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Pediatrics 2007;119;109-117
DOI: 10.1542/peds.2006-1592

STATE-OF-THE-ART REVIEW ARTICLE

New Developments in the Treatment of Hypoplastic Left Heart Syndrome

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

In the current decade, the prognosis of newborns with hypoplastic left heart syndrome, previously considered a uniformly fatal condition, has dramatically improved through refinement of rapidly evolving treatment strategies. These strategies include various modifications of staged surgical reconstruction, orthotopic heart transplantation, and hybrid palliation using ductal stenting and bilateral pulmonary artery banding. The variety of treatment approaches are based on different surgical philosophies, and each approach has its unique advantages and disadvantages. Nonetheless, multiple experienced centers have reported improved outcomes in each one of those modalities. The purpose of this review is to outline recent developments in the array of currently available management strategies for neonates with hypoplastic left heart syndrome. Because the vast majority of deaths in this patient population occur within the first months of life, the focus of the review will be evaluation of the impact of these management strategies on survival in the neonatal and infant periods.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-1592

doi:10.1542/peds.2006-1592

Key Words
hypoplastic left heart syndrome, cardiovascular anomalies, heart transplantation

Abbreviations
HLHS— hypoplastic left heart syndrome
RV-PA—right ventricle to pulmonary artery
BDCPA— bidirectional cavopulmonary anastomosis
PAB/DS—pulmonary artery band and ductal stent

Accepted for publication Jul 28, 2006

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HYPOPLASTIC LEFT HEART syndrome (HLHS) is a term used to describe a heterogeneous group of cardiac malformations that are characterized by various degrees of underdevelopment of the left heart-aorta complex, resulting in obstruction to systemic cardiac output and the inability of the left heart to support the systemic circulation.[1] The anatomic lesions associated with HLHS are summarized in Fig 1. Because the neonate with HLHS depends on right ventricular ejection through the ductus arteriosus for systemic cardiac output, continuous infusions of prostaglandins are required to maintain ductal patency. Consequently, surgical stabilization by any strategy requires revision of the aorta, ductus arteriosus, and pulmonary artery anatomy to achieve 4 objectives: (1) unobstructed systemic cardiac output; (2) a controlled source of pulmonary blood flow; (3) a reliable source of coronary blood flow; and (4) unobstructed egress of pulmonary venous effluent across the atrial septum. The earliest successful palliative first-stage operation was reported by Norwood in 1980; the surgery met the treatment objectives described above and has become a mainstay of surgical management for neonates with HLHS.[2]

The natural history of HLHS without surgical intervention is universally fatal. Although "no therapy" has been considered the only appropriate option in the past; this alternative is not commonly offered to otherwise healthy neonates in any advanced congenital cardiac center because of rapidly improving prognosis in the recent era. Nonetheless, "no therapy" remains a valid choice in those neonates with severe associated malformations or chromosomal abnormalities that would preclude meaningful survival and quality of life.

The purpose of this review is to evaluate the current results and limitations of several recent developments in the array of currently available management strategies for neonates with HLHS, including staged surgical reconstruction, orthotopic heart transplantation, and hybrid palliation.[3–10]

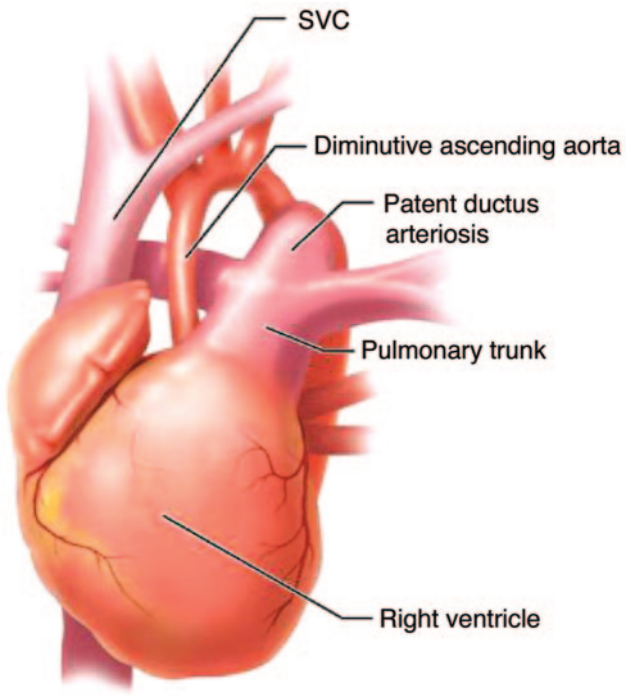

FIGURE 1
Anatomic manifestations of HLHS: mitral stenosis or atresia, hypoplasia of the left ventricle, aortic stenosis or atresia, hypoplastic aortic arch, and ductal-dependent systemic cardiac output. SVC indicates superior vena cava.

STAGED SURGICAL RECONSTRUCTION

Overview

The Norwood procedure is the most commonly performed initial palliative procedure for patients undergoing staged surgical palliation in the neonatal period.[2] Because the pulmonary vascular resistance is high in the neonatal period, an aortopulmonary shunt or, more recently, a right ventricle to pulmonary artery (RV-PA) conduit is used to provide a controlled source of pulmonary blood flow at the cost of volume loading the right ventricle (Fig 2 A and B). A second-stage procedure, the superior bidirectional cavopulmonary anastomosis (BDCPA) or hemi-Fontan procedure is typically performed at 4 to 6 months of age and results in removal of the ventricular volume load by the anastomosis of the superior vena cava to the pulmonary arteries (Fig 2C). At a third stage, typically at 2 to 4 years of age, a Fontan procedure is performed to channel the remaining systemic venous return from the inferior vena cava return to the pulmonary arteries (Fig 2D). Several modifications in operative techniques in each stage have evolved and contributed to improved surgical results.

The Standard Norwood Operation Using an Aortopulmonary Shunt

The standard Norwood procedure (Table 1) uses an aortopulmonary shunt as the source of pulmonary blood flow (Fig 3A). Current operative survival in experienced centers exceeds 70%. Several risk factors for increased operative mortality have been identified, such as low birth weight, prematurity, significant associated noncardiac congenital conditions, severe preoperative obstruction to pulmonary venous return, and smaller ascending-aorta diameter.[1,3–6,11–13]

Achieving consistent early survival after the Norwood procedure remains a major challenge. Because pulmonary blood flow is derived from systemic cardiac output, conventional postoperative management strategies have focused on limitation of pulmonary blood flow by increasing pulmonary vascular resistance using ventilator manipulations with induction of hypoxemia and hypercarbia.[14,15] Recently adopted intraoperative and postoperative strategies have included reduction in the size

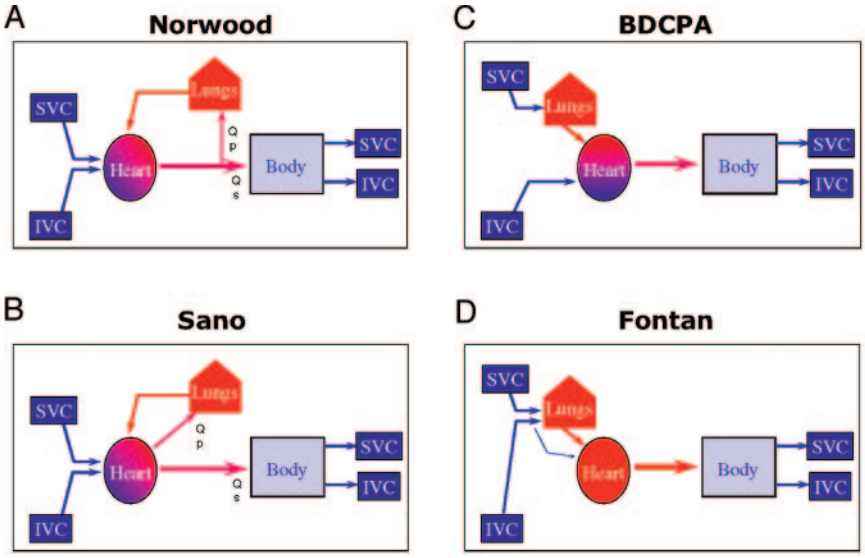

FIGURE 2
Schematic representation of the systemic and pulmonary circulation after a Norwood operation with aortopulmonary shunt (A), Sano modification with RV-PA shunt (B); superior BDCPA (C); and Fontan procedure (D). SVC indicates superior vena cava; IVC, inferior vena cava; QS, systemic blood flow; QP, pulmonary blood flow. Red denotes oxygenated blood, and blue denotes deoxygenated blood. The small arrow in D represents a fenestration in the Fontan circuit.

TABLE 1 **Surgical Outcomes of Standard Norwood First-Stage Reconstructive Surgery in the Treatment of Patients With HLHS**

Study (Year)	Surgery Year	No. of Patients	Operative Mortality, %	Time-Related Survival, %
Bove and Lloyd[3] (1996)	1990–1995	158	24	5 y: 58
Daebritz et al[4] (1999)	1990–1998	131	37	1 y: 49
Poirier et al[11] (2000)	1993–1999	59	17	1 y: 72
Mahle et al[5] 2000	1984–1999	840	36	1 y: 51
				5 y: 40
				15 y: 39
Azakie et al[6] (2001)	1990–2000	171	18	1 y: 48
				5 y: 45
Tweddell et al[7] (2002)	1992–2001	115	19	1 y: 66
				5 y: 61
Gaynor et al[12] (2002)	1998–2001	158	22	1 y: 66
Ashburn et al[13] (2003)[a]	1994–2000	710	28	1 y: 60
				5 y: 54

[a] Prospective multiinstitutional study.

of the aortopulmonary shunt,[16] use of systemic vasodilators such as phenoxybenzamine,[17] and continuous monitoring of mixed venous saturation.[8] Using these contemporary measures in the postoperative management after the Norwood operation, some centers were able to achieve hospital survival exceeding 90% in selected groups of patients.[7,8,17]

Several refinements of operative technique have also been introduced to improve the short-term and long-term surgical results. Many studies have suggested that prolonged deep hypothermic circulatory arrest is a risk factor for increased operative and interstage mortality.[18] Modifications in perfusion management aiming to reduce or eliminate deep hypothermic circulatory arrest by the use of continuous regional cerebral perfusion during arch reconstruction have been adopted by many centers in an effort to decrease operative mortality and the incidence of neurologic injury.[19–22] Although significant advantage has not been collectively demonstrated yet, many surgeons gained increased experience in performing complex arch-reconstruction surgery while maintaining continuous selective cerebral perfusion and diminishing or eliminating the duration of brain ischemia.

Interim mortality remains high, and 4% to 15% of hospital survivors die at home before the second-stage operation.[6,12,23] Residual aortic-arch obstruction, restrictive atrial septal defects, imbalance of pulmonary and systemic blood flow, diastolic run-off with coronary ischemia, shunt stenosis or thrombosis, and chronic volume overload of the single ventricle have all been implicated as major causes for interstage mortality. In a postmortem study, impairment of coronary perfusion (27%), excessive pulmonary blood flow (19%), obstruction to pulmonary blood flow (17%), neoaortic obstruction (14%), and right heart failure (13%) were identified as important causes of interim mortality.[24]

Recovery from the critical early postoperative period marks the transition to chronic treatment protocols. Although these protocols are different among various centers, they are usually guided by the early postoperative hemodynamics. Most patients are discharged on chronic diuretic therapy, with the dose titrated on the basis of clinical findings. Caution is taken to avoid inducing vascular volume depletion with subsequent reduction in cardiac output or hyperviscosity with increased risk for shunt thrombosis. Digoxin is given to patients by some centers, whereas afterload reduction with an angiotensin-converting enzyme inhibitor is given selectively to patients with increased pulmonary blood flow/systemic blood flow ratio, those who have congestive heart failure, moderate or greater atrioventricular valve insufficiency, or as part of an ongoing trial using captopril as an afterload-reducing agent. For prophylaxis against shunt thrombosis, the protocol varies among centers, with

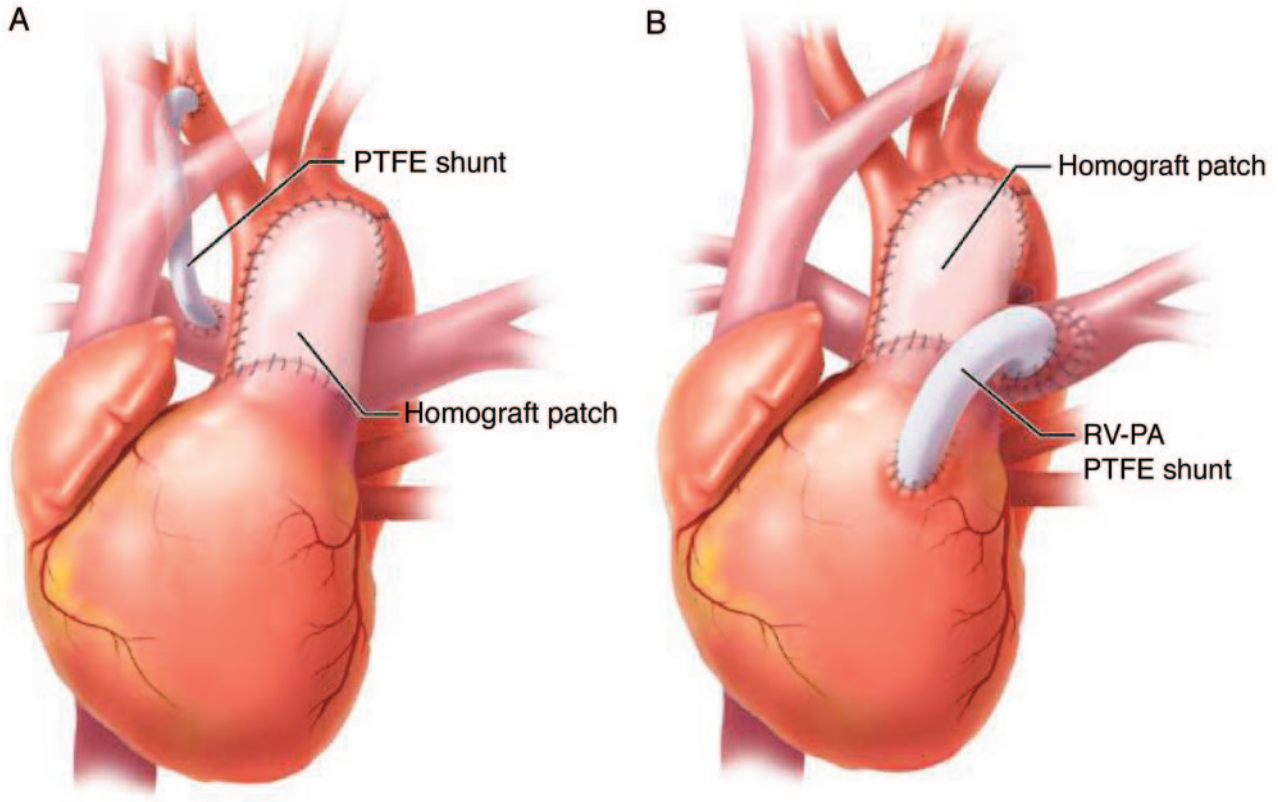

FIGURE 3
A, The final appearance of a completed Norwood operation. The ascending aorta and arch have been reconstructed with homograft patch augmentation. The shunt between the distal innominate artery and the central pulmonary arteries is demonstrated. B, The final appearance of a completed Sano modification using the RV-PA shunt. The ascending aorta and arch have been reconstructed with homograft patch augmentation. The shunt between the right ventricle and the central pulmonary arteries including an autologous pericardium cuff is demonstrated. PTFE indicates polytetrafluoroethylene.

most using antiplatelet therapy with aspirin along with low molecular weight heparin via subcutaneous injection. There is a great emphasis on feeding and nutritional support, because the infants are commonly incapable of maintaining adequate caloric intake in the early postoperative period. A temporary nasogastric feeding tube is used initially, and if necessary, an open gastrostomy tube is placed before hospital discharge.

Finally, aggressive monitoring strategies during this vulnerable period for evidence of cyanosis or overcirculation have resulted in decreased interim mortality.[25] Vigilant postoperative care and monitoring are crucial elements for any successful treatment strategy for HLHS. Although the postoperative care details are beyond the scope of this review, they have been discussed in an excellent review by Ghanayem et al.[25]

Second-stage superior BDCPA removes ventricular volume loading and results in a more stable in-series circulation (Fig 2C). Superior BDCPA is associated with low operative mortality, and subsequent risk of death remains low.[13,26–29] The third-stage Fontan procedure (Fig 2D) is also associated with low operative mortality and a long hazard phase with low mortality.[13]

The Sano Modification Using an RV-PA Shunt

The RV-PA shunt to reestablish pulmonary blood supply in first-stage palliation for HLHS (Table 2) was first introduced by Norwood in 1981 using large shunts.[30] Because of poor outcomes secondary to excessive pulmonary blood flow and right ventricular failure, the shunt was abandoned in favor of aortopulmonary shunts. Renewed interest in the use of RV-PA shunts has followed increased awareness of its many potential advantages.[31,32] This modification has largely been popularized by Sano et al,[32] and it is called the "Sano procedure" in many centers (Fig 3B). Elimination of diastolic run-off into the pulmonary circulation (associated with aortopulmonary shunts) results in higher diastolic pressure and improved coronary perfusion.[33–36] In addition, RV-PA shunts are associated with decreased ventricular volume loading and may result in decreased ventricular dilatation, tricuspid valve regurgitation, and reduced interim mortality.[37] Finally, insertion of the RV-PA shunt in the central portion of the pulmonary arteries provides pulsatile flow that may promote better and more symmetric growth of pulmonary artery.[38]

Nonetheless, there are some potential disadvantages

TABLE 2 **Surgical Outcomes of the Sano Modification First-Stage Reconstructive Surgery in the Treatment of Patients With HLHS Using an RV-PA Shunt**

Study (Year)	Surgery Year	Surgery Type	Operative Mortality, %	Time-Related Survival, %
Mahle et al[36] (2003)	1999–2002	RV-PA ($n = 11$)	19	1 y: 81
		Norwood ($n = 22$)	19	1 y: 73
Sano et al[33] (2004)	1998–2002	RV-PA ($n = 73$)	16	1 y: 65
Pizarro et al[37] (2004)	2000–2003	RV-PA ($n = 50$)	8	—
		Norwood ($n = 46$)	27	—
Bradley et al[40] (2004)	2000–2003	RV-PA ($n = 19$)	11	—
		Norwood ($n = 25$)	20	—
McGuirk et al[39] (2005)	1992–2004	RV-PA ($n = 73$)	29	1 y: 58
		Norwood ($n = 258$)	—	10 y: 50
Tabbutt et al[61] (2005)	2002–2004	RV-PA ($n = 54$)	17	—
		Norwood ($n = 95$)	14	—

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of an RV-PA shunt. The necessity for a right ventriculotomy may affect the contractile function of the systemic ventricle and may promote ventricular arrhythmias. Moreover, free pulmonary regurgitation of the nonvalved conduit may cause ventricular dilatation and contribute to ventricular dysfunction and arrhythmia. RV-PA shunts may be associated with obstruction, occlusion, and the development of false aneurysms as well as central pulmonary artery stenosis at the site of shunt insertion.[38] Lower postoperative oxygen saturations associated with RV-PA shunts may force an early need for the second-stage procedure.[33]

To address the knowledge gap in comparing the aortopulmonary and RV-PA shunts, a multicenter prospective randomized clinical trial sponsored by the National Heart, Lung, and Blood Institute is currently underway to evaluate early and intermediate-term outcomes for patients undergoing a Norwood procedure. End points include death or cardiac transplantation. In addition, the effect of shunt type on ICU morbidity, unintended cardiovascular interventional procedures, right ventricular function, tricuspid valve regurgitation, pulmonary artery growth, and neurodevelopmental outcome will be assessed.

Until more data are available to support the benefit of RV-PA shunts, the choice of shunt remains a surgeon's preference. It may have a special role, however, in some high-risk patients such as those with low birth weight, extremely small aorta, preoperative hypotension, right ventricular dysfunction or tricuspid valve insufficiency, and an aberrant right subclavian artery.

HYBRID STRATEGIES IN THE MANAGEMENT OF HLHS

Despite major improvements in the outcome of patients after the Norwood procedure, operative and interstage mortality remains substantial. Because the effects of cardiopulmonary bypass and circulatory arrest may contribute to this morbidity and mortality,[41,42] achieving the critical 4 objectives enumerated above without using cardiopulmonary bypass is potentially an important advance in the management of neonates with HLHS (Table 3). In addition, suboptimal neurocognitive function among survivors after staged reconstruction has prompted efforts to explore alternatives that avoid cardiopulmonary bypass and circulatory arrest in the neonatal period.[43–45]

Ruiz et al[46] reported experience with stenting of the ductus arteriosus as a bridge to cardiac transplantation in infants with HLHS. Gibbs et al[47] reported the use of a hybrid approach that combined surgery and interventional catheterization to achieve bilateral pulmonary artery banding, creation of an atrial septal defect, and stenting of the arterial duct as an alternative form of neonatal palliation for HLHS (Fig 4A). Multiple authors have subsequently reported small series of neonates undergoing initial palliation with pulmonary artery banding/ductal stenting (PAB/DS) hybrid procedures with outcomes comparable to those in the current registry data of Norwood procedures.[48–51]

The first-stage PAB/DS hybrid procedure is typically performed under general anesthesia in a cardiac catheterization laboratory that is equipped for surgical procedures with available cardiopulmonary bypass support.

TABLE 3 **Surgical Outcomes of the Initial Experience With Hybrid Strategy in the Treatment of Patients With HLHS**

Study (Year)	Surgery Year	*n*	First-Stage Mortality, *n*/*N* (%)	Interstage Mortality, *n*/*N* (%)	Second-Stage Mortality, *n*/*N* (%)	Late Death, *n*/*N* (%)
Akintuerk et al[48] (2002)	1998–2000	11	0/0 (0)	1/11 (9)	1/11 (9)	0/0 (0)
Galantowicz et al[49] (2005)	2001–2004	29	2/29 (7)	3/29 (10)	2/14 (14)	1/12 (8)
Pizarro and Murdison[50] (2005)	2001–2004	10	2/10 (20)	2/10 (20)	1/4 (25)	0/0 (0)
Bacha et al[51] (2006)	2003–2005	14	3/14 (21)	2/14 (14)	2/8 (25)	1/6 (17)

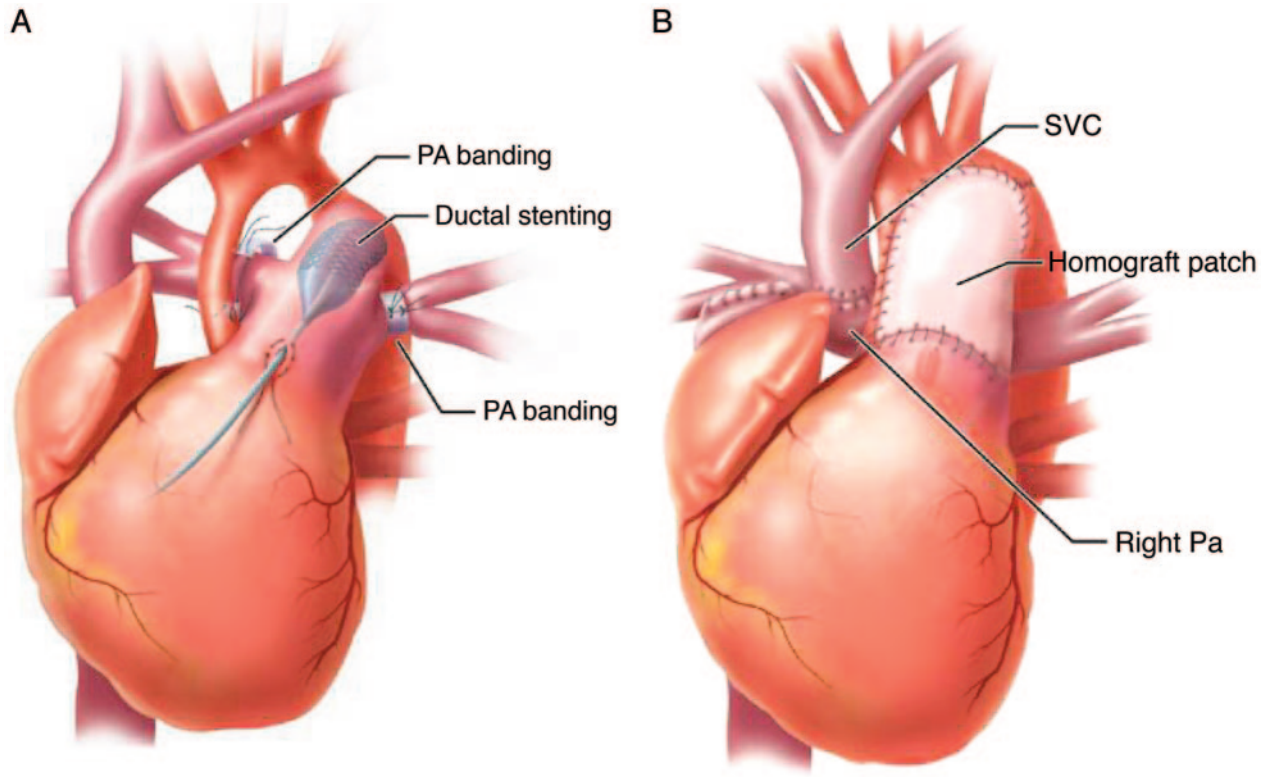

FIGURE 4
A, First-stage hybrid pulmonary artery banding and ductal stenting. B, Second-stage reconstruction. The ascending aorta and arch have been reconstructed with homograft patch augmentation. BDCPA between the superior vena cava and the right pulmonary artery is demonstrated.

The second-stage reconstruction is usually performed at 4 to 6 months of age and consists of stent removal, aortic arch reconstruction, and superior BDCPA (Fig 4B).

Although unproven, the rationale supporting first-stage hybrid palliation with PAB/DS procedures is predicated on 3 hypotheses: (1) avoidance of cardiopulmonary bypass and cardioplegic arrest during the neonatal period will result in improved long-term myocardial function; (2) deferring reconstruction of the aortic arch (which requires cardiopulmonary bypass and some alteration in cerebral blood flow and/or circulatory arrest) to an older age (eg, 3–6 months) will result in improved long-term neurologic outcomes; and (3) a 3- to 6-month-old leaving the operating room with an in-series circulation (cavopulmonary shunt) will be more stable than a neonate leaving the operating room with a balanced circulation (aortopulmonary or RV-PA shunt) after a similar operation.

Nonetheless, potential complications of PAB/DS hybrid procedures include ductal and atrial stent migration, pulmonary artery band migration, stent stenosis, and thrombosis.[48–51] Frequent monitoring is needed to detect these complications, which may require urgent catheter-based reinterventions or early second-stage reconstruction surgery.[48–51] Immediate or delayed obstruction in the aortic isthmus after stent deployment can become lethal in patients with no prograde aortic flow (eg, aortic atresia) resulting from acute coronary and cerebral hypoperfusion. In those patients, we routinely place a main pulmonary artery to innominate artery graft, which is analogous to a reversed modified Blalock-Taussig shunt, to avoid this problem.[52] Development of intrapulmonary artery flow restrictors, such as the Amplatzer flow restrictor, may allow complete first-stage palliation in the catheterization laboratory without sternotomy.[49]

ORTHOTOPIC HEART TRANSPLANTATION

Since introduced by Bailey,[53] cardiac transplantation (Table 4) became a therapeutic alternative for infants with HLHS and remains the preferred treatment in some centers.[8,9,54,55] The main advantage of cardiac transplantation is that normal physiology is achieved after a single operation. Although survival after transplantation has been excellent, this approach cannot be offered to all infants with HLHS because of limitations in the availability of donor hearts. The overall reported mortality while awaiting transplantation for patients with HLHS is 21% to 37%.[8,9,55–57] Furthermore, this approach requires lifelong immunosuppression with the attendant risks of rejection, infection, graft atherosclerosis, and malignancies. Although operative mortality is relatively low, survivors continue to experience attrition at a rate of 2%

TABLE 4 **Surgical Outcomes of Orthotopic Heart Transplantation in the Treatment of Patients With HLHS**

Study (Year)	Surgery Year	Surgery Type	Transplant Waiting List Mortality, %	Operative Mortality, %	Time-Related Survival, %
Razzouk et al[8] (1996)	1985–1995	Transplantation ($n = 176$)	19	9	1 y: 84 5 y: 76
Bando et al[54] (1996)	1989–1995	Transplantation ($n = 22$)	—	—	1 y: 82
		Norwood ($n = 28$)	—	—	1 y: 50
Jenkins et al[57] (2000)[a]	1989–1994	Transplantation ($n = 122$)	25	—	1 y: 61 5 y: 55
		Norwood ($n = 109$)	—	—	1 y: 42 5 y: 38
Chrisant et al[9] (2005)[a]	1993–1998	Transplantation ($n = 262$)	25	11	1 y: 92 5 y: 85

— indicates that the data were not reported.
[a] Multiinstitutional study.

per year.[55] Survival after transplantation for infants has improved dramatically in the last decade, and future improvements can be expected with the continued advance in understanding of the immune system and the development of new immunosuppressive agents.

One exciting and notable development is the use of ABO-incompatible heart transplantation, which exploits the immaturity of the neonatal immune system.[56,58] Newborn infants do not produce isohemagglutinins, and serum anti-A or anti-B antibody titers usually remain low until the age of 12 to 14 months of age. Furthermore, the complement system is not fully competent in young infants. Thus, the primary factors that would initiate hyperacute rejection are absent during early infancy.[56,58,59] This unique immunologic opportunity allows the use of ABO-incompatible donor hearts and can decrease waiting-list attrition through expansion of the effective organ-donor pool.[56,58]

Another recent development that may increase infant survival while awaiting transplantation is the development of the PAB/DS hybrid procedures described above. These procedures are equally effective in palliation for neonates who are awaiting transplantation and allow cessation of prostaglandins, extubation, and discharge home while awaiting a suitable donor. In addition, controlling the pulmonary blood flow may help to minimize the early postoperative pulmonary hypertension, hypoxemia, and donor right heart failure after transplantation.[48–51] Of note, the use of PAB/DS pretransplant hybrid palliation does not preclude "crossing over" to the staged surgical palliation strategy if a donor heart remains unavailable.

Neonates undergoing transplantation may require subsequent retransplantation as a result of the development of allograft vasculopathy and graft dysfunction. Freedom of retransplantation at 15 years is ~74%.[55,56] Recent reports from experienced centers suggest that survival in children requiring retransplantation is similar to primary transplantation.[55,60]

Nonetheless, very few centers offer orthotopic heart transplantation as the primary treatment for neonates with HLHS, and staged reconstruction remains the primary procedure offered by most other centers, with transplantation performed on those with significant ventricular dysfunction and/or valvular deformity and regurgitation or those with a failing heart after the first, second, or third stage of the reconstruction strategy.[3–10]

SUMMARY

Although HLHS was once considered uniformly fatal, the prognosis of newborns with this condition has improved dramatically with recent advances in staged reconstructive procedures, PAB/DS hybrid procedures, and heart transplantation. These techniques are evolving rapidly, and because individual centers tend to focus on single management strategies with variable reporting of selection and exclusion criteria, it is difficult to reliably compare management strategies across the spectrum of currently available techniques. Consequently, multiinstitutional databases may be the only way in which this comparative knowledge can be generated within a clinically relevant time frame. The current National Institutes of Health trial that is comparing the aortopulmonary and RV-PA shunt is an excellent example of a collaborative approach to address an important operative decision.

A multiinstitutional study currently underway by the Congenital Heart Surgeons Society is enrolling patients into an observational study across the entire range of neonates with critical left ventricular outflow tract obstruction (of which HLHS is a subset). This important study will allow comparison of all currently practiced management strategies, will include operative and nonoperative patients, and will maintain lifelong follow-up of this cohort. This study was designed to identify optimum management strategies on the basis of individual patient anatomic, physiologic, and demographic criteria. In addition, because neonatal survival continues to im-

prove, it is becoming increasingly important to evaluate the long-term consequences of each neonatal management strategy. Lifelong follow-up of the Congenital Heart Surgeons Society cohort, and similar studies, will be needed to allow evaluation of the long-term functional outcomes and health-related quality of life and to relate these outcomes to the neonatal choice of management strategy.

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