Comparison of Hybrid and Norwood Strategies in Hypoplastic Left Heart Syndrome

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ABSTRACT

Current surgical palliation for neonates with single ventricle physiology includes Norwood-based and Hybrid-based surgical strategies. When transplantation is not available, clinicians must choose between these two strategies with distinctly different learning curves and risk profiles. The Norwood strategy has evolved over several decades while the rising popularity of the Hybrid strategy is a much more recent addition to our therapeutic options. Based upon the premise that avoiding cardiopulmonary bypass in the neonatal period and deferral of aortic arch reconstruction until a second stage procedure have an important influence on outcomes, the Hybrid strategy has compelling theoretical advantages and disadvantages in comparison to the Norwood strategy. The purpose of this review is to summarise the currently available data to support – or refute – the theoretical advantages of the Hybrid strategy within the context of the Norwood strategy.

INTRODUCTION

The Norwood-based strategy for single ventricle palliation has improved with technical innovations and refinements over the last decades; such as regional cerebral perfusion during aortic arch reconstruction [1], placement of a right ventricle-to-pulmonary artery (RV-PA) shunt rather than a systemic-to-pulmonary shunt [2, 3], and the concept of aggressive afterload reduction to maximise oxygen delivery following Norwood procedure [4, 5].

However, Norwood-based palliation continues to have significant early and interstage mortality in the current era with the majority of deaths occurring in the peri-operative period after the Norwood procedure [3, 6]. After Stage I Norwood procedures, the presence of a systemic-to-pulmonary shunt contributes to the intrinsic instability of an ‘in-parallel’ circulation in which blood flow distribution may be altered significantly with perturbations in the ratio of systemic to pulmonary vascular resistance and this vulnerability is compounded in the early post-operative period with post-cardiopulgia related depression of cardiac output. Cardiopulmonary bypass (CPB) and deep hypothermic circulation arrest (DHCA) contribute to a subsequent systemic inflammatory response which also has a negative impact on the Norwood physiology in the early postoperative period.

Interstage mortality between Stage I and Stage II palliation is also significant (10.5 - 22%) [3, 6] and may be influenced by chronic volume loading of the systemic ventricle [8], arrhythmias and shunt-related problems. These intrinsic problems with the Norwood strategy have encouraged the development of an alternative ‘Hybrid’ strategy.

The hybrid palliative strategy has evolved rapidly in the last decade [9, 10] and is based on the placement of bilateral pulmonary artery (PA) bands, stenting of the ductus arteriosus, and atrial septostomy as Stage I palliation during the neonatal period, followed by arch reconstruction and bidirectional cavopulmonary shunt as Stage II palliation at the age of four to six months. Stage I hybrid procedures avoid CPB, cardioplegic arrest, and CPB-associated postoperative systemic inflammatory response.

Furthermore, by deferring aortic arch reconstruction, the hybrid strategy avoids surgical alterations in cerebral blood flow (DHCA and/or regional cerebral perfusion) in the neonatal period when the brain may be more susceptible to neurologic injury [11]. Potential disadvantages of hybrid palliation include obstruction of the aortic isthmus by stent deployment, subsequent coronary and cerebral malperfusion, and mechanical distortion of the branch pulmonary arteries.
Several institutions have reported a significant learning curve with the hybrid strategy\cite{9, 12, 13} and we have recently reported measurable trends toward improvement in outcomes, suggesting that institutional learning is an important component in the development of this strategy.

**COMPARISON BETWEEN HYBRID AND NORWOOD STRATEGIES**

**Early postoperative physiology after Stage I palliation**

Pulmonary blood flow after Stage I palliation in Norwood and hybrid patients is derived from systemic-to-pulmonary artery shunts with the objective of providing pulmonary blood flow which is sufficient for pulmonary gas exchange but controlled by the geometry of the shunts/bands to prevent excessive volume loading of the heart. In Norwood patients an aorto-pulmonary or a RV-PA shunt is used, whereas in hybrid patients banding of the proximal branch pulmonary arteries is used to control pulmonary blood flow.

The postoperative haemodynamics after first stage hybrid palliation have not been extensively studied. As the hybrid strategy has evolved, avoidance of cardiopulmonary bypass was postulated to better preserve myocardial function when compared to first stage Norwood palliation. Using respiratory spectrometry, we compared postoperative hemodynamics and oxygen delivery between Stage I hybrid and Norwood patients and noted that the hybrid patients had higher systemic vascular resistance (SVR) during the first postoperative 48 hours after the Stage I procedure\cite{14}.

This change was associated with lower cardiac output, low systemic blood flow (Qs) and oxygen delivery. Interestingly, despite bilateral PA banding, total pulmonary vascular resistance and pulmonary blood flow (Qp) were not different between early postoperative Hybrid and Norwood patients.

The ratio of pulmonary to systemic blood flow (Qp/Qs) after Stage I Norwood palliation was between 0.3 and 3.3 (mean 1.2±0.5) and, despite bilateral pulmonary artery banding, the Qp/Qs ranged from 0.4 to 5.7 (mean 1.7±1.0) after Stage I Hybrid palliation\cite{14}. However, in the absence of post-cardioplegia deficits in myocardial performance, this level of overcirculation appears to be well tolerated in Hybrid patients with normal myocardial reserve. It is important to note, however, that this was an uncontrolled comparison and the administration of vasodilators and inotropes was routinely used for the Norwood patients\cite{15} and uncommonly used for the Hybrid patients. The noted differences between the groups may have reflected the management strategy rather than differences in the palliative strategies.

These data suggest that systemic afterload reduction such as milrinone and phenoxybenzamine may be important in the early postoperative period for post-Stage I Hybrid patients. Based on these findings, we have adopted a low threshold to employ systemic afterload reduction and inotropic support for neonates following Hybrid Stage I procedures – especially for those patients known to have diminished preoperative myocardial reserve. We also recognize the potential for pulmonary overcirculation in patients with diminished myocardial reserve and utilize standard intensive care unit (ICU) measures to limit pulmonary blood flow in patients with evidence of inadequate distal oxygen delivery.

**Survival**

Several centers initially reported high mortality after Stage I Hybrid palliation\cite{9, 13}. After a learning curve, outcomes tended to improve and were comparable with Norwood procedure in terms of mortality. Hospital survival after Stage I Hybrid palliation has been reported ranging from 80 to 97% in more recent studies\cite{10, 16, 17}, although some studies excluded high-risk patients from the analysis. In our recent hybrid and Norwood experience (Figure 1)\cite{18}, we performed 47 hybrid procedures between 2004 and December 2010.

*Figure 1: Clinical outcomes of patients who underwent Hybrid or Norwood strategy. Tx: cardiac transplantation (Citation from\cite{18} with publisher’s permission)*
These hybrid patients consist of all neonates palliated with the hybrid strategy excluding patients treated as a planned bridge to cardiac transplantation or critically ill patients who underwent the hybrid procedure as a salvage strategy. During the same period, the Norwood procedure was performed in 63 patients.

There was no difference in mortality following Stage I palliation between the groups (Figure 1). Freedom from death or transplant after Stage II was comparable between two groups (Hybrid 88% vs. Norwood 84%, p=0.95) [18]. There was no significant difference in 1 year overall survival between two groups (Hybrid 68.5% vs. Norwood 64.3%, p=0.88, Figure 2).

**Hemodynamics and pulmonary artery growth**

Comparison of pre-Fontan catheterisation data between Hybrid and Norwood procedures is shown in Table 1[18]. There were no statistically significant differences in ventricular end-diastolic pressure and mixed venous saturation between the two groups. Mean PA pressures are also equivalent between the groups. There was, however, a non-significant trend toward larger Nakata index in the Norwood group compared with the Hybrid group. Both groups had equivalent PA growth and haemodynamics at the pre-Fontan catheterisation. These data suggest that the hybrid procedure leads to comparable candidates for the Fontan procedure.

**Table 1: Comparison in pre-Fontan hemodynamics, pulmonary artery growth and ventricular function between Hybrid and Norwood groups.**

<table>
<thead>
<tr>
<th>Catheterization</th>
<th>Hybrid</th>
<th>Norwood</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right PA diameter (mm)</td>
<td>7.9 ± 1.7</td>
<td>9.0 ± 1.3</td>
<td>0.16</td>
</tr>
<tr>
<td>Left PA diameter (mm)</td>
<td>5.9 ± 1.4</td>
<td>6.7 ± 1.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Nakata PA index (mm²/m²)</td>
<td>157 ± 57</td>
<td>189 ± 49</td>
<td>0.25</td>
</tr>
<tr>
<td>Total LL index (mm²/m²)</td>
<td>99 ± 31</td>
<td>96 ± 29</td>
<td>0.93</td>
</tr>
<tr>
<td>Neo ascending aorta (mm)</td>
<td>18.2 ± 2.8</td>
<td>21.4 ± 4.8</td>
<td>0.17</td>
</tr>
<tr>
<td>Distal transverse arch (mm)</td>
<td>16.5 ± 2.8</td>
<td>17.9 ± 3.3</td>
<td>0.69</td>
</tr>
<tr>
<td>Descending aorta (mm)</td>
<td>8.3 ± 1.4</td>
<td>8.4 ± 2.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Original ascending aorta (mm)</td>
<td>7.4 ± 2.5</td>
<td>7.5 ± 1.8</td>
<td>0.66</td>
</tr>
<tr>
<td>Ventricular - EDP (mmHg)</td>
<td>7.9 ± 1.6</td>
<td>7.8 ± 0.7</td>
<td>0.85</td>
</tr>
<tr>
<td>Mean PA pressure (mmHg)</td>
<td>9.9 ± 1.7</td>
<td>11.4 ± 1.7</td>
<td>0.12</td>
</tr>
<tr>
<td>Mixed venous saturation (%)</td>
<td>68.9 ± 8.4</td>
<td>66.4 ± 5.7</td>
<td>0.37</td>
</tr>
<tr>
<td>Arterial saturation (%)</td>
<td>88 ± 2.4</td>
<td>86 ± 4.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
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<tr>
<td>AVVR</td>
<td>1.5 ± 0.7</td>
<td>1.8 ± 0.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Ventricular function</td>
<td>1.1 ± 0.3</td>
<td>1.04 ± 0.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

AVVR = atrioventricular regurgitation; EDP = end diastolic pressure; LL = lower lobe; PA = pulmonary artery.

AVVR: none/trivial=1, mild=2, moderate=3, severe=4

Ventricular function: normal=1, mild impairment=2, moderate=3, severe=4

(Citation from [18] with publisher’s permission)
Ventricular function and atrioventricular valve regurgitation

Preservation of ventricular function and prevention of atrioventricular valve regurgitation (AVVR) are critical determinants in the success of a single ventricle palliative strategy. These parameters may be jeopardised at many points in the Norwood single ventricle management strategy including:

1) myocardial ischemia-reperfusion injury after cardioplegic arrest at Norwood Stage I palliation, 2) volume overloading of the systemic ventricle during the interstage period, and 3) impairment of the right ventricular function due to ventriculotomy at the site of construction of RV-PA conduits in Norwood patients treated with the Sano modification. On the other hand, the Hybrid procedure has potential for diminished myocardial function due to potential for restriction in coronary perfusion due to obstruction of retrograde aortic arch flow through the aortic isthmus after ductal stenting.

The influence of the obstruction of retrograde aortic arch on the Hybrid strategy

Obstruction of retrograde aortic arch flow in patients with diminished prograde aortic flow (e.g. aortic atresia) can be associated with coronary and cerebral ischemia. Obstruction can occur during the Hybrid Stage I procedure immediately after ductal stent deployment or the obstruction can develop in the interstage period due to progressive ingrowth of fibrous tissue as the site of intersection between the ductal stent and the aortic isthmus. Stoica et al. described a treatment strategy for patients with retrograde aortic arch malperfusion based upon surveillance, detection, and catheter-based treatment including retrograde stenting of the aortic isthmus in the subset of patients in whom surveillance resulted in detection of the stenosis. The strategy was associated with a high incidence of death or transplantation among patients in whom retrograde aortic arch obstruction was treated – suggesting that a treatment strategy may not be the optimal management plan for addressing retrograde aortic arch obstruction. Because of the lack of success with a treatment strategy, the authors favour the Norwood strategy for patients who are considered at risk for retrograde aortic arch obstruction.

As an alternative to a treatment-based strategy, we have developed a preventative strategy to address potential for retrograde aortic arch obstruction in Hybrid patients. In this strategy, we utilise the creation of prophylactic reverse Blalock-Taussig (BT) shunts for patients with restricted antegrade aortic flow and potential retrograde aortic arch obstruction. Importantly, we have not needed to utilise retrograde stenting of the aortic isthmus as a treatment for arch malperfusion in any of the patients with a prophylactic reverse BT shunt. The reverse BT shunt may have helped to neutralise the risk of retrograde aortic arch obstruction. Because we have not detected a significant survival disadvantage in the high-risk subset of patients with severely diminished prograde arch flow, we are continuing to utilise the reverse BT shunt as a prophylactic component of our hybrid management strategy in this high-risk group.

Ventricular function and AVVR were not different in a comparison of the hybrid and Norwood groups at the pre-Fontan evaluation as shown in Table 1 (p-value = 0.7 and 0.27 respectively). These data indicate that the Hybrid strategy has equivalent results with Norwood strategy in terms of preservation of ventricular function and atrioventricular valve function.

Influence upon neurological development

Neurological development is a major concern with any treatment strategy for single ventricle palliation. The mean neurocognitive test results in school-aged children with HLHS who underwent the Norwood procedure or cardiac transplantation are significantly below population normative values. In addition, pre-operative brain magnetic resonance imaging revealed that brains of HLHS patients are smaller and less mature before surgery than patients without congenital heart disease. Thus, the impact on neurological development is of critical importance for the single ventricle strategies.

The Hybrid strategy has a potential advantage in terms of preservation of neurologic function in comparison to the Norwood strategy. By delaying aortic arch reconstruction until the second stage procedure at four-six months of age for Hybrid patients, there is indirect evidence suggesting that the delay may have a favorable impact on the neurological development. Galli et al. reported that the development of periventricular leukomalacia (PVL) after cardiac surgery is more prevalent in neonates compared with those at the age of more than one month suggesting age-related vulnerability to neurologic injury. PVL in preterm infants is associated with subsequent cerebral palsy, mental retardation, and learning disabilities. Thus, there is an age-dependent window of vulnerability to brain injury and the Hybrid strategy may have an advantage in delaying aortic arch reconstruction from the neonatal period to four-six months of age. Objective demonstration of this advantage, however, will require a controlled clinical trial.

In contrast to the age-related potential neurological advantage of the Hybrid strategy, there is a potential disadvantage with the Hybrid strategy. As mentioned above, the obstruction of retrograde aortic arch flow can limit cerebral blood flow for four to six months prior to arch reconstruction at the Stage II procedure and long periods of limited cerebral blood flow may be detrimental to neurologic development. If the reverse BT shunt can successfully maintain arch perfusion, it may neutralise this problem. Further long term neurologic evaluation is required to compare the Norwood and Hybrid strategies in the context of neurologic function.

Intubation time, intensive care unit stay and hospital stay

Another potential benefit of Hybrid procedure is that Hybrid patients have shorter total intubation time, ICU stay, and hospital length of stay (combined Stage I and II among survivors). Galantowicz et al. reported that 85% of Hybrid patients at both Stage I and II were extubated in the first 24 hours. Interestingly, in our experience, we have noted a time-related tendency toward improvement in the intubation time, the length of ICU stay, and hospital stay at the Hybrid Stage II, while concurrent Norwood patients did not have evidence of time-related improvements in these parameters suggesting that we had reached a plateau in terms of refinement of the Norwood strategy.

Although there is less consumption of conventional measures of resource utilisation including intubation time, ICU stay, and hospital length of stay in Hybrid strategy, unplanned reinterventions were more frequent in the Hybrid patients compared with the Norwood patients (Hybrid 31.3% vs. Norwood 9.3%, p=0.016). Any comparison of resource utilisation must include quantification of planned and unplanned hospital admissions, procedures and interventions. Therefore, we are currently undertaking a study to examine total resource utilisation in a comparison of two palliative strategies.
**CONCLUSIONS**

Hybrid palliation is an evolving surgical strategy with comparable survival to reported Norwood-based series. The Hybrid strategy provides equivalent pre-Fontan haemodynamics and pulmonary artery growth, preserves ventricular and atrioventricular valve function, and reduces resource utilisation. The comparative impact of the two different surgical strategies on neurological outcome is not defined and should be a subject of prospective trials.

**FUTURE DIRECTIONS**

Important questions to frame comparisons of the Hybrid and Norwood strategies include:

1. **Which strategy is associated with better long term neurodevelopmental outcomes?**

   There are compelling arguments for and against each strategy. In the past, the timing of arch intervention was immutable — and hypoplastic aortic arches required repair in the neonatal period. With the Hybrid strategy, it is now possible to defer aortic arch reconstruction and test the hypothesis that age is an important mediator of the vulnerability to injury after aortic arch reconstruction.

2. **Which strategy produces the better Fontan candidate?**

   The Fontan procedure represents the convergence point for both management strategies. Parameters for this comparison include haemodynamics, ventricular function, valvular competence and pulmonary artery growth.

3. **Which strategy is associated with the most efficient use of resources when quantifying the entire resource burden from birth to Fontan procedure?**

   If all other factors are equal, the superior strategy is the one that utilizes the least resources and poses the smallest burden on institutions and families.

   Based on demonstration of equivalent survival, a prospective randomised trial should be undertaken to compare the Norwood and Hybrid strategies in the context of these three fundamental questions.
REFERENCES


