Early Stage 2 Palliation Is Crucial in Patients With a Right-Ventricle-to-Pulmonary-Artery Conduit

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Background. Improved survival after Norwood stage 1 palliation is giving more patients the opportunity to reach stage 2 palliation; thus, more patients are exposed to the risk of interstage death.

Methods. A single-center review of patients who underwent stage 1 palliation from January 1998 to December 2007 (n = 58) was performed. Pulmonary blood flow was established either by a modified Blalock-Taussig shunt (mBTS, n = 33) or a right ventricle–to–pulmonary artery conduit (RVPAC, n = 25).

Results. Hospital, interstage, and 1-year survival was not significantly different between groups. However, Kaplan-Meier survival analysis reflected a significantly higher survival probability for RVPAC patients until the age of 120 days (RVPAC, 92% ± 5% [standard error of the mean]; 95% confidence interval, 82 to 100; mBTS, 63% ± 9%; 95% confidence interval, 48 to 82; p = 0.01). During a 1-year follow-up, all 11 nonsurvivors with mBTS died at an age younger than 120 days, including 2 patients with early stage 2 palliation. In contrast, besides 2 early deaths, all RVPAC patients (n = 5) showed later attrition at an age older than 120 days while awaiting stage 2 palliation. Interstage death occurred significantly later among RVPAC patients (RVPAC, 146 ± 60 days versus mBTS, 81 ± 23 days; p = 0.01). After stage 2 palliation, all patients with RVPAC survived, including 7 patients with surgery at an age younger than 120 days. All interstage and late deaths were related to compromising cardiac lesions with no statistical difference between groups.

Conclusions. After Norwood stage 1 palliation, survival was improved with RVPAC for the first 4 months. However, a loss of the favorable primary outcome was present by delaying stage 2 palliation beyond the age of 120 days. Progressive volume load as a result of conduit regurgitation may play a crucial role for later attrition. Residual lesions should be addressed early to preserve cardiac function.


Since its presentation by Norwood and associates in 1980 [1], two surgical modifications are commonly used to establish pulmonary blood flow during stage 1 palliation: the modified Blalock-Taussig shunt (mBTS) and, since 2000, the right ventricle–to–pulmonary artery conduit (RVPAC) [2]. In RVPAC, pulmonary blood flow occurs exclusively during systole, distinct from mBTS in which pulmonary blood flow continues into diastole. Diastolic runoff from the systemic circulation into the pulmonary circulation may be responsible for lower diastolic blood pressure, exposing the patients to coronary steal and pulmonary overcirculation [3–8].

Comparing patients with RVPAC to historic patients with mBTS has shown that RVPAC provides a more stable postoperative early balance between the pulmonary and systemic circulations [4–6, 9], and in consequence, less ventilatory manipulations [4, 6], improved coronary perfusion pressure [9], better ventricular performance [10], and higher early survival rates in RVPAC patients [5, 6, 10, 11] were reported.

On the other hand, concerns were raised regarding long-term performance of single ventricles after RVPAC insertion caused by an incision into the systemic ventricle, which might be associated with higher incidence of ventricular arrhythmias, pseudoaneurysm formation [12], and deterioration of right ventricular function resulting in progressive tricuspid valve regurgitation [7].

For both surgical modifications of pulmonary blood supply, some centers have reported hospital survival rates of more than 90% [2, 4–6, 13] and significant improvement in survival during the last several years [3, 6, 13]. Improved early survival is giving more patients the opportunity to reach stage 2 palliation (S2P); thus, more patients are exposed to the risk of interstage death (ISD).

This study represents 1-year outcomes after the Norwood procedure comparing both types of shunt perfusion. Special interest is dedicated to the interstage period focusing on the ideal timing of S2P.

Patients and Methods

Patient Population

The records of all consecutive patients with hypoplastic left heart syndrome and its variants undergoing staged surgical palliation between January 1998 and
December 2007 at the Pediatric Cardiac Surgery Department of the University Hospital Hamburg-Eppendorf were reviewed. “True hypoplastic left heart syndrome” was echocardiographically defined as evidence of a hypoplastic left ventricle as a result of aortic and mitral atresia or stenosis with retrograde flow in the ascending aorta. Other forms of functional single ventricle with systemic outflow obstruction and ductal dependency of the systemic circulation were classified as “variants of hypoplastic left heart syndrome” (Table 1). Restrictive pulmonary venous return was considered if the interatrial communication was smaller than 3 mm in diameter or the mean gradient across the atrial septal defect was greater than 5 mmHg, or if pulmonary venous obstruction was present.

Immature newborns born before the 37th week of gestation and those with low birth weight (<2,100 g) were excluded from the study.

Patients were divided into two groups with respect to surgical management for pulmonary blood flow (mBTS group and RVPAC group).

**Surgical Management**

Norwood stage 1 palliation (S1P) contained division of the main pulmonary artery, atrial septectomy, and neo-aortic reconstruction with respect to the individual surgeon’s preference. The first RVPAC was performed in November 2001 in our institution and has been preferred since then (Fig 1). Nevertheless, there has been consistent use of both shunt types, with 13 patients receiving mBTS until the end of the study period, which may reflect patient anatomy, such as 9 single left ventricles, 3 hypoplastic left heart syndrome with coronary arteries crossing the infundibulum, and 1 situs inversus totalis. Cerebral protection during aortic arch reconstruction was performed either in deep hypothermic circulatory arrest in 38 patients or, since January 2000, with antegrade cerebral perfusion by means of the innominate artery in 20 patients. Myocardial protection was provided by crystalloid cardioplegia, and since February 2006, 5 patients (4 RVPAC, 1 mBTS) were operated on with a beating heart modification during distal aortic arch repair.

Patients were scheduled for S2P at the age of 5 to 6 months or whenever progressive cyanosis occurred. Stage 2 palliation implied construction of a Glenn anastomosis (bidirectional or bilateral) during 35°C cardiopulmonary bypass and included shunt resection and end-to-side anastomosis of the superior vena cava to the pulmonary artery. Additional cardiac procedures were performed in 4 patients with RVPAC and 8 patients with mBTS, and included tricuspid valve reconstruction (n = 5), pulmonary artery patch plasty (n = 3), aortic arch augmentation (n = 4), and right ventricular aneurysm resection (n = 2).

**Data Collection and Follow-Up**

Follow-up was complete for 57 patients (98%) and was established by review of the medical records and contact with the referring cardiologist; 1 mBTS patient was lost to follow-up during the interstage period.

Hospital mortality reflects all deaths during hospital stay after S1P. Interstage period was defined as the interval between hospital discharge after S1P and S2P. Late death was defined as death occurring after S2P.

Data of cardiac catheterization before S2P were evaluated

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mBTS</th>
<th>RVPAC</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>33</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>23</td>
<td>14</td>
<td>0.41</td>
</tr>
<tr>
<td>Age (days)</td>
<td>11 ± 8</td>
<td>8 ± 6</td>
<td>0.08</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>40 ± 1</td>
<td>39 ± 2</td>
<td>0.55</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3,371 ± 483</td>
<td>3,258 ± 445</td>
<td>0.42</td>
</tr>
<tr>
<td>Aorta (mm)</td>
<td>3.7 ± 1.5</td>
<td>3.9 ± 1.3</td>
<td>0.39</td>
</tr>
<tr>
<td>Aortic atresia</td>
<td>13</td>
<td>11</td>
<td>0.79</td>
</tr>
<tr>
<td>True HLHS</td>
<td>16</td>
<td>14</td>
<td>0.61</td>
</tr>
<tr>
<td>Variants of HLHS</td>
<td>17</td>
<td>11</td>
<td>0.60</td>
</tr>
<tr>
<td>Dominant left ventricle*</td>
<td>11</td>
<td>1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mitral stenosis or atresia with ventricular septal defect</td>
<td>3</td>
<td>7</td>
<td>0.12</td>
</tr>
<tr>
<td>Unbalanced atrioventricular septal defect</td>
<td>1</td>
<td>2</td>
<td>0.80</td>
</tr>
<tr>
<td>Others*</td>
<td>2</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Restrictive pulmonary venous return</td>
<td>1</td>
<td>9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are represented as number or mean ± standard deviation.

* Dominant left ventricle is a double-inlet left ventricle or tricuspid atresia with ventriculoarterial discordance.

* Others includes Ebstein’s disease with congenitally corrected transposition (n = 1, mBTS), and mirror image HLHS (n = 1, mBTS, n = 1 RVPAC).

HLHS = hypoplastic left heart syndrome; mBTS = modified Blalock-Taussig shunt; RVPAC = right ventricle-to-pulmonary artery conduit.
and studied for recoarctation, shunt or conduit stenosis, pulmonary artery stenosis, and right ventricular aneurysm.

**Statistical Analysis**

Continuous data are presented as mean value (± standard deviation) or median (range), and categorical data are presented as proportion of cases. Statistical significance was analyzed using Fisher’s exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. Survival analysis was calculated according to Kaplan-Meier method, and log-rank (Mantel-Cox) test was applied to compare survival functions. Statistical analysis was performed using the R-system for statistical computing (version 2.9.0, R Development Core Team 2009, Vienna, Austria). Probability values less than 0.05 were considered significant.

**Results**

**Baseline Variables**

After excluding 3 patients from the survey because of prematurity and low birth weight, a total of 58 patients with Norwood S1P entered the study. Thirty-three patients received mBTS and 25, RVPAC. A 3.5-mm shunt was used in 82.1% of patients with mBTS and 5 patients received a 4-mm shunt, whereas with RVPAC, a 5-mm polytetrafluoroethylene tube was used in 90.5% of cases, and 1 patient each received a 6-mm and a 4-mm prosthesis.

Patient characteristics are presented in Table 1. There was no significant difference regarding gestational age, age at operation, birth weight, and aortic diameter or presence of aortic atresia between both groups. Significantly more patients with mBTS had an anatomic single left ventricle. The presence of restrictive pulmonary venous return was significantly more often described with RVPAC.

**Hospital Mortality**

Summary of outcomes for all patients until 1-year follow-up is shown in Figure 2. No significant difference was observed in early mortality between mBTS and RVPAC patients (18.2% versus 8.0%; p = 0.24). Death occurred on days 0 (n = 4), 1, and 19 in the mBTS group, whereas 2 patients with unbalanced atrioventricular septal defects died on days 19 and 50 in the RVPAC group.

**120-Day and 1-Year Survival**

Kaplan-Meier survival curves of both groups until the age of 120 days reflected a significantly higher probability of survival for patients with RVPAC (92% ± 5% [standard error of the mean]; 95% confidence interval [CI], 82 to 100; versus 63% ± 9%; 95% CI, 48 to 82; p = 0.01; Fig 3A). Kaplan-Meier 1-year survival was 63% ± 9% with mBTS.
(95% CI, 48 to 82) and 65% ± 10% with RVPAC (95% CI, 48 to 88; Fig 3B).

**Interstage Period**

Nine patients died during the interstage period, 4 with mBTS and 5 with RVPAC. There was no ISD before the 30th postoperative day after S1P. A significant difference between groups was found for age at ISD (mBTS, 84 days; range, 51 to 104 days versus RVPAC, 161 days; range, 124 to 237 days; p = 0.02). Additionally, the interval between S1P and ISD was significantly longer among RVPAC compared with mBTS patients (mBTS, 70 days; range, 42 to 97 days versus RVPAC, 147 days; range, 116 to 235 days; p = 0.02).

The estimated cumulative hazard curves for the interstage period show an increase in mortality between 50 and 104 days followed by a constant hazard thereafter in mBTS patients, whereas there was a dramatic increase in ISD beyond the age of 4 months in RVPAC patients (Fig 4). Patients with RVPAC had the highest probability (94% ± 6%) of survival until the age of 124 days during the interstage period (95% CI, 83 to 100; Fig 5).

A timeline of ISD with cardiac diagnosis and circumstances of death is shown in Figure 6. All patients dying in the interstage period had additional cardiac or extracardiac problems. Three patients in each group had aortic recoarctation; 1 patient with mBTS had pulmonary artery stenosis and severe tricuspid regurgitation; 1 patient with RVPAC experienced conduit stenosis and died after cardiopulmonary resuscitation after conduit-stent implantation. Only 1 patient in each group died out of hospital; all other ISDs were associated with hospitalization and scheduled or conducted interventions.

**Cardiac Catheterization and Interventions Before Stage 2 Palliation**

Cardiac catheterization before S2P revealed no significant difference between groups regarding the incidence of acquired cardiac lesions and number of related interventions (Fig 7).

**Stage 2 Palliation**

Forty patients reached S2P, 22 with mBTS and 18 with RVPAC. Median age at S2P was not significantly different between groups (mBTS, 145 days; range, 108 to 232 days versus RVPAC, 140 days; range, 72 to 230 days; p = 0.39). Additional lesions during S2P had to be addressed in 8 patients with mBTS and 4 with RVPAC.

Two mBTS patients with residual postoperative cardiac lesions showed progressive deterioration in cardiac function and were referred early to surgery at an age of 108 and 118 days. Both patients had to undergo simultaneous cardiac procedures, like tricuspid valve patch closure and right ventricular volume reduction owing to congenitally corrected transposition with Ebstein’s disease in the first, and aortic arch reconstruction with pulmonary artery patch plasty in the second patient, respectively. Cause of death was cardiac failure in both patients on the first postoperative day after S2P.

All patients with RVPAC survived S2P and were discharged home, 7 of them at an age younger than 120 days at S2P (72, 89, 91, 91, 111, 114, and 117 days). Reasons for
early reoperation were compression of RVPAC (n = 1), restrictive atrial septum (n = 3), infundibular aneurysm at conduit insertion site (n = 1), progressive tricuspid regurgitation (n = 1), and aortic recoarctation (n = 1).

Comment

Hospital Mortality

Comparing the present cohort of patients with RVPAC with historic and contemporary patients with mBTS, hospital mortality was not significantly different between groups. In the current literature an actual reduction of early mortality after RVPAC compared with mBTS was shown; however, these studies were predominantly retrospective and historically controlled [5, 6, 11, 14, 15]. On the other hand, no significant difference in early survival was found with the use of RVPAC by other case series using historic [12, 16] or contemporary control patients [4, 7, 17]. A small, randomized trial [18] revealed no survival difference between groups by implanting exclusively 6-mm RVPA conduits.

120-Day and 1-Year Survival

Kaplan-Meier survival in the first 4 months showed a significantly improved survival among patients with RVPAC. As previously described by our group [11], improved coronary perfusion [5, 6, 11], and a more balanced ratio of pulmonary to systemic blood flow [4–6, 9] might have positively influenced survival in these patients.

On the other hand, this difference in survival disappeared at 1 year. One possible reason might have been anatomic; the mBTS group contained significantly more dominant left ventricles, whereas more restrictive atrial septal defects were found in the RVPAC group. Reflecting the published results in the literature, this might have influenced long-term outcome favoring patients with mBTS [19, 20].

Interstage Period

Mortality was not different during the interstage period; however, a distinct “timing of ISD,” with a significant difference in age at ISD between patients with mBTS or
RVPAC, was established. The probability of ISD rose dramatically among RVPAC patients after the age of 124 days.

The recently reported results from Philadelphia underline our observation regarding the early occurrence of ISD among patients with mBTS. In that cohort with use of mBTS in 91%, the median age at ISD was 64 days [21], whereas in our mBTS group it was 70 days (range, 42 to 97 days). In addition, our results are also consistent with the published data from Wisconsin, in which all deaths before S2P occurred at an age younger than 120 days [22].

Different authors have presented a lower incidence of ISD among patients with RVPAC [5, 10, 14, 15]. Lower diastolic blood pressures with mBTS increase the patient’s susceptibility to perfusion-related acute myocardial failure and may have a significant impact not only on early but also on interstage mortality [3].

All ISDs in our observed patient cohort were related to postoperatively compromising conditions like recoarctation, shunt or pulmonary artery stenosis, and recurrent pulmonary vein stenosis. Factors enhancing myocardial hypertrophy like systemic outflow obstruction and increasing volume load may diminish sufficient coronary perfusion and finally result in myocardial ischemia. However, a substantial proportion of these anatomic barriers are potentially correctable [23], and therefore immediate treatment is necessary to prevent the patient from an increasing risk for sudden death. Both approaches, interventional or surgical, can be individually discussed.

**Timing of Stage 2 Palliation**

In the followed cohort, age at S2P was not different between groups. Timing of performing S2P was mainly saturation driven and not adopted to a patient’s different shunt physiology. All patients with RVPAC were alive at 1 year after S2P, 7 of them with early S2P at an age younger than 4 months. On the other hand, 2 deaths among patients with mBTS occurred after performing early S2P with concomitant cardiac procedures.

In the present cohort, ISD in both groups was mostly attributed with diminished pulmonary perfusion and increased cyanosis may play an important role. On the other hand, patients with mBTS grow out of the initially too big ventricle afterload and enhances ventricular hypertrophy and remodeling. Furthermore, patient outgrowth associated with diminished pulmonary perfusion and increasing cyanosis may play an important role. On the other hand, patients with mBTS grow out of the initially too big shunt with coronary steal and pulmonary overcirculation, and experience the late advantages of a systolic and diastolic perfusion to the pulmonary arteries resulting in higher saturations measured before S2P compared with RVPAC patients [9, 10, 19]. Additionally, there is no
volume load attributable to pulmonary valve incompetence in mBTS patients. It seems that the longer patients remain in the interstage period, they stay on the safer side with mBTS than with RVPAC.

Conclusions

Timing of S2P is crucial. It has to be adapted to the different underlying postoperative physiology and normal patient’s maturation as both surgical modifications of pulmonary artery perfusion behave differently. Especially in the presence of a systemic right ventricle, patients with RVPAC are more prone to an increased volume overload and profit from early volume reduction. Furthermore, optimized treatment implies the early correction of any compromising condition. Thus patients with RVPAC should undergo scheduled cardiac catheterization at 2 months with addressing residual lesions by intervention or surgery, followed by S2P at an age of 120 days. This currently reflects our strategy, being the ideal compromise between an early reduction of volume load and maturation of the pulmonary vasculature.

Limitations

The observed cohort is a heterogeneous population of patients undergoing a challenging operation. Two different periods of shunt modifications were present in this retrospective study, with an earlier solely mBTS cohort and a later simultaneous use of RVPAC and mBTS. After introduction of RVPAC into surgical practice, anatomic reasons influenced the decision as to which type of shunt was used. Most of the dominant left ventricles were operated on using mBTS, thus favoring late outcome of mBTS [19, 20]. This study was neither blinded nor randomized. The number of patients in both groups is too small to perform a meaningful risk factor analysis. Results from the Single Ventricle Reconstruction Trial are eagerly awaited.

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References