Hypoplastic Left Heart Syndrome

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Introduction

Hypoplastic left heart syndrome (HLHS) is a type of congenital heart disease that results in the underdevelopment of the left-sided structures of the heart, including the mitral valve, left ventricle, aortic valve, the ascending aorta, and aortic arch. HLHS was first described as a syndrome in 1958 by Nadas and NoonanFontanwho referred to it as combined aortic and mitral atresia.[1] HLHS affects 1 in 5,000 neonates or 3% of all infants born with congenital heart disease.[2][3] Thirty years ago, there were no treatment options for these neonates, and mortality was 100% within the first week of life.[4] Neonates born with HLHS are dependent on a patent ductus arteriosus and an interatrial communication for survival until surgical intervention. A continuous infusion of prostaglandin E1 (PGE1) is needed to maintain ductal patency. Today, there are several treatment options available in the prenatal or neonatal period, which include the Norwood procedure, hybrid stage 1, heart transplantation, palliative care, and fetal intervention. A series of three palliative surgical operations (Norwood/Hybrid, Hemi-Fontan/Bidirectional Glenn, and Fontan) are typically necessary for survival beyond the neonatal period and infancy. Though rare, a diagnosis of HLHS is responsible for 23% of all cardiac deaths in the first week of life.[1]

Etiology

The etiology of HLHS is multifactorial and results in underdevelopment of the left-sided structures of the heart.[3] The factors leading to this defect can be categorized into two groups, obstruction of outflow from the left ventricle (obstruction of the left ventricular outflow tract, aortic valve atresia or stenosis) or obstruction of flow into the left ventricle (mitral valve atresia or stenosis, restrictive foramen ovale). Aortic valve stenosis is the most common cause of underdevelopment of the left ventricle.[3]

During fetal development, obstruction to left ventricular (LV) outflow secondary to aortic stenosis increases LV afterload and causes LV hypertrophy, eventually leading to LV dilatation and decreased LV contractility. Additionally, reduced blood flow through the LV inhibits the growth of the ventricle leading to hypoplasia. As a result, the pressure in the left atrium increases leading to bidirectional blood flow or flow reversal through the foramen ovale. The physiologic sequela is a further decrease in blood flow to the LV. Obstruction of flow into the left ventricle due to mitral stenosis or mitral atresia will also cause hypoplasia of the LV due to decreased preload and pressure in the left ventricle. A reduction in blood flow to any developing cardiac structure will lead to abnormal development in-utero.[3]

Neonates with HLHS are dependent on a patent ductus arteriosus (PDA) to provide a blood source for the systemic circulation and coronary arteries. After birth, a continuous infusion of prostaglandin E1 (PGE1) is necessary to maintain ductal patency.[5] These patients are considered to have systemic and pulmonary circulations in parallel, unlike the series circulation of the normal heart.[3] The LV in an infant with HLHS does not serve any function. In neonates with HLHS and a patent ductus arteriosus, blood is ejected from the heart through the pulmonary valve and into the main pulmonary artery to provide a source of blood for the pulmonary circulation. After the main pulmonary

artery, blood flows into the right and left branch pulmonary arteries, and from the left pulmonary artery, a portion of the blood flows through the ductus arteriosus. Blood flow through the ductus arteriosus supplies the aortic arch, ascending aorta and coronary arteries in a retrograde fashion and the descending aorta in an antegrade direction, thereby supplying blood to the systemic circulation. The proportion of blood flow to the systemic versus pulmonary circulation can vary depending on the ratio of pulmonary vascular resistance (PVR) to systemic vascular resistance (SVR). To a certain extent, PVR and SVR can be manipulated, either medically or surgically, to maintain a balance of pulmonary and systemic blood flow in a 1 to 1 ratio.[6][7] Neonates have high pulmonary vascular resistance at birth, which would favor blood flow to the systemic circulation.[8] However, as the pulmonary vascular resistance begins to fall shortly after birth, an increasing amount of blood flow is directed to the pulmonary circulation at the expense of the systemic circulation.[5] Additionally, if the ductus arteriosus closes completely, systemic circulation is severely reduced, and cardiovascular collapse rapidly ensues.[3][9][10]

Since the LV is nonfunctional in HLHS, there is little to no egress of blood from the left ventricle. As such, oxygenated pulmonary venous blood in the left atrium exits the left heart through an interatrial communication, either the foramen ovale (FO) or an atrial septal defect (ASD). Oxygenated pulmonary venous blood mixes with deoxygenated systemic blood returning to the right atrium, which then flows into the right ventricle and is ejected to the systemic and pulmonary circulation, as described above. As a result of mixing, typical arterial oxygen saturation is between 75% to 85% and is responsible for the observed cyanosis. Neonates with a restrictive foramen ovale or intact atrial septum may require an emergent percutaneous balloon atrial septostomy in the cardiac catheterization lab after birth to create a larger interatrial communication.[11]

Epidemiology

HLHS accounts for 1.4% to 3.8 % of congenital heart disease.[1] There are approximately 1000 to 2000 infants born with HLHS in the United States every year.[2] This cardiac defect alone is responsible for 23% of cardiac deaths during the first week of life.[1]

History and Physical

HLHS is commonly diagnosed by prenatal ultrasound. Neonates with HLHS are usually born at term with birthweights in the normal range for gestation. A heart murmur is often not present.[7] Their delivery room course and systemic oxygenation may be normal during the first few hours of life because the ductus arteriosus is still widely patent during the first 24 to 28 hours.

Universal pulse oximetry screening is endorsed and recommended by the American Academy of Pediatrics (AAP).[12] All newborns should have preductal and postductal pulse oximetry measurements 24 hours after delivery.[12] One probe should be placed on the right hand (preductal)and the other one on either foot (postductal) to detect lesions with right-left shunting through the PDA.[12] Newborns who fail the pulse oximetry screening should be referred to cardiology and receive an echocardiogram.

A newborn with undiagnosed HLHS will often present with symptoms of low cardiac output: poor perfusion, tachycardia, acidosis, hypotension, and weak pulses.[7] The ductus arteriosus is beginning to close, and systemic perfusion is compromised.

Evaluation

Echocardiography can detect HLHS in utero or after birth. The pathophysiology of HLHS is evolutionary during fetal life. The left ventricle will decrease in size as gestation progresses, and the defect may not be detected by echocardiography until the third trimester.[13] The prenatal diagnosis rates vary from 39% to 75%.[5] Echocardiography will reveal a small left ventricle, abnormal mitral/aortic valve, small ascending aorta, and aortic arch. The right ventricle and right atrium will often appear dilated from the increased volume load during the prenatal period.[13] A four-chamber view is ideal for comparing the size of both ventricles. Echocardiography is also

used to evaluate the flow through the foramen ovale and the potential need for emergent cardiac intervention, such as a percutaneous balloon atrial septostomy.

The chest x-ray will usually reveal an enlarged cardiac silhouette and signs of pulmonary venous hypertension.[14]

Blood work consisting of arterial blood gas, complete blood count, electrolytes, and lactate should be obtained to evaluate acid-base status, oxygenation and ventilation, kidney function, and hematocrit. Genetic testing should also be obtained as HLHS has been associated with multiple chromosomal abnormalities including Turner, DiGeorge, and Down syndrome. Neonates with a chromosomal abnormality have a higher morbidity and mortality rate as well as a longer hospital stay after surgery.[15]

Neonates with severe congenital heart disease have an increased incidence of intraventricular hemorrhage and will often require a head ultrasound before surgical repair.[16]

Treatment / Management

Management after birth

Neonates with HLHS are critically ill and will need to be managed in the ICU and stabilized before surgical intervention during the first week of life. Initial management will include: (1) maintaining ductal patency, (2) avoid excess pulmonary blood flow, and (3) ensure adequate blood flow from the left atrium to the right atrium.

1. Any neonate with prenatal or postnatal suspicion of HLHS will have a transthoracic echocardiogram shortly after birth. Once the diagnosis of HLHS is confirmed, a low dose intravenous prostaglandin E1 (PGE1) infusion must be started to ensure ductal patency and maintain systemic circulation. An initial PGE1 dose of 0.05 to 0.1 mcg/kg/minute is started. Once ductal patency is confirmed, the infusion is gradually titrated down to 0.02 mcg/kg/minute. The lowest effective dose of PGE1 should be used to avoid side effects of respiratory depression and hypotension.

2. Neonates with HLHS may experience significant systemic hypoperfusion as the PVR decreases after birth. The pulmonary and systemic circulations will need to remain balanced. Supplemental oxygen administration should be avoided as an oxygenation saturation in the 70s and 80s is acceptable. If the oxygen saturations are high, then the neonate can be intubated and ventilated to increase PVR by keeping the PCO2 around 45 to 50 mmHg.[9] Any metabolic acidosis should be corrected with sodium bicarbonate, and the oxygen-carrying capacity should be optimized by maintaining a hematocrit of 40% to 45%. If necessary, sub-ambient FIO2 of 15% to 19% can be used to increase PVR and shunt more blood to the systemic circulation.[9]

3. The atrial septum will also be evaluated during the echocardiogram. If there is a restrictive foramen ovale or intact atrial septum, the newborn will be taken emergently to the cardiac catheterization lab shortly after birth to enlarge this interatrial communication and decompress the left atrium. If the atrial septum remains intact or restrictive, an irreversible increase in pulmonary vascular resistance (PVR) will occur.[11] This elevation in PVR is associated with a higher mortality and morbidity rate in newborns with HLHS. There are several percutaneous catheter procedures commonly performed, including the Rashkind balloon atrial septostomy, static balloon septal dilation, and the Park's blade septostomy. Rarely, an interatrial stent may be needed to relieve a severe restriction.[11][9]

Palliative Surgical Management

A series of three palliative repairs are necessary for survival. The ultimate goal is to separate the systemic and pulmonary circulations. The right ventricle will become the systemic ventricle and pump oxygenated blood to the body while all deoxygenated venous return from the body will flow passively into the pulmonary circulation. The first stage occurs during the first week of life. The second stage is performed around 4-6 months of age, and the third stage is performed around two years old.[4]

Stage 1 palliative repair HLHS (first week of life)

The **Stage I Norwood procedure**, first described by Norwood et al. in 1979, has become the standard of care for neonates with HLHS.[1] The surgery allows the right ventricle to become the systemic ventricle while the pulmonary flow is provided through a Gortex tube graft called a modified Blalock Taussig shunt (BT shunt). This stage usually requires the use of deep hypothermic circulatory arrest due to the abnormal aortic arch anatomy.

- The atrial septum is removed to allow free flow of oxygenated blood entering the left atrium from the pulmonary veins to reach the right ventricle

- A neoaorta is created by sewing the hypoplastic ascending aorta to the main pulmonary artery to provide a common outflow tract to the systemic circulation from the right ventricle.

- A systemic-to-pulmonary shunt (Blalock Taussig shunt) is created by connecting the right subclavian or innominate artery to the right pulmonary artery. This replaces the ductus arteriosus as the source of pulmonary blood. Consequently, prostaglandin E1 is no longer needed to maintain ductal patency. [1] The size of the shunt provides partial restriction to pulmonary blood flow and may reduce the incidence of pulmonary over circulation.

The **Sano procedure** was introduced in the late 1990s as a modification of the Stage I Norwood procedure. The Sano procedure involves the creation of a neoaorta similar to the stage I Norwood procedure, but rather than a BT shunt uses a nonvalved right ventricle to pulmonary artery (RV-PA) conduit to provide a source of pulmonary blood. The advantage is higher diastolic pressures and improved coronary perfusion. The disadvantage is an increased risk of right ventricular arrhythmias or right ventricular impairment from the ventricular incision.[1] The Single Ventricle Reconstruction (SVR) Trial was formed to compare the two techniques.

The **Hybrid procedure** was developed as an alternative for neonates who are not candidates for the Norwood procedure. [1] The Hybrid procedure is associated with a decreased 30-day mortality rate in high risk premature and low birth weight neonates as compared to the stage I Norwood procedure.[17] This procedure was first described by Gibbs et al. in 1993 as a hybrid of a cardiac catheterization lab intervention and an off-cardiopulmonary bypass surgical procedure.[1] The technique achieves the same circulatory and physiologic objectives as the stage I Norwood procedure without the physiologic stress of the stage I Norwood surgical procedure on cardiopulmonary bypass. The hybrid procedure is composed of the following:

- Sternotomy with bilateral pulmonary band placement to restrict pulmonary blood flow and prevent pulmonary over circulation at the expense of systemic perfusion [3]

- Cardiac catheterization with stent placement in the ductus arteriosus to maintain systemic perfusion without the need for prostaglandin E1.

- Cardiac catheterization with stent placement in the interatrial septum or balloon septostomy.[1]

Following the Hybrid procedure, patients continue to have an in parallel circulation. The pulmonary and systemic circulations must be carefully balanced to achieve a 1:1 ratio of pulmonary to systemic blood flow. The systemic oxygen saturation following the stage I Norwood range from 75% to 85% due to the mixing of oxygenated and deoxygenated blood in the right or common atrium. Postoperative management is often very challenging, and extracorporeal membrane oxygenation (ECMO) support may be necessary. Following a Norwood, these neonates are critically ill and face an interstage mortality rate of 5% to 15%.[9]

Stage 2 palliative repair HLHS - Hemi-Fontan/Bidirectional Glenn (4-6 months old)[4]

The Hemi-Fontan and the Bidirectional Glenn are surgical procedures that direct systemic venous return from the upper body directly into the lungs via a superior cavopulmonary connection. Both of these procedures result in a decreased volume load on the right ventricle, thereby preventing right ventricular hypertrophy/increased wall thickness and potentially improving diastolic function.[5] The systemic venous return via the inferior vena cava empties into the

common atrium where there is a mixing of oxygenated and deoxygenated blood. Before this procedure, cardiac catheterization will be performed to document normal pulmonary artery pressures. Elevated pulmonary pressures would need to be corrected before proceeding with the second stage repair. After the second stage repair, the pulmonary and systemic systems are changed from a parallel circulation to a partial in series circulation.[3] The following are steps involved with each procedure:

Hemi-Fontan

- Systemic-to-pulmonary artery shunt removal (Blalock-Taussig shunt)

- Anastomosis between the SVC and right atrial (RA) confluence and the central and branch pulmonary arteries (PAs) to direct the SVC blood to the pulmonary circulation

- Homograft patch augmentation of the central and branch PAs

- Interruption of the SVC blood from reaching RA using the homograft stopper [5]

Bidirectional Glenn

- Systemic-to-pulmonary artery shunt removal (Blalock-Taussig shunt)

- End-to-side anastomosis of the SVC to a branch pulmonary artery, typically right pulmonary artery [5]

Hybrid procedure 2nd stage repair

- Superior cavopulmonary anastomosis (SVC to PA anastomosis) via Hemi-Fontan or Bidirectional Glenn

- Creation of a neoaorta, as described in the Stage I palliation, with aortic arch reconstruction

- Atrial septectomy

- Removal of the pulmonary artery bands and pulmonary arterioplasty if needed

- Removal or resection of the ductus/stent complex [18]

Stage 3 palliative repair HLHS - Completion Fontan/Lateral Caval Tunnel Fontan/Extracardiac Fontan (2-3 years old)[4]

This procedure directs the systemic venous return from the lower half of the body directly to the lungs via a connection between the inferior vena cava (IVC) to one of the branch pulmonary arteries, typically the right pulmonary artery. Once this is established, essentially, all of the systemic venous return will drain directly into the pulmonary arteries. Because the blood flow into the pulmonary arteries is passive, cardiac catheterization is required before this procedure. The pulmonary artery pressures must be normal, or the Fontan procedure will fail. With this physiology, oxygenated blood from the pulmonary veins will enter the common atrium and be delivered to the systemic circulation via the single functional ventricle. The systemic oxygen saturations will be near normal or slightly lower if there is a fenestration between the Fontan pathway and the common atrium.

- Anastomosis of the underside of the right pulmonary artery and superior aspect of the right atrium

- An intra-atrial tunnel is created with synthetic material that connects the opening of the IVC to the opening of the cavopulmonary anastomosis (anastomosis of the right pulmonary artery to the superior aspect of the right atrium) for the lateral tunnel Fontan [3]

- 18 to 20 mm synthetic tube graft anastomosis between the IVC and the underside of the right pulmonary artery for the extracardiac Fontan

- Creation of fenestration or a 3 to 5 mm communication created between the common atrium and the total

cavopulmonary pathway. The fenestration allows right-left shunting, thereby preserving cardiac output in the face of high pulmonary arterial pressure or pulmonary vascular resistance.

Heart Transplantation

Due to the scarcity of donor hearts for newborns, the multistage palliative surgical repair is currently the mainstay treatment for HLHS.[9] Primary heart transplantation is usually reserved for HLHS newborns who are too high risk to undergo a staged repair.[19] Currently, about 20% of newborns listed for a heart transplant will die waiting for an organ.[20] Some centers have adopted the Hybrid stage 1 procedure as a bridge to transplant to increase waitlist survival.[19]

Differential Diagnosis

Differential diagnosis of left heart obstructed lesions (systemic circulation is ductal dependent)

- Critical aortic stenosis

- Hypoplastic left heart syndrome

- Coarctation of the aorta

- Shone's complex

- Interrupted aortic arch [10]

Prognosis

Only two-thirds of children with HLHS survive to 5 years of age and approximately 1% of Fontan patients die every year.[5]

One-third of neonates with HLHS die before any palliative surgical intervention can take place.[5]

Neonates with a single ventricle are at increased risk for cardiac arrest (12.7%) and mortality (62.3%)[5]

Some centers are reporting a Stage 1 Norwood palliation survival rate of 90%.[5]

The Society of Thoracic Surgeons Congenital Heart Surgery Database (STS CHSD) reported in 2019 procedure mortality rates of stage I palliation 15%, Hemi-Fontan/Glenn 1.8%, and Fontan 1.0%.[21]

The Aristotle score (range 1.5 to 25) was recently created through the collaboration of pediatric cardiac surgeons to better predict the potential for mortality, surgical complexity, potential morbidity and quality of care. The score takes into account not only the complexity of the procedure but adds points due to the patient's current condition. Patient adjusted points are frequently added for anatomic variants, respiratory failure, shock, prematurity, and low weight. An Aristotle score greater than 20 has correlated with a high procedure mortality rate. A score greater than 20 is often seen with the Norwood procedure. The Aristotle score should be calculated preoperatively and may be used to counsel parents and give them realistic expectations.[22]

Complications

Stage 1 Norwood Complications

- BT shunt thrombosis reduces pulmonary blood flow and results in life-threatening hypoxemia

- Coronary steal due to excessive pulmonary blood flow through the BT shunt resulting in inadequate systemic perfusion, which can lead to sudden death.

- Arrhythmias

- Respiratory failure

- Bleeding

- Infection

- Renal dysfunction [5]

Stage 2

- Decreased pulmonary flow leading to hypoxia and decreased cardiac output

- Arrhythmias

- Thromboembolic events

Stage 3

- Failing Fontan physiology

- Atrial arrhythmias

- Plastic bronchitis (3% to 10%)[23]

- Protein-losing enteropathy (1%)[23]

- Liver congestion, cirrhosis, and increased risk for hepatocellular carcinoma[24]

- Pulmonary thromboembolic events[24]

Postoperative and Rehabilitation Care

Stage 1 palliation (Norwood, Sano, Hybrid)

Post Stage I palliation patients are critically ill postoperatively and require ICU level care. Postoperatively, mechanical ventilation, inotropic support, and ongoing resuscitative efforts are required in a dedicated cardiothoracic intensive care unit. The hemodynamic goals for these patients post stage I Norwood include the following:

- Mean arterial blood pressure 40 to 45 mmHg

- pH 7.4

- pCO2 40 mm Hg

- pO2 40 mm Hg

- Hematocrit (Hct) 40%

- Systemic oxygen saturation 75$ to 85%

- Normal lactic acid

 These parameters are maintained by altering pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR), alternating ventilation strategy and transfusing blood products as needed to maintain Hct of 40%.

Increase SVR/decrease SVR

Vasopressin/milrinone

Epinephrine/nitroprusside

Norepinephrine/alpha-antagonists

Dopamine/nicardipine

Increase PVR/decrease PVR

Increase pCO2/decrease CO2

(decrease ventilation or add inhaledCO2)/increase FiO2

Decrease FiO2/inhaled nitric oxide

Stage 2 palliation- (Hemi-Fontan/Bidirectional Glenn)

Pulmonary vascular resistance must remain low to encourage pulmonary blood flow and maintain cardiac output. These patients benefit from early extubation as positive pressure ventilation, and thus, increased intrathoracic pressure reduces the passive pulmonary blood flow from the superior vena cava to the pulmonary circulation.[5] Spontaneous ventilation will improve systemic venous return.[5] Goals for the postoperative period include the following:

- Systemic oxygen saturation between 75% to 85%

- Modest hypercapnia (pCO2 from 35 to 45 mmHg) may improve cerebral perfusion and pulmonary blood flow, thereby improving systemic oxygen saturation

- Optimize mixed venous saturation [5]

Stage 3 palliation (Completion Fontan)

Fontan physiology is dependent upon passive flow of blood from the systemic circulation into the pulmonary circulation. Therefore, the maintenance of adequate volume status is key. Maintaining low intrathoracic pressure encourages blood flow throughout the Fontan circuit and into the pulmonary arteries. Early postoperative extubation is highly desirable to decrease the length of exposure to positive pressure ventilation, reduce intrathoracic pressure, and thereby increase cardiac output.[5] Typically, systemic oxygen saturation is near normal. Over time, the right ventricle, which was never designed to be systemic, may begin to fail. The Fontan physiology creates a state of chronic systemic venous hypertension due to impedance of blood flow through the pulmonary vasculature and decreased cardiac output. It is these two factors that are the root cause of the physiologic impairments collectively referred to as the failing Fontan physiology. Physiologic impairments of the failing Fontan circulation contribute to Fontan associated liver disease, cirrhosis, protein-losing enteropathy, lymphatic dysfunction, and plastic bronchitis. The heart is susceptible to long term stressors, including chronic preload deprivation and increased systemic vascular resistance, which can lead to both systolic and diastolic dysfunction.[25] In many patients with a failing Fontan physiology, heart transplantation may be the outcome.

Deterrence and Patient Education

Pregnant women who receive a fetal ultrasound consistent with a diagnosis of HLHS are referred to a pediatric cardiologist. Most pediatric cardiologists evaluate an expectant mother around 20 to 24 weeks gestation. The parents are given the treatment options and a frank discussion about the high morbidity and mortality associated with this congenital heart defect.

Enhancing Healthcare Team Outcomes

Hypoplastic left heart syndrome is one of the most commonly diagnosed cardiac lesions on routine screening with fetal ultrasound.[13] Once diagnosed, the parents will need counseling and education on the surgical options available, as well as the option to choose comfort care only after birth. These sensitive conversations should involve cardiac specialists as well as social workers who may also direct parents to family support groups. Reported elective

termination of pregnancy after a diagnosis of hypoplastic left heart syndrome varies from 12% to 48%.[5]

Parents who choose to proceed with a three-stage repair after birth need to be closely followed with serial fetal cardiac exams and receive obstetrical care close to a pediatric cardiac center. Obstetricians, cardiologists, cardiac surgeons, neonatologists, and anesthesiologists all have to coordinate as an interprofessional team to have a plan ready before the birth of a neonate with HLHS. Emergent atrial septostomy or ECMO (extracorporal membrane oxygenation) cannulation may be necessary to save these patients shortly after birth. In general, neonates with HLHS are at a higher risk for premature birth.[5] Data from the National Paediatric Cardiology Quality Improvement Collaborative and single-center studies have shown that neonates with prenatal HLHS diagnosis are delivered earlier than those with a postnatal diagnosis.[5] This is thought to be out of concern for in utero fetal demise, although the recommendation is to wait until 39 weeks gestation if there is no other indication for early delivery.[5]

These patients are critically ill before and after each stage of surgical repair and require open communication and specialized care from neonatal and ICU nurses, intensivists, cardiologists, cardiac surgeons, nutritionists, respiratory therapists, anesthesiologists, and pharmacists. Knowledge of the cardiac lesions, surgical repair, and the physiologic changes associated with each stage of the repair are important to the survival of these infants. Each discipline will perform the function pertinent to their specialty but must chart and keep the entire team informed so that all members of the interprofessional team operate from the same, most current information available on the patient, leading to better outcomes. [Level 5]

Questions

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