Review Article

Hypoplastic left heart syndrome: current perspectives

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Abstract: Since the first successful intervention for hypoplastic left heart syndrome (HLHS) was undertaken by Norwood in 1983, there have been many advancements in the pre-, intra-, and postoperative care of these children for a diagnosis that just 25 years ago was almost certainly a fatal one. This paper aims to describe the most recent trends and perspectives on the treatment of HLHS. In particular, we will discuss the five current options for HLHS, including Norwood stage I as the beginning to 3-stage palliation, transplant, true hybrid, hybrid-bridge-to-Norwood, and compassionate care.

Keywords: Hypoplastic left heart syndrome (HLHS); single ventricle; congenital cardiac anomalies

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Hypoplastic left heart syndrome (HLHS): current perspective

The term HLHS describes a heterogeneous group of diagnoses that encompass a wide array of pathophysiology. The term potentially pertains to any malformation that involves underdevelopment of the left sided cardiac structures from aortic stenosis and coarctation of the aorta to the other extreme of aortic atresia, mitral atresia, and hypoplasia of the ascending aorta. The Congenital Heart Surgery Nomenclature and Database Committee (1) attempted to precisely define those abnormalities. The proposed definition is that "*HLHS is a spectrum of cardiac malformations, characterized by a severe underdevelopment of the left heart-aorta complex, consisting of aortic and/or mitral valve atresia, stenosis, or hypoplasia with marked hypoplasia or absence of the LV, and hypoplasia of ascending aorta and of the aortic arch.*" The treatment options for these malformations are discussed in this manuscript.

It is estimated that each year about 960 babies in the United States are born with HLHS (2). Since the first successful intervention for HLHS was undertaken by Norwood in 1983 (3), there have been many advancements in the pre-, intra-, and postoperative care. Just 25 years ago, this diagnosis would certainly be a fatal one. Currently there are five options and paths of treatment for these neonates. The potential interventions include staged palliation that starts with a Norwood procedure, a hybrid treatment strategy, a hybrid-bridge-to-Norwood, transplant, or compassionate care.

There is a subset of HLHS patients who have a mild form and could potentially undergo a biventricular repair. This complex decision-making process is out of the scope of the current manuscript.

Norwood procedure

The goal of staged palliation for HLHS is to end up with a Fontan circulation, also known as a total cavo-pulmonary connection (TCPC). This is typically done in three stages. The three stages include the Norwood stage I procedure, the middle stage is a partial cavo-pulmonary connection (PCPC), also known as a bidirectional Glenn anastomosis or Hemi-Fontan, and the final stage is a TCPC. The goal of the Norwood procedure is to relieve systemic ventricular outflow obstruction, have unrestricted pulmonary venous

return, and controlled pulmonary arterial perfusion. This is accomplished with a Damus-Kaye-Stansel (DKS) procedure, an ascending arch aortoplasty, an atrial septectomy, and a source of pulmonary blood flow (PBF), either a systemic to pulmonary artery shunt or a right ventricle-pulmonary artery (RV-PA) conduit.

The source of PBF initially used and still used frequently today is the modified Blalock-Taussig (MBT) shunt, which is a Gore-Tex graft between the innominate artery and the right pulmonary artery. This was the predominant shunt until Sano revived the RV-PA modification, initially described by Norwood, but long ignored (4). The RV-PA conduit has seen a dramatic revival in popularity since its reintroduction, and the choice between the two sources of PBF is currently surgeon/institution-dependent. There have been multiple retrospective, single-center studies comparing the outcomes between the two shunts (5-7), with contradictory results, and no definitive advantage of one technique versus the other. The MBT shunt gives continuous flow to the right pulmonary artery from the innominate artery even during diastole. The concern is for diastolic runoff leading to coronary steal that could potentially cause death during the initial hospitalization or in the interstage period. The RV-PA shunt requires a right ventriculotomy which could potentially lead to ventricular dysfunction in an already stressed univentricular heart.

The Pediatric Heart Network published a multicenter, randomized trial on infants with HLHS undergoing the Norwood procedure, known as the Single Ventricle Reconstruction (SVR) trial (8). Infants were randomized to either a MBT shunt or an RV-PA conduit. Between May 2005 and July 2008, 555 patients were enrolled in the study. The primary outcome was the rate of death or cardiac transplantation 12 months after randomization. There were 72 deaths or cardiac transplants in the RV-PA shunt group, and 100 deaths or cardiac transplants in the MBT shunt group. On the basis of the data, the RV-PA shunt as compared to the MBT was associated with an improved transplantation free-survival at 12 months. When using all available data and not stopping at the pre-specified 12 months end point, the primary outcome approached but did not cross statistical significance (P=0.06). After 12 months, 10 deaths and 6 transplantations occurred in the RV-PA shunt group, as compared with 7 deaths and 0 transplantations in the MBT shunt group.

A study that investigated complications after the Norwood stage I used the Society of Thoracic Surgeons database to find preoperative risk factors that led to postoperative complications (9). These risk factors were relatively uniform across multiple studies and included weight less than 2.5 kg, preoperative shock, non-cardiac/genetic abnormality, and preoperative mechanical ventilator or circulatory support. Two studies from the Pediatric Heart Network Investigators described in hospital and inter-stage mortality associated with the Norwood procedure. The hospital mortality rate during the Norwood stage I was 16%, irrespective of shunt type. The inter-stage mortality between stages I and II was 6% for the RV-PA conduit, and 18% for the MBT shunt. The 3-year follow-up to the SVR trial was published in 2014 (10). Transplantation-free survival did not differ by shunt type.

In the largest and most recent study from the Congenital Heart Surgeons' Society (11) propensity scores were used to match 169 RV-PA conduit patients with 169 MBT shunt patients. Six year survival was better after RV-PA conduit (70%) versus the MBT shunt (55%). In contradistinction to the SVR trial, there was also more moderate or severe atrioventricular valvular regurgitation and right ventricular dysfunction and lower transplant-free survival in the MBT shunt group.

The Norwood procedure is undertaken during a time when the pulmonary vascular resistance is too elevated to allow a cavo-pulmonary anastomosis. The second stage is usually undertaken between 4–6 months of age. The goal of the second stage is to unload the right ventricle. This is accomplished with either a bidirectional Glenn or a Hemi-Fontan. The advantages of the bidirectional Glenn is that it can potentially be performed off-pump and is an easier connection. The Hemi-Fontan makes the final stage more straightforward.

This second stage originally was proposed as an interim palliation only for high risk babies before undergoing the Fontan operation (12,13), instead of proceeding directly from a shunted physiology to TCPC in one step, which is a huge physiological change associated with high risk of failure. After staged palliation with an interim Glenn operation, breaking the adaptation to new cardio-pulmonary flows into two lower-risk steps with better results, the Glenn operation became a standard staging procedure even in babies with a low-risk profile, leading to the current 3-stage approach. The goal is to unload the ventricle as early as possible, minimize potential steal from coronary blood flow, and limit the amount of time the pulmonary vasculature is exposed to systemic pressures before the baby can tolerate a Fontan (14).

Traditionally, the bidirectional Glenn anastomosis was between the superior vena cava and the pulmonary arteries.

The inferior vena cava to pulmonary artery anastomosis was abandoned in the animal lab by Dr. Glenn after repeated failure in an animal model. In patients with unfavorable upper body systemic venous anatomy, the SVC-PA connection is suboptimal or not feasible, and an alternative is needed to unload the heart. We have found that this subset of patients can benefit from a primary IVC-PA connection, the "Southern Glenn", which we have performed successfully in two patients (15).

The Fontan operation typically connects the IVC to the RPA leading to a total cavopulmonary connection so that all PBF is achieved passively. In-series circulation is restored and saturations achieve near-normal levels. This typically happens between 24 and 48 months of age. There is a wide breadth of single-institution series looking at short and long-term outcomes and predictors of mortality and morbidity after Fontan completion (16-18). The consistent predictors of poor outcome across multiple studies are longer cross-clamp times, longer length of hospital stays, heterotaxy, and atrioventricular valve anomaly.

Despite studies showing the success of either type of PBF, MBT or RVPA conduit for the Norwood stage I, the majority of centers have not changed their practice. Those centers that have solid technical and postoperative results with either the RV-PA conduit or the MBT shunt have continued to palliate the patients in the same way they always have. Current expected benchmark results for Norwood stage I palliation, as harvested by the STS congenital heart surgery database, is 85.1% in-hospital survival (19).

The "true" hybrid approach

Concerns about placing a neonate on cardiopulmonary bypass with significant cardiac and non-cardiac comorbidities, especially neurological ones, which could lead to intracranial hemorrhage, led to the advent of hybrid approaches to the HLHS baby. High risk factors included weight less than 2.5 kg, preoperative shock, non-cardiac/genetic abnormality, preoperative mechanical ventilator or circulatory support, small ascending aorta, intact/restrictive interatrial septum, and the variant of HLHS with aortic atresia and mitral stenosis. The goals of the first stage are the same as the standard Norwood procedure including securing adequate systemic perfusion, unrestricted pulmonary venous return, and controlling PBF; relief of systemic ventricular outflow obstruction with a DKS, which requires cardiopulmonary bypass, is not performed. Using a conjunction of catheter-based intervention and surgery without cardiopulmonary bypass, systemic perfusion is maintained with a ductal arteriosus stent, unrestricted pulmonary venous return is accomplished with a balloon atrial septostomy if needed and controlled (diminished) PBF is accomplished with bilateral PA bands. The concern with this approach is that the ductal stent could potentially limit retrograde blood flow into the ascending aorta, leading to coronary compromise and myocardial ischemia.

After the inter-stage period, the comprehensive stage I + II includes removal of the PA bands, removal of the ductal stent, connecting the ascending aorta with the pulmonary valve (DKS), and repair of the aortic arch and pulmonary arteries. Removing the ductal stent is probably the most challenging. It takes a technique similar to an endarterectomy to safely extract the stent without injuring the descending thoracic aorta. Initially, the hybrid approach was used for high risk infants. With formal or relative contraindications to a Norwood stage I operation, single center studies showed the feasibility of the approach, and others started using it on standard risk patients as an alternative to the Norwood stage I procedure (20,21).

Pioneering work by Galantowicz and colleagues (22) has been very illustrative in what can be accomplished with the hybrid approach for HLHS. Sixty-two patients underwent a hybrid stage I procedure between 2002 and 2007. High risk patients were excluded from their study so that the cohort of patients would have a more typical risk profile to the usual HLHS patient. The results are impressive, with a hospital survival after the hybrid stage I reaching 97.5%. The interstage I–II interval had two deaths. The hospital survival during the comprehensive stage I + II was 92%. The most important point from this early experience is that in certain patients with unfavorable anatomy, namely those with aortic atresia and no antegrade flow to the coronary arteries, jailing by the ductal stent may create stenosis of the retrograde orifice to the transverse arch. These patients should be identified before intervention, because a ductal stent can acutely lead to head vessel and/or coronary artery flow compromise, potentially leading to death from myocardial infarction and circulatory collapse. The options are to offer these patients a standard Norwood procedure or to stent the retrograde orifice at the time of the PDA stent (23).

The group in Giessen recently described 182 babies that underwent this hybrid strategy (24,25). At 10 years, the probability of survival is 77.8%. Aortic arch reinterventions were only needed in 16.7% of patients. A benefit of this approach is that several of the patients were able to be

transitioned to a biventricular repair after the hybrid approach instead of the single ventricle palliation.

The hybrid approach is theoretically attractive by reducing the early insult to an already stressed neonate while limiting pulmonary overcirculation and securing systemic perfusion. Uneven results in other centers and concerns with the technical aspects of the comprehensive stage I + II have kept the true hybrid approach from garnering widespread support for low to intermediate risk patients.

Hybrid-bridge-to-Norwood

In the above study by Galantowicz there were 12 reinterventions in the catheterization lab during the interstage I to II interval. The majority (n=7) dealt with issues with regards to the position of the ductal stent to improve antegrade systemic flow, and four were placed to relieve retrograde stenosis into the transverse aortic arch. Despite the need for reintervention, all patients went on to a comprehensive stage I + II. The need for more catheterizations and the concerns with removing the stent during the comprehensive stage I + II has led to the revival of another sequence of operations once described by Dr. Norwood, coined the hybrid-bridge-to-Norwood or the "salvage-bridge-to-Norwood" (26).

In high-risk HLHS neonates with concomitant cardiac and non-cardiac comorbidities, in whom an initial Norwood stage I operation is deemed prohibitive, the sequence starts with bilateral pulmonary artery bands in the early period after birth. The ductus is kept open with prostaglandins, instead of a mechanical stent. The Norwood stage I is then performed after the baby is stabilized, typically at about 2 weeks. We described our experience with 47 consecutive babies with HLHS between April 2010 and June 2014. Nine of these patients had a hybrid-bridge-to-Norwood. Seven of these high-risk patients had significant preoperative cardiac and non-cardiac comorbidities, including severe seizure disorders with cerebral infarction, and great vessel arrangements that precluded ductal stenting. Two patients were salvaged intraoperatively with the hybrid-bridge-to-Norwood: one had severe abdominal distension and suspected sepsis with total anomalous pulmonary venous return, and another baby with standard risk HLHS had hemo-pericardium and tamponade upon sternal entry. Seven of the patients required extracorporeal membrane oxygenation support postoperatively. Eight patients went on to a deferred Norwood stage I at a mean of 14.3 days. Six survived to hospital discharge.

The Great Ormond Street group had 17 of 147 patients between January 2006 and October 2011 who underwent what they label as the "rapid 2-stage Norwood strategy" (27). These patients were defined as high risk by having multiple risk factors, including age >2 weeks, weight <2.5 kg, prolonged mechanical ventilation, systemic sepsis, necrotizing enterocolitis, cardiac, renal or hepatic failure, coagulopathy, pulmonary edema, sustained hypotension, significant inotropic requirements, generalized edema, and previous cardiac arrest. Five patients died after the bilateral PA bands. The other 12 patients underwent a Norwood stage I procedure.

The "hybrid-bridge-to-Norwood" or "salvage-to-Norwood" approach gives the baby time to recover and allows time for the surgeon to undertake the Norwood stage I at a more advantageous moment. Although the in-hospital mortality with the "salvage-to-Norwood" approach is high compared to other approaches in neonates with HLHS, it is the only alternative to certain death in an otherwise very high-risk and unstable situation.

Cardiac transplantation

Cardiac transplantation is an attractive option in the sense that there is a dramatic change in the patient's physiology to that of a normal one. The downsides are the use of an organ in short supply for a disease that has other options, life-long immunosuppression, a 20% mortality rate while on the waiting list, and the almost inevitable prospect of future retransplantation beyond the first one to two decades of life. If transplantation is undertaken after staged palliation, the outcomes are similar to those who undergo transplantation as their primary therapy (28).

Despite these hurdles, since Bailey's first description in 1986 (29), cardiac transplantation remains a valid option for some patients with HLHS. The main difference between transplantation of a heart into a patient with HLHS and other pathologic conditions is that the donor arch and proximal descending aorta must be procured to reconstruct the recipient's arch past the isthmus. The 5-year survival is comparable between staged palliation and cardiac transplantation. As mentioned, cardiac transplantation has an upfront cost due to the shortage of available organs and potential attrition while on the waiting list. This has led some centers to palliate these patients with pulmonary artery bands to allow a more stable and safe waiting period.

The Loma Linda group has probably published the most on the subject of primary transplantation (30). In their series, only 64% of patients listed for transplantation

completed and survived through transplantation. The risk factors for mortality with transplantation are pretransplant circulatory support, posttransplant mechanical circulatory support, and donor heart cross-clamp time.

Given the shortage of organs required for this age and size of patients and the high mortality while waiting for an organ, most centers have abandoned this approach. It is now offered in only a handful of highly specialized and geographically centralized high-volume referral centers in the world.

Compassionate care

With the advent of multiple options for these complex patients, the decision "to do nothing" has been a less frequently sought option, making this line of parent counseling rarer for the majority of practitioners. When other major, uncorrectable genetic, anatomic, or physiologic cardiac or non-cardiac malformations preclude a satisfactory final outcome, comfort care may be an option. If no intervention is chosen, the mortality is about 98% in the first 6 weeks of life. The keys to this discussion should encompass counseling, facts, and ultimately letting the family decide.

Conclusions

Before 1980, HLHS was a uniformly fatal diagnosis. There have been great advancements with the treatment of these patients, which have led to an initial survival rate of 90–92% in the neonatal period for standard-risk patients undergoing surgery. There are now four viable pathways for these patients to become long-term survivors. The future holds refinement of surgical techniques, lessening of risks, catheter-based advancements, and improved perioperative care with a better understanding of the physiology. Factors influencing the long-term prognosis of these patients after successfully undergoing all three stages of palliation remain to be determined.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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