliation strategy ($P=0.019$; Figure 5B). Relative to those without adverse events, patients with adverse events experienced significantly more ventricular dysfunction (60% versus 22%; $P=0.003$).

Right-Dominant Morphology Subgroup Analysis

The results did not change significantly when the analysis was repeated excluding patients with dominant left heart morphology, with 1 minor exception. Adverse events being associated with more ventricular dysfunction after stage II went from being statistically significant to a trend ($P=0.088$).

Risk Factor Analysis

Adverse events ($P=0.007$), longer deep hypothermic circulatory arrest time ($P=0.040$), and the development of moderate/severe AVVR in the early postoperative period ($P=0.023$) were predictors for the development of ventricular dysfunction. Surgical palliation strategies were not significant risk factors in univariable analysis (Sano: $P=0.928$; Norwood: $P=0.462$; Hybrid: $P=0.414$). Moderate/severe ventricular dysfunction in the early postoperative period ($P=0.001$) was the only risk factor for AVVR.

Discussion

Substantial efforts have been made to improve early survival after stage I palliation for infants with HLHS in the last 2 decades. Many recent clinical series have reported in-hospital survival >85%. Nonetheless, it is also true that we still face significant interstage mortality of ≤20%, which remained unchanged in the past decade, despite refinements in follow-up management. Our hypothesis was that ventricular function plays an important role in interstage morbidity and mortality in this particular patient group, which has not been well investigated in the past. We also investigated the 2 major factors that could influence ventricular function: surgical palliation strategy and significant adverse events. The risk factor analysis did not show any modifiable factors to improve outcomes. Rather, this study revealed the limitations of current staged single-ventricle palliation strategies.

The key finding from our study is that palliation strategy does not have an impact on ventricular function throughout the interstage palliation period. In other words, none of the palliation strategies has a protective effect on ventricular function. Ventricular dysfunction at any point, even if transient, had a significant negative impact on survival and atrioventricular valve function. Adverse events had a profound effect on ventricular function and survival.
Single-Ventricle Palliation and Ventricular Function

The systemic single right ventricle in HLHS is exposed to the significant volume overload of Norwood or Hybrid stage I physiology until stage II volume-unloading palliation. Because the single right ventricle is known to be less adaptive to volume overload, there is an underlying vulnerability whereby myocardial failure can occur even without any additional stress in this entity. The in-parallel circulation has a less favorable coronary perfusion profile with poorly matched myocardial oxygen supply and demand. Additional events, such as cardioplegic cardiac arrest, inflammatory response related to cardiopulmonary bypass/DHCA, and cardiac arrest/ECMO, can be the terminal trigger for irreversible injury to the already susceptible myocardium.

Palliation-Specific Mechanisms of Myocardial Injury

The timing and mechanism of myocardial injury differs in each of the 3 palliation strategies currently being used. All strategies can be affected by the universal risks of myocardial injury as mentioned above. The major difference among strategies is the timing of major ischemic insult of cardioplegic cardiac arrest and DHCA and the associated systemic inflammatory response. Norwood and Sano procedures require cardiopulmonary bypass/DHCA in the neonatal period, whereas the Hybrid patient is exposed to cardioplegic arrest at 4 to 6 months of age at the time of comprehensive stage II palliation. Neonatal myocardium is known to be more vulnerable to cardioplegic cardiac arrest with increased myocardial apoptosis compared with mature myocardium, which led us to hypothesize that hybrid palliation may better preserve ventricular function. However, our results did not support our hypothesis, indicating the multifactorial nature of myocardial injury in the Hybrid group. The impact of predominantly retrograde perfusion of the coronary circulation through the isthmus in Hybrid physiology on myocardial perfusion and subsequent ventricular function is currently unknown. Of note, relatively longer cardioplegic arrest at comprehensive stage II palliation in the Hybrid group did not have a negative impact on post-stage II ventricular function.

Creation of a ventriculotomy is a potential source of ventricular dysfunction in the Sano procedure. Tanoue et al showed reduced contractility but comparable global ventricular performance in Sano patients as compared to Norwood patients. Right ventricular function has been reported to be essentially equivalent between Sano and Norwood patients at 3-year follow-up in the recent Pediatric Heart Network randomized trial. In our study, the risk profile for ventricular dysfunction in the Sano group is almost identical compared with the other strategies. Overall, none of the hypothesized advantages or disadvantages of palliation strategies has a tangible effect on ventricular performance in this cohort.

Impact of Ventricular Function on AV Regurgitation

Development of ventricular dysfunction and AVVR is closely inter-related. AVVR can be a cause or a result of ventricular dysfunction in single-ventricle patients. In this study, many patients had reasonable atrioventricular valve competency until ventricular function deteriorated. This is an indication that the development of AVVR was largely secondary to ventricular dysfunction and dilatation. We have previously reported the importance of ventricular function in patients with functionally single-ventricle physiology who underwent atrioventricular valve repair. Significant AVVR did not predict poor survival as long as atrioventricular valve repair was successful, but survival was extremely poor when the patients had poor ventricular function after atrioventricular valve repair. Similar results were reported among patients with HLHS who underwent tricuspid valve repair. This study shows that significant AVVR occurs equally among the 3 palliation strategies. Hence, ventricular dysfunction is a much stronger factor triggering the development of AVVR compared with palliation strategy.

Impact of Adverse Events on Ventricular Dysfunction and Survival

There is a strong negative relationship between adverse events and survival. After stage I palliation, the rate of poor clinical outcomes is high, with survival estimates ranging from 31% to 38% in patients requiring ECMO and 37% in patients who had cardiac arrest requiring CPR. The impact of adverse events on ventricular function is less defined. Our data revealed that there was an association between adverse events and ventricular dysfunction, with higher rates of transient and persistent dysfunction present in patients with adverse events after both stage I and stage II palliation. These data raise the hypothesis that volume-loaded, single-ventricle myocardium is more vulnerable to adverse events than myocardium in a heart with biventricular physiology. Our analysis has some limitations in that some patients could have pre-existing or developing ventricular dysfunction. Therefore, it is not entirely clear whether ventricular dysfunction after adverse events is actually the result or the cause. Further prospective studies would be useful in answering this question. Adverse events are definitely associated with increased rates of ventricular dysfunction and learning new strategies to better understand the relationship between the 2 could help improve functional and clinical outcomes in this entity.

Study Limitations

The main limitations of this study are its retrospective and nonrandomized nature. Data were not available at consistent follow-up periods in all patients. Institutional bias may have affected selection of palliation strategy for some patients. It was difficult to make definitive conclusions about the Sano group because of the small number of patients in this group and the possible impact of an institutional learning curve. Given the small number of patients in some of the subgroup analysis, results should be interpreted cautiously because they can only detect large clinical effects, and further study is certainly warranted. Grading of ventricular function and AVVR was performed qualitatively using a single imaging modality (echocardiography). Qualitative analysis and grading are not the most accurate methods to assess ventricular function. MRI is the ideal modality to assess ventricular function. However, it could not be performed frequently enough to document time-related changes in ventricular function in this cohort. Inter-rater variability in grading could exist.
Conclusions
Surgical palliation strategy does not affect mortality, interstage ventricular function, or interstage AVVR in children with HLHS. Ventricular dysfunction has a significant negative impact on atrioventricular valve function and transplant-free survival. Cardiac arrest, CPR, and ECMO are associated with the development of ventricular dysfunction. Since there is no current palliation strategy that is better able to preserve ventricular function, our focus is to learn a strategy that leads to better ventricular function.

Disclosures
None.

References
Surgical Palliation Strategy Does Not Affect Interstage Ventricular Dysfunction or Atrioventricular Valve Regurgitation in Children With Hypoplastic Left Heart Syndrome and Variants

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