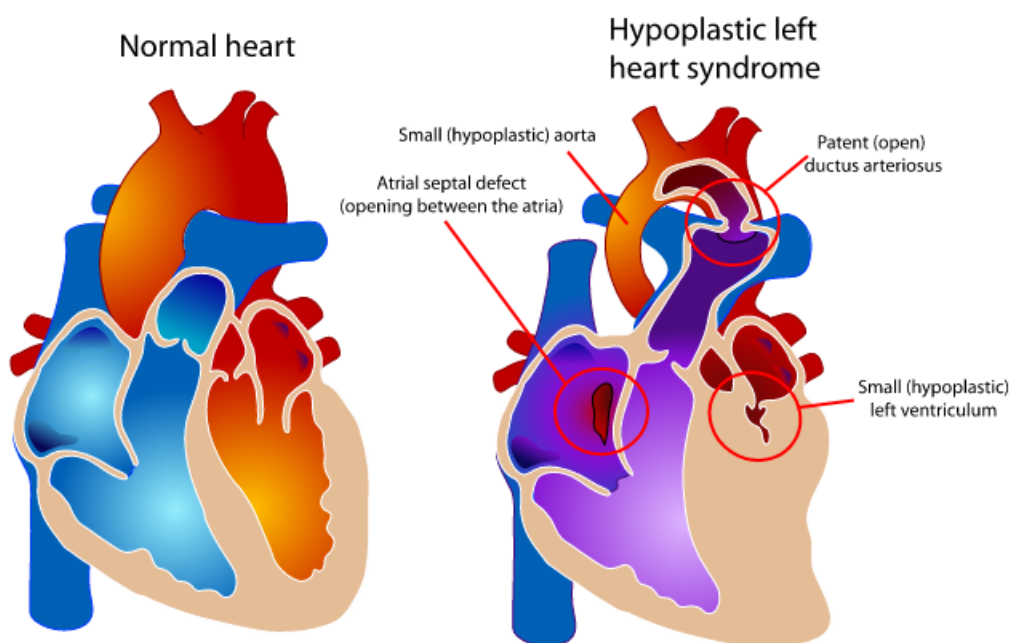


Hypoplastic Left Heart Syndrome (HLHS) — Surgery and Survival Rate

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Patients with the hypoplastic left heart syndrome have a hypoplastic left ventricle, mitral and aortic valves atresia with or without coarctation of the aorta. Blood flow to the systemic circulation is dependent on a patent ductus arteriosus and a patent foramen ovale for adequate mixing of blood in the atria. The diagnosis is confirmed in cyanotic neonates by performing an echocardiography. A three-stage procedure is performed aiming to separate the systemic from the pulmonary circulation. Survival after the completion of the three-stage procedures is as high as 95%.



Definition of HLHS

Hypoplastic left heart syndrome (HLHS) was first described by Noonan and Nadas. The syndrome is characterized by **hypoplasia “decreased mass” of the left ventricle and the ascending aorta**. Patients with HLHS also have aortic and mitral valves atresia or stenosis. Patients with the condition usually have other cardiovascular abnormalities, including a patent ductus arteriosus, systemic arterial desaturation and coarctation of the aorta.

Hypoplastic left heart syndrome (HLHS) refers to a range of congenital heart defects and associated manifestations. **As the name suggests, in hypoplastic left heart syndrome, multiple heart structures are involved:**

- Hypoplasia of left ventricle
- Mitral valve atresia
- Hypoplastic ascending aorta
- Patent Ductus Arteriosus (PDA)

According to the classical definition of HLHS, within the first month of birth, the under-developed left ventricle is unable to perform its function properly i.e., systemic circulation.

Epidemiology of HLHS

The exact mode of inheritance of HLHS is poorly understood. Approximately **0.16 to 0.36 per 1000 live births have HLHS**, making it a common congenital heart disease. If left untreated, up to one-quarter of the patients with HLHS are going to die during the neonatal period.

Survival rate after surgical correction of HLHS is estimated to be as high as 75 % nowadays. Certain factors have been associated with an adverse outcome, such as the presence of other congenital abnormalities, prematurity and major chromosomal anomalies. Patients with low cerebral oxygen saturation within the first 48 hours postoperatively usually do worse compared to those with improved cerebral oxygen saturation. Finally, patients who undergo the bidirectional Glenn/hemi-Fontan or Fontan procedures have a survival rate of 95 %.

Etiology of HLHS



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Patients with HLHS develop a Hypoplastic left ventricle most likely due to decreased or almost absent blood flow through the left ventricle early in cardiac development. It is believed that the initial pathogenic step in the development of HLHS is the development of a developmental abnormality in the aortic and mitral valves. When the development of these valves is altered, it is hypothesized that blood flow to and from the left ventricle becomes abnormal, which leads to hypoplasia of the left ventricle.

Another possible cause of HLHS is the **premature closure of the foramen ovale**. The premature closure of foramen ovale obscures the blood return from the inferior vena cava

to the left atrium in the fetus. It is hypothesized that the decreased blood return through the foramen ovale from the right atrium to the left atrium leads to a hypoplastic left ventricle by a similar mechanism to mitral and aortic valve atresia, i.e., by decreasing blood flow to a structure in the developing heart that structure fails to develop normally.

Despite notable efforts, the etiology of HLHS remains poorly understood. There is, however, some evidence supporting the suspected risk factors that might play a significant role in the causation of HLHS.

Genetic factors

Genetic factor, underlying chromosome mutation, is thought to be the most significant cause for all CHDs in general and HLHS in particular. The evidence is there supporting the recurrence of HLHS in siblings with 0.5 % to 2 % recurrence risk in families already having an affected child.

Environmental factor

Industrial land use with the release of solvents as the predisposing factors for HLHS. These include polychlorinated biphenyls and dioxin into the atmosphere.

Infectious factors

Pharyngeal infection might lead to HLHS due to the formation of antibodies affecting the left ventricle, according to a report.

Classification of HLHS

The classification of HLHS is based on the severity of the complex and ranges from severe to the mild end of the spectrum. This classification is as follows:

1. Aortic valve atresia with mitral valve atresia

It is the most severe form of HLHS, whereby the left ventricle is almost diminutive and close to non-existent. The ascending aorta and arch are extremely hypoplastic, resulting in entirely ductal-dependent systemic output.

2. Aortic valve atresia with patent mitral valve

Contrary to the entirely ductal-dependent systemic output in the most severe form, there is an inflow of the blood without any outflow, eventually resulting in left ventricle hypertrophy.

3. Aortic valve stenosis with patent mitral valve

This is comparatively a mild form of HLHS in which there is an outflow of the blood from the left ventricle supporting systemic circulation. Moreover, the hypoplasia of the left ventricle and aorta is also mild as compared to other more severe forms.

Pathophysiology of HLHS

HLHS is composed of a complex of congenital heart anomalies characterized by hypoplastic left ventricle and ascending along with atresia or stenosis of the mitral valve and aortic valve. In the severe form of HLHS, there is hypoplasia of the left ventricle and aorta, along with atresia of the mitral valve and aortic valve. Usually, in HLHS, the valves are not entirely atretic, but hypoplastic.

Infants with hypoplastic left heart syndrome often remain well in-utero and in the first few days of life due to the presence of a patent ductus arteriosus (PDA) and patent foramen ovale (PFO).

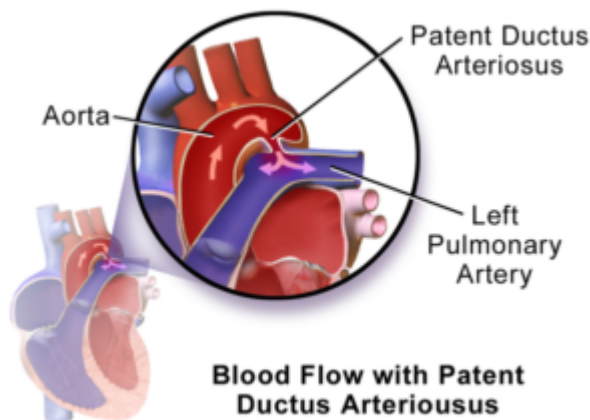


Image: "Patent Ductus Arteriosus." b< BruceBlaus. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

At this stage, blood from the pulmonary veins shunts to Right Atrium (RA) via foramen ovale.

The blood from RA flows into the Right Ventricle, from where it shunts in the aorta (entering into systemic circulation) through patent ductus arteriosus (PDA). Here, the blood perfuses into coronary and cerebral circulation with a retrograde flow.

Maintained by blood from the Right Ventricle via patent ductus arteriosus (PDA).

As the pulmonary vascular resistance is lower as compared to systemic vascular resistance, it results in more blood flow into pulmonary circulation as compared to limited blood flow in the systemic circulation. This eventually leads to pulmonary edema.

On the other hand, oxygenated blood returning from the pulmonary veins into the Left Atrium (LA) cannot pass into the Left Ventricle (LV) due to its hypoplasia and mitral valve hypoplasia; therefore, it flows into the RA through patent foramen ovale (PFO) or atrial septal defect (ASD).

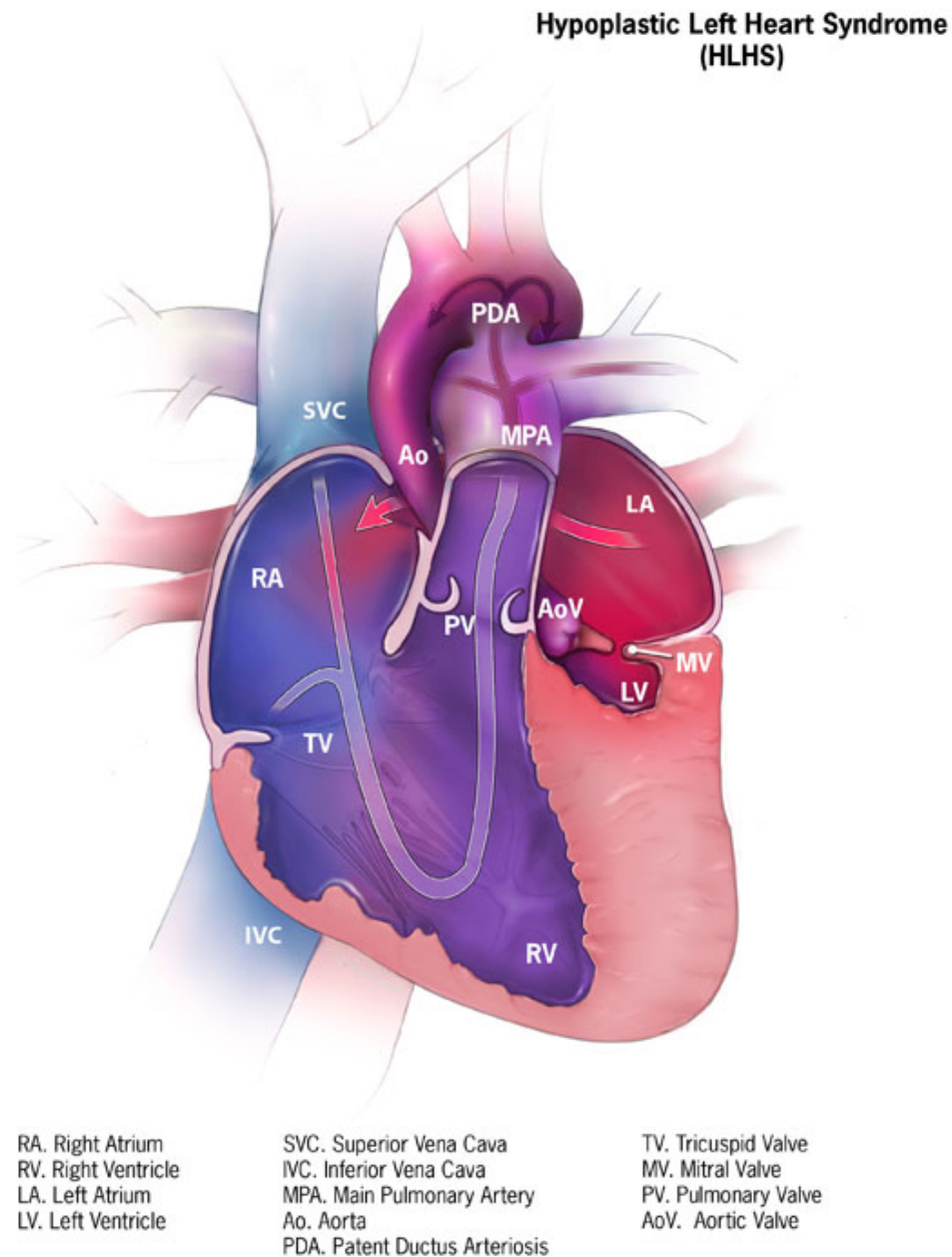
Prenatally, fetuses with HLHS are found to have a lower cerebral blood flow compared to their normally developing peers. This observation might influence the brain at the cellular level, but not on the gross level because the total volume of brain tissue in patients with HLHS was not found to be different compared to those with a normal left ventricle.

Early in the disease, **pulmonary resistance is usually very low** and therefore most of the blood escapes from the right ventricle back to the lungs instead of going to the systemic circulation; this is believed to be responsible for the development of poor perfusion of the kidneys and other organs which result in metabolic acidosis and oliguria. On the other hand, when the pulmonary circulation becomes high, most of the blood is pumped into the systemic circulation without passing to the lungs first. This is associated with [hypoxemia](#) and ischemic injuries to the brain and other end-organs. For the blood to flow from the right ventricle to the systemic circulation, a patent ductus arteriosus must be present.

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Clinical features of HLHS



Most patients with HLHS are **full-term, normally developing babies who appear normal on their initial examination**. In the subsequent hours, once the patent ductus arteriosus begins closing, patients start developing symptoms. **The most common symptoms are cyanosis, respiratory distress, lethargy and oliguria.**

Some cases can be diagnosed prenatally if on a routine prenatal ultrasonography. Prenatal ultrasonography can identify cardiac anomalies very easily, but most obstetricians do not concentrate on that unless it is indicated by a family history of

cardiac anomalies.

Nowadays, most patients with HLHS are diagnosed by an echocardiography once they become symptomatic and prostaglandin E1 infusion is started to re-establish the patency of the ductus arteriosus. This approach made it very unlikely to see the cardiogenic shock in infants with HLHS. In the past, a full-blown picture of cardiogenic shock was common in infants with HLHS. Hypothermia, central cyanosis, weak pulses in upper and lower limbs, and hepatosplenomegaly, were commonly seen in HLHS in the past.

Nowadays, physical examination usually only reveals tachycardia, tachypnea and mild cyanosis. Because of the association between HLHS and coarctation of the aorta, decreased the strength of pulses in the arms, compared to the legs, is commonly seen.

Symptoms

Symptoms might appear in the wake of the narrowing of PDA and PFO. Underlying pathology may involve congestive cardiac failure (CCF), metabolic acidosis, pulmonary edema and circulatory collapse in severe cases. **These conditions might present in the form of the following symptoms:**

- Dyspnea (shortness of breath)
- Hypoxemia (arterial oxygen deficiency)
- Tachycardia (increased heart rate)
- Pulmonary crackles
- Cold extremities
- Increasing lethargy, visible in 2—4 weeks of life

The symptoms are likely to get worse with activity like feeding or agitation.

Signs

On Physical Examination

On auscultation, the first heart sound is normal, while the second heart sound is loud and single due to the presence of aortic atresia. Usually, no heart murmur is heard. The pulses are poor and often non-palpable due to low cardiac output. There is visible mottling of the skin that reflects poor tissue perfusion. Extremities are usually vasoconstrictive.

Congestive Cardiac Failure (CCF)

Signs of CCF are visible because of left atrium hypertension. This might happen due to constriction or eventually closing of PDA and PFO leading to pulmonary edema and tachycardia. This further leads to the development of congestive cardiac failure.

Hepatomegaly

In neonates with HLHS, hepatomegaly might be the associated sign and often seen secondary to CCF.

Left atrium hypertension

Left atrium hypertension often found in infants with HLHS as a result of restriction to blood shunting from left to right atrium via PFO. This may start developing within 2 weeks of birth due to constriction of PFO and become severe with further closing of atrial

communication.

Low systemic and pulmonary circulation

This happens secondary to the constriction of PDA and PFO after birth. Low systemic circulation might be predicted through poor pulse and low cardiac output, while low pulmonary circulation leads to pulmonary edema and eventually CCF.

Pulmonary edema

Pulmonary edema forms due to left atrium hypertension. The restriction to shunting of blood from left to right leads to a back-flow of blood into the lungs resulting in pulmonary edema.

Cardiomegaly

The left atrium and right ventricle are usually reported to be hypertrophied.

Metabolic acidosis

Metabolic acidosis results secondary to the decreased cardiac output. Arterial blood gasses (ABG) are reported to usually show decreased PO₂ with normal PCO₂.

Cardiogenic shock

Cardiogenic shock is presented in severe cases of HLHS and is the result of absent atrial communication. This required immediate intervention for left atrium decompression, and is done by catheter-based or surgical septostomy.

Investigations of HLHS

Patients with HLHS are rarely anemic and usually have a **normal white blood cell count**. Regardless, a complete blood count should be ordered in these patients to exclude anemia and sepsis – two common causes of shock in neonates.

Patients with HLHS **might develop metabolic acidosis**; therefore, arterial carbon dioxide levels should be checked. A low arterial carbon dioxide level indicates metabolic acidosis, while a high carbon dioxide level points towards possible respiratory failure. Respiratory failure might complicate the clinical picture of HLHS in a small set of patients.

Due to decreased peripheral perfusion, patients might develop kidney or liver injury. Increased serum creatinine levels are indicative of possibly kidney injury, while elevated serum aspartate aminotransferase or alanine aminotransferase levels can be seen in patients with impaired liver function.

Infants who have dysmorphic features are more likely to have chromosomal abnormalities than normal looking infants; therefore, the decision to perform karyotyping should be reserved for dysmorphic infants or patients who appear to have a familial form of HLHS.

Imaging studies are very important in establishing the diagnosis of HLHS. Chest radiography usually shows increased pulmonary markings or an enlarged heart. Echocardiography is the investigation of choice for establishing the diagnosis of HLHS.

Patients with HLHS have a hypoplastic left ventricle and ascending aorta on echocardiography. **The right atrium and right ventricle are usually larger than normal** due to the increased return of oxygenated blood through the patent foramen

ovale and the pumping of blood against systemic vascular resistance respectively.

The presence or absence of tricuspid regurgitation by Doppler study is very important because its presence has been associated with a worse outcome. Echocardiography is also useful in the evaluation of the aortic arch and the thoracic aorta, the two most common sites for coarctation.

Today, in many cases, HLHS get diagnosed in the prenatal period. This has been made possible with the screening of obstetric ultrasound which shows an abnormal four-chamber view of the fetal heart. The **following investigations are significant in infants presenting with HLHS:**

Echocardiogram

Transthoracic echocardiogram is a Gold Standard diagnostic tool for HLHS.

Shows hypoplastic LV and ascending aorta as well as a dilated RV, mitral valve atresia and aortic valve atresia.

| | |
|-------------------------------------|---|
| Chest Radiograph CXR | CXR is usually non-specific and of limited use in the diagnosis of HLHS Absence of apical portion of the cardiac silhouette on CXR suggests LV Hypoplasia Prominent pulmonary artery segment Cardiomegaly |
| Electrocardiograph (ECG) | ECG shows decreased LV voltage and increased RV voltage. |
| Cardiac Catherization | Cardiac catheterization is usually unnecessary and not needed for diagnosis. However, it is needed for atrial septostomy in severe cases presented with cardiogenic shock and circulatory collapse. |
| CMR | Cardiovascular magnetic resonance imaging (CMR) of HLHS in neonates plays a significant complementary role to ECG and angiography in the evaluation of HLHS. |

Management of HLHS

The first step in the management of HLHS is to re-open the ductus arteriosus by the administration of prostaglandin E1. Metabolic acidosis is also associated with an adverse clinical outcome and should be corrected before going for the surgical correction of the heart anomaly.

Preoperatively, patients should be examined for the possible signs of sepsis. Septic infants should receive inotropic transiently until they are clinically stable. Additionally, infants should receive a loop diuretic such as furosemide.

Medical Management

HLHS is initially managed through medical means. This short-term management focuses on metabolic acidosis, maintaining patency of PDA and PFO and hemodynamic stability. Long-term management almost always considers surgical means.

Correcting Metabolic Acidosis

This is managed through IV infusion and maintaining oxygen perfusion to an adequate level.

Hemodynamic Stability

Hemodynamic stability is achieved through maintaining patency of PDA and PFO to provide sufficient cardiac output.

Prostaglandin Infusion

Prostaglandin infusion (prostaglandin E1) is required to start immediately for maintaining the patency of PDA and PFO. This further maintains hemodynamic stability and sufficient cardiac output.

Balloon atrial septostomy

Cardiogenic shock is presented in severe cases of HLHS and is the result of absent atrial communication. This required immediate intervention for left atrium decompression and is achieved by catheter-based or surgical septostomy.

Surgical management: Norwood operation

The surgical option is considered after the initial stability. Neonatal surgical management for HLHS is imperative owing to the ductal-dependent systemic circulation. Corrective operations are not available in the case of HLHS. However, palliative operations currently include two options i.e. Norwood operation (series of staged functionally univentricular palliations) and cardiac transplant.

The Norwood operation is a 3-step repair which ultimately results in systemic circulation through right-sided heart structures and passive flow of venous return into the pulmonary circulation bypassing the heart entirely.

Norwood stage I

The first stage procedure is known as the Norwood procedure. An atrial septectomy is performed to allow for unrestricted blood flow between the left and right atria. Ligation of the ductus arteriosus and the establishment of an anastomosis between the main pulmonary artery and the aorta follows. Finally, an aorta to pulmonary shunt is placed.

The two goals of this procedure are to establish a reliable systemic circulation that is independent on the ductus arteriosus and to allow enough blood to flow to the pulmonary circulation for adequate oxygenation. This procedure should be performed in the first weeks of life.

Norwood stage II (Glenn Procedure)

The second stage is known as the bidirectional Glenn procedure and is usually performed six months after the Norwood procedure. The superior vena cava is anastomosed to the right pulmonary artery. The aorta-to-pulmonary shunt should be ligated at this stage.

Norwood stage III (Fontan Procedure)

After the second stage procedure, patients should be started on digoxin, diuretics, aspirin and captopril. The third stage procedure, known as the Fontan procedure, the inferior vena cava and the pulmonary arteries are anastomosed. By the completion of the third procedure, patients have a passive systemic-to-pulmonary circulation and the right ventricle is no longer responsible for the pulmonary blood flow.

The right ventricle right now is only responsible for the adequate pumping of blood into the systemic circulation. Therefore, by the completion of the Fontan procedure, infants are considered as having separate systemic and pulmonary circulations. The third procedure is typically performed 12 months after the second stage procedure.

Cardiac Transplantation

Currently, cardiac transplantation is being performed in a limited number of centers worldwide. It has been less favorable because of the wait for transplantation and scarcity of donor organs during the neonatal period. Although Cardiac Transplantation renders the need for multistage surgical repair redundant, it, however, usually ends up in complications arising from immune suppression, graft rejection and coronary artery disease (CAD).

Moreover, according to a study, more frequent deaths are reported in Transplantation as compared to a Norwood operation.

Complications of HLHS

The mortality rate of HLHS is highest as compared to other Congenital Heart Diseases (CHD). It is reported that almost 40 % of children with HLHS die within the age of 5 years.

Complications may arise before or after surgical operations. These include:

- Severe metabolic acidosis
- [Hypoxia](#)
- Circulatory collapse
- [Coronary artery disease](#)
- Risk of infection
- Neurological complications
- Cardiorespiratory collapse
- Thromboembolism
- Recurrent arrhythmias
- CCF
- Hepatic dysfunction

Differential Diagnosis of HLHS

Differential diagnosis is needed to be made with other left-sided obstructive lesions in which systemic circulation is ductal-dependent. **These include:**

- Critical aortic stenosis
- Coarctation of the aorta; however, it is often found in association with HLHS in nearly 75 % of the cases
- Interrupted aortic arch
- Neonatal myocarditis
- Neonatal sepsis

All the above-mentioned conditions, present with sign and symptoms such as those seen with HLHS. They could be differentiated by using Echocardiography.

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