International Journal of Medical Science in Clinical Research and Review
Online ISSN: 2581-8945
Available Online at http://www.ijmscrr.in Volume 6|Issue 06 (November-December)|2023 Page: 1051-1060

Review Paper

Heart Transplantation in Neonate and Childs with Congenital Heart Disease and Hypoplastic Left Heart Syndrome

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Article Received: 14-October-2023, Revised: 04-November-2023, Accepted: 24-November-2023

ABSTRACT:

Introduction: There may be several causes for the main congenital heart defects. Genetic factors and maternal factors, including poorly controlled chronic diseases such as diabetes or phenylketonuria. Heart transplantation is the gold standard surgical approach for treating heart failure. **Objectives**: To carry out a literature review on the physiological processes of heart transplantation in neonates with congenital heart disease, and to verify the main indications and contraindications for heart transplantation. **Material and Methods**: This article is a literature review, based on the methodology that sought to identify the physiological processes of heart transplantation in neonates with congenital heart disease through the analysis of pre-performed studies, and thirty-three (33) articles were selected for the preparation of this literature review. **Results and discussion**: Heart transplantation in children has become an option in complex congenital heart diseases and cardiomyopathies refractory to conventional therapy. Diagnostic research into the etiology of heart disease has advanced in the last decade, which significantly increases the chances of survival for children with congenital heart dysfunction. Another cardiac complication is babies with hypoplastic left heart syndrome. Final considerations: The shortage of organ donors is still a major obstacle to transplantation in Brazil. Even in cases where the organ can be obtained from a living donor, the number of transplants is small compared to the demand from patients waiting for surgery.

Keywords: Congenital heart disease; Heart transplantation in neonates and children; Organ donors; hypoplastic left heart syndrome

INTRODUCTION:

Congenital heart disease (CHD) is defined as any abnormality in the structure or function of the heart in the first eight weeks of pregnancy, the stage at which the baby's heart is formed. Embryonic development is altered and the heart structure is compromised (PASCHOTTO, 2012; MORHY et.al, 2020; RODRIGUES et.al, 2023).

Data from the Brazilian Organ Transplant Association (ABTO) on transplants show that, in the first half of

2023, 208 heart transplants were carried out in Brazil. The organ was the third most transplanted organ, behind the kidney (2,847) and liver (1,103). According to Amaral et al (2002), there are various types of congenital malformations, but among the most common are anomalous communication between the left and right interatrial communications and interventricular communications. There can be several causes for the main congenital heart defects. Genetic factors and maternal factors, which include chronic diseases such as diabetes or poorly controlled phenylketonuria (AMARAL et. al, 2002; ROELEVELD, 2019).

According to Cappellesso et.al (2017), the lethality attributed to critical congenital heart disease is high, with mortality proportional to 12.0% of neonates. The survival rate at 28 days of life decreased by almost 70% in newborns with congenital heart disease. According to Barbosa et al (2017), the most common form of congenital heart disease is ventricular septal defect. The diagnosis can be made during pregnancy using a fetal echocardiogram, the only test capable of detecting congenital heart disease while the baby is still in the mother's womb, carried out between 21 and 28 weeks of pregnancy. According to data from the Brazilian Society of Cardiology, approximately 28,000 children are born with heart problems every year in Brazil, i.e. one (1) out of every 100 babies born alive has a heart condition. Of these, around 80% will require heart surgery during their development (SBC, 2021). Congenital heart defects may not cause symptoms or may only manifest themselves in adulthood (BORN, 2009). According to Barbero & Marcial et.al (1996), there are different types of heart disease, which can be mild and only discovered in adulthood, up to the most serious, which are cyanotic heart diseases, capable of causing altered blood flow to the body. The most serious type of CHD is cyanotic, as the heart defect can significantly affect blood flow and the oxygenation capacity of the blood and, depending on its severity, can cause symptoms such as pallor, blue skin, shortness of breath, fainting and even convulsions and death (AZEKA, 2005). Other CHDs to highlight are Tetralogy of Fallot; Ebstein's anomaly; Pulmonary atresia; Acyanotic congenital heart disease; Atrial septal defect (ASD); Ventricular septal defect (VSD); Persistent ductus arteriosus (PDA); Atrioventricular septal defect (AVSD) (BARBERO & MARCIAL et. al, 1996). The main symptoms of complex heart defects can be Cyanosis, which is the purple coloration of the fingertips or lips; Excessive sweating; Excessive tiredness during feedings; Pallor and apathy; Low weight and poor appetite; Rapid and short breathing even at rest; Irritation (LIMBERGER et.al, 2017; KINDEL et. al, 2017). In older children, the symptoms are dyspnea on low exertion; frequent respiratory infections; easy tiredness compared to other children of the same age (BARBERO & MARCIAL et. al, 1996; AZEKA, 2005). Aragão et.al (2013) cites that in most neonatal units, the baby is discharged from hospital between 36 and 48 hours of life. At this stage, the clinical manifestation of critical heart disease may not yet have occurred, especially in heart disease with arterial channel-dependent systemic flow. According to Jatene et.al (2008), cardiac auscultation may be apparently normal at this stage. The authors also point out that early diagnosis is essential, as it can prevent shock, acidosis, cardiac arrest or neurological problems before the heart disease is treated.

Early diagnosis can reduce the neonatal mortality rate. The ideal method for diagnosing congenital heart disease is echocardiography with color flow mapping, whether fetal or postnatal, but its use as a screening tool is unfeasible (LIMBERGER et.al, 2017; KINDEL et. al, 2017).

According to John et.al (2019), heart transplantation for children is a highly complex surgery that can last several hours. After transplantation of the patient's compatible organ, the child or adolescent needs intensive care during hospitalization and after discharge, to avoid infections and rejection of the organ.

OBJECTIVES:

To carry out a literature review on the physiological processes involved in heart transplantation in neonates with congenital heart disease and Hypoplastic left heart syndrome.

To verify the main indications and contraindications for heart transplantation in neonates and children.

MATERIAL AND METHODS:

This article is a literature review, based on a methodology that sought to identify the physiological processes of heart transplantation in neonates with congenital heart disease by analyzing previous studies.

A search strategy was developed based on the evaluation of an objective on the subject in question, which forms the basis of the study.

The search descriptors were selected from the Descriptors in Health Sciences (DeCS) website and then combined with the Boolean operator "AND". The databases used for the search were: PubMed and the Virtual Health Library (VHL), where cross-sectional, cohort and case-control studies were evaluated, covering the Portuguese, English and Spanish languages.

The inclusion criteria were cross-sectional studies, freely available and focused on the early diagnosis of critical congenital heart disease in neonates and the need for transplantation

In all, the result of the search in the databases using the descriptors, but without the application of filters, resulted in sixty - seven (67) available articles. After pre-selecting the articles, a research protocol was created which clearly illustrated the aim of the study, the data collection process and the criteria involved in including the articles.

After the analysis, twenty-seven (27) studies were

excluded. Forty (40) articles were therefore selected for this literature review.

LITERATURE REVIEW:

Heart Transplantation:

According to John et.al (2019), heart transplantation is a surgical procedure in which a heart is transplanted into another person. It is the most effective therapeutic modality for significantly prolonging the lives of people with heart disease.

The statistics show that 95% of people who have a heart transplant are able to exercise and carry out their daily activities substantially better than before the transplant. According to the author, more than 70% of heart transplant recipients return to work. Heart transplants are performed when the heart disease is severe and the use of drugs is insufficient. However, the great difficulty is finding donors, despite the positive results of heart transplantation (TREVISAN et.al, 2014).

According to Miana et al (2014), transplant patients need drugs after surgery.

Physiology Applied to Heart Transplantation:

For Kindel et.al (2017), the only absolute contraindication for heart transplantation is pulmonary hypertension refractory to preoperative treatment. Relative contraindications are organ failure (e.g. lung, kidney or liver) and local or systemic infiltrative diseases (e.g. cardiac sarcoma and amyloidosis). For the transplant to take place, all donated hearts come from brain-dead donors, who normally need to be <60 years old, have normal lung and heart function and no history of coronary heart disease or other heart diseases. The donor and recipient must have compatible ABO blood types and heart sizes. Around 25% of eligible recipients die before a donated organ becomes available. Left ventricular assist devices and artificial hearts provide intermediate hemodynamic support for patients awaiting transplantation. However, these devices pose a high risk of sepsis, device failure and thromboembolism (HOFFMAN, 2004).

Procedures for Heart Transplantation:

Paschotto et.al (2012) cites that donor hearts should be preserved by hypothermic storage and transplanted within 4 to 6 hours. The technique described shows that the recipient is placed on a bypass pump and the recipient's heart is removed, with preservation of the right posterior atrial wall in situ. The donor heart is then transplanted orthotopically (in the normal position) with anastomoses of the aorta and pulmonary arteries, as well as pulmonary veins; a single anastomosis joins the retained posterior atrial wall to the donor organ (FIGURE 1).

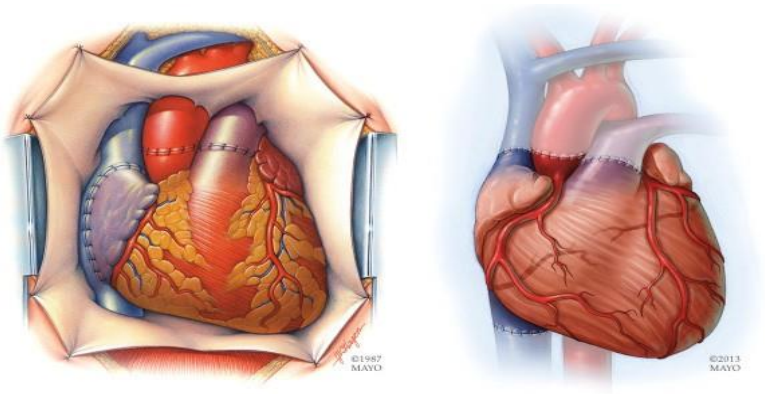

Figure 1 - Multimodal non-invasive imaging in pediatric heart transplant monitoring. Source: Kindel et.al (2017).

According to Jatene et al (2008), the main indications for pediatric heart transplantation are divided into three classes. Class I - patients with complex congenital heart disease and/or cardiomyopathies refractory to conventional therapy, Class II - patients with complex congenital heart disease and/or cardiomyopathies refractory to conventional therapy, Class III - patients with complex congenital heart disease and/or cardiomyopathies refractory to conventional therapy.

Cappellesso et.al (2017) describes in their studies that heart transplantation in children has been an option in complex congenital heart diseases and cardiomyopathies refractory to conventional therapy.

Feitoza (2016) points out that pediatric heart transplantation is a highly complex therapy. FIGURE 2 shows the reconstruction of a patient with anomalies of the great vessels.

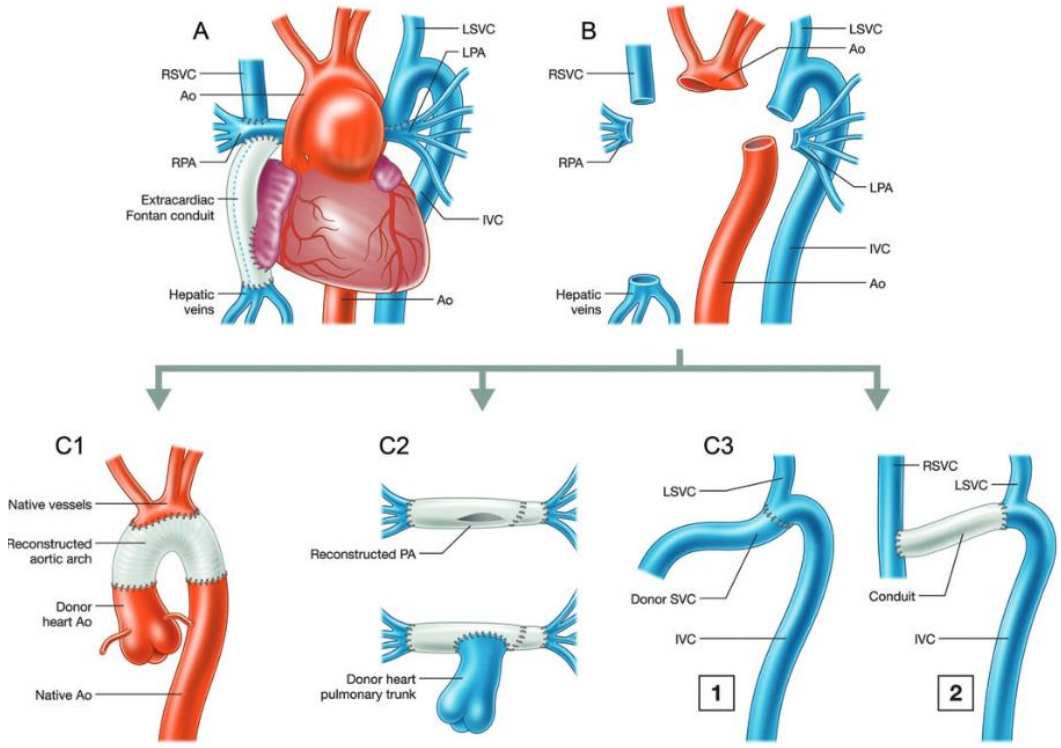

Figure 2 - Great vessel reconstructions in a patient with anomalies of all great vessels. (A) Prior to excision of the recipient's heart. (B) After excision of the recipient's heart and great vessels. (C1) Reconstruction of the aortic arch using a prosthetic graft. (C 2) Hilum-to-hilum PA reconstruction using GoreTex tubes. (C 3) Anastomosis of hemiazygos continuation of the inferior vena cava to the donor right SVC using donor SVC (1) or a pericardial conduit (2). Source: A.J. Iyengar et al. / European Journal of Cardio-Thoracic Surgery (2014).

Cardiac Allograft Vasculopathy:

According to Rivera et.al (2007), the main complication of heart transplantation is cardiac allograft vasculopathy, a form of atherosclerosis that causes diffuse stenosis or obliterates the lumen of the vessels (25% of patients). Its cause is probably multifactorial and related to donor age, cold and reperfusion ischemia, dyslipidemia, immunosuppressants, chronic rejection and viral infection [CMV] in adults).

Pio et.al (2016), described that for early detection, a screening stress test or coronary angiography with or without intravascular ultrasound is usually performed at the time of endomyocardial biopsy.

Prognosis and Heart Transplant Rejection:

According to Williams (2019), fever is one of the main symptoms associated with rejection. Hypotension and pulmonary edema are also symptoms. If evidence of rejection is found, immunosuppressive drugs must be administered.

Infections cause almost half of all deaths following a heart transplant.

Another complication is arteriosclerosis (blocked arteries), which occurs in the coronary arteries in approximately a quarter of heart transplant recipients (LIN et.al, 2021).

According to Roeleveld (2019), around 50 to 80% of patients have at least 1 episode of rejection (2 to 3 on average); most patients are asymptomatic, but around 5% develop left ventricular dysfunction or atrial arrhythmias. The peak incidence of acute rejection occurs in the 1st month, decreases in the following 5 months and reaches equilibrium in 1 year. The risk factors for rejection are: younger age, female recipient, female donor or donor of African descent, incompatibility with human leukocyte antigen, possible cytomegalovirus infection. According to Rajab et.al (2021), rejection is classified according to onset and duration. Histologically, rejection ranges from 1 to 4. Mild rejection (grade 1) with no detectable clinical sequelae does not require treatment; moderate or severe rejection (grades 2 to 4) requires specific treatments. According to Roeleveld (2019), 1-year survival rates after heart transplantation are 85% to 90% and annual mortality thereafter is around 4%. The pre-transplant indicators of 1-year mortality are; need for pre-operative ventilation or left ventricular assist devices; cachexia; female recipient or donor.

Indicators After Transplantation:

According to the studies by Roeleveld et.al (2019), high concentrations of C-reactive protein and troponin are indicators for the occurrence of transplantation. In general, the cause of death within 1 year results from rejection or acute infection; after 1 year, it most often results from cardiac allograft vasculopathy or lymphoproliferative disease.

Recipient Contraindications to Transplantation:

For Roeleveld et.al (2019), absolute contraindications to transplantation include: Clinically active infection, possibly with the exception of infection in the recipient if it is limited to the organ to be replaced (e.g. liver abscesses), Cancer (except hepatocellular carcinoma confined to the liver, non-melanoma skin cancer and certain neuroendocrine tumors); Positive cross-compatibility identified by lymphocytotoxic tests. Table 1 shows some aspects of the indications and contraindications for heart transplantation.

TABLE 1- Indications and contraindications for heart transplantation

Indications	Contraindications
Refractory HF using inotropic drugs or VAD	Paulmonary hypertension (PVR>5 wood)
Persistent Functional Class III or IV	Severe cerebrovascular disease
VO2<12 Ml/kg/min (beta-blocker use)	Severe Peripheral Vascular Diseases
Ischemic diseases with refractory angina and no possibility of revascularization	Severe liver failure
Persistent and refractory ventricular	arrhythmia ABO incompatibility in the crossmatch test
LV/VC02>35 or 6-minute walk test<300 m	Severe psychiatric illness, drug addiction and poor adherence to therapy

Heart failure; VAD: ventricular assist device; VO 2 : oxygen consumption; VE/VCO 2: ventilatory equivalent of carbon dioxide; PVR: pulmonary vascular resistance. Source: modified Bacal F et al. HF (2010).

Indications for Heart Transplantation in Children:

Heart transplantation has been the therapy of choice for children with complex congenital heart diseases and cardiomyopathies refractory to the use of anticongestive medication1-5 (ZIMMERMAN et.al, 2020). Croti et.al (2010) points out that children who have ventricular dysfunction after surgical correction and even those who have undergone heart transplantation and develop primary graft failure, ventricular dysfunction after rejection treatment and those who have graft vascular disease and will need a new transplant. Jatene et. al (2008) points out that according to the pediatric age group. In children under one year of age, congenital heart diseases are the most frequent, while in children between one year and 10 years of age, cardiomyopathies become the main indications. Table 2 shows the main complications of transplantation in children.

TABLE 2. Main complications of transplantation in children

Primary Graft Failure
Rejection
Infection
Systemic hypertension
Nephrotoxicity
Hyperlipidemia
Biliary lithiasis

Source: KINDEL, Steven J. et al. 2017.

Facts about Hypoplastic Left Heart Syndrome:

Hypoplastic (pronounced hi-puh-PLAS-tik) left heart syndrome or HLHS is a birth defect that affects normal blood flow through the heart (BARRON et.al, 2009). According to the studies by Feinstein et.al (2012), the hypoplastic left heart syndrome (HLHS) is a birth defect that affects normal blood flow through the heart. As the baby develops during pregnancy, the left side of the heart does not form correctly. Hypoplastic left heart syndrome is one type of congenital heart defect. Congenital means present at birth. Because a baby with this defect needs surgery or other procedures soon after birth, HLHS is considered a critical congenital heart defect (CCHD) (BARDO et.al, 2001). Connor (2007), cite about the hypoplastic left heart syndrome affects a number of structures on the left side of the heart that do not fully develop, for example:The *left ventricle* is underdeveloped and too small; The *mitral valves* is not formed or is very small; The *aortic valve* is not formed or is very small; The ascending portion of the *aorta* is underdeveloped or is too small; Often, babies with hypoplastic left heart syndrome also have an atrial septal defect, which is a hole between the left and right upper chambers (atria) of the heart (TCHERVENKOV, 2006). In a baby without a congenital heart defect, the right side of the heart pumps oxygen-poor blood from the heart to the lungs. The left side of the heart pumps oxygen-rich blood to the rest of the body. When a baby is growing in a mother's womb during pregnancy, there are two small

openings between the left and right sides of the heart: the *patent ductus arteriosus* and the *patent foramen ovale*. Normally, these openings will close a few days after birth (BARRON et.al, 2009). In babies with hypoplastic left heart syndrome, the left side of the heart cannot pump oxygen-rich blood to the body properly. During the first few days of life for a baby with hypoplastic left heart syndrome, the oxygen-rich blood bypasses the poorly functioning left side of the heart through the patent ductus arteriosus and the patent foramen ovale. The right side of the heart then pumps blood to both the lungs and the rest of the body. However, among babies with hypoplastic left heart syndrome, when these openings close, it becomes hard for oxygen-rich blood to get to the rest of the body (TCHERVENKOV, 2006). The Centers for Disease Control and Prevention (CDC) estimates that each year about 1,025 babies in the United States are born with hypoplastic left heart syndrome.[1] In other words, about 1 out of every 3,841 babies born in the United States each year is born with hypoplastic left heart syndrome (FEINSTEIN et.al, 2012). The causes of heart defects such as hypoplastic left heart syndrome among most babies are unknown. Some babies have heart defects because of changes in their *genes* or *chromosomes*. These types of heart defects also are thought to be caused by a combination of genes and other risk factors, such as things the mother comes in contact with in the environment or what the mother eats or drinks or the medicines the mother uses (TCHERVENKOV, 2006). Hypoplastic left heart syndrome may be diagnosed during pregnancy or soon after the baby is born (BARRON et.al, 2009). During pregnancy, there are screening tests (also called prenatal tests,) to check for birth defects and other conditions. Hypoplastic left heart syndrome may be diagnosed during pregnancy with an ultrasound, (which creates pictures of the body). Some findings from the ultrasound may make the health care provider suspect a baby may have hypoplastic left heart syndrome. If so, the health care provider can request a fetal *echocardiogram*, an ultrasound of the baby's heart, to confirm the diagnosis. This test can show problems with the structure of the heart and how the heart is working with this defect (FEINSTEIN et.al, 2012).

Treatments for some health problems associated with hypoplastic left heart syndrome might include: Medicines; Some babies and children will need medicines to help strengthen the heart muscle, lower their blood pressure, and help the body get rid of extra fluid (TCHERVENKOV, 2006). Some babies with hypoplastic left heart syndrome become tired while feeding and do not eat enough to gain weight. To make sure babies have a healthy weight gain, a special high-calorie formula might be prescribed. Some babies become extremely tired while feeding and might need to be fed through a *feeding tube* (FEINSTEIN et.al, 2012). According to the studies by Feinstein et.al (2012), soon after a baby with hypoplastic left heart syndrome is born, multiple surgeries done in a particular order are needed to increase blood flow to the body and bypass the poorly functioning left side of the heart. The right ventricle becomes the main pumping chamber to the body. These surgeries do not cure hypoplastic left heart syndrome, but help restore heart function. Sometimes medicines are given to help treat symptoms of the defect before or after surgery. Surgery for hypoplastic left heart syndrome usually is done in three separate stages.

This surgery usually is done within the first 2 weeks of a baby's life. Surgeons create a "new" aorta and connect it to the right ventricle. They also place a tube from either the aorta or the right ventricle to the vessels supplying the lungs (pulmonary arteries). Thus, the right ventricle can pump blood to both the lungs and the rest of the body. This can be a very challenging surgery. After this procedure, an infant's skin still might look bluish because oxygen-rich and oxygen-poor blood still mix in the heart (TCHERVENKOV, 2006).

The Bi-directional Glenn Shunt Procedure usually is performed when an infant is 4 to 6 months of age. This procedure creates a direct connection between the pulmonary artery and the vessel (the superior vena cava) returning oxygen-poor blood from the upper part of the body to the heart. This reduces the work the right ventricle has to do by allowing blood returning from the body to flow directly to the lungs (FEINSTEIN et.al, 2012).

The Fontan Procedure is done sometime during the period when an infant is 18 months to 3 years of age. Doctors connect the pulmonary artery and the vessel (the inferior vena cava) returning oxygen-poor blood from the lower part of the body to the heart, allowing the rest of the blood coming back from the body to go to the lungs. Once this procedure is complete, oxygen-rich and oxygen-poor blood no longer mix in the heart and an infant's skin will no longer look bluish (TCHERVENKOV, 2006). For Hinton et.al (2007), the infants with hypoplastic left heart syndrome may have lifelong complications. They will need regular follow-up visits with a cardiologist (a heart doctor) to monitor their progress. If the hypoplastic left heart syndrome defect is very complex, or the heart becomes weak after the surgeries, a heart transplant may be needed. Infants who receive a heart transplant will need to take medicines for the rest of their lives to prevent their body from rejecting the new heart (FIGURE 3).

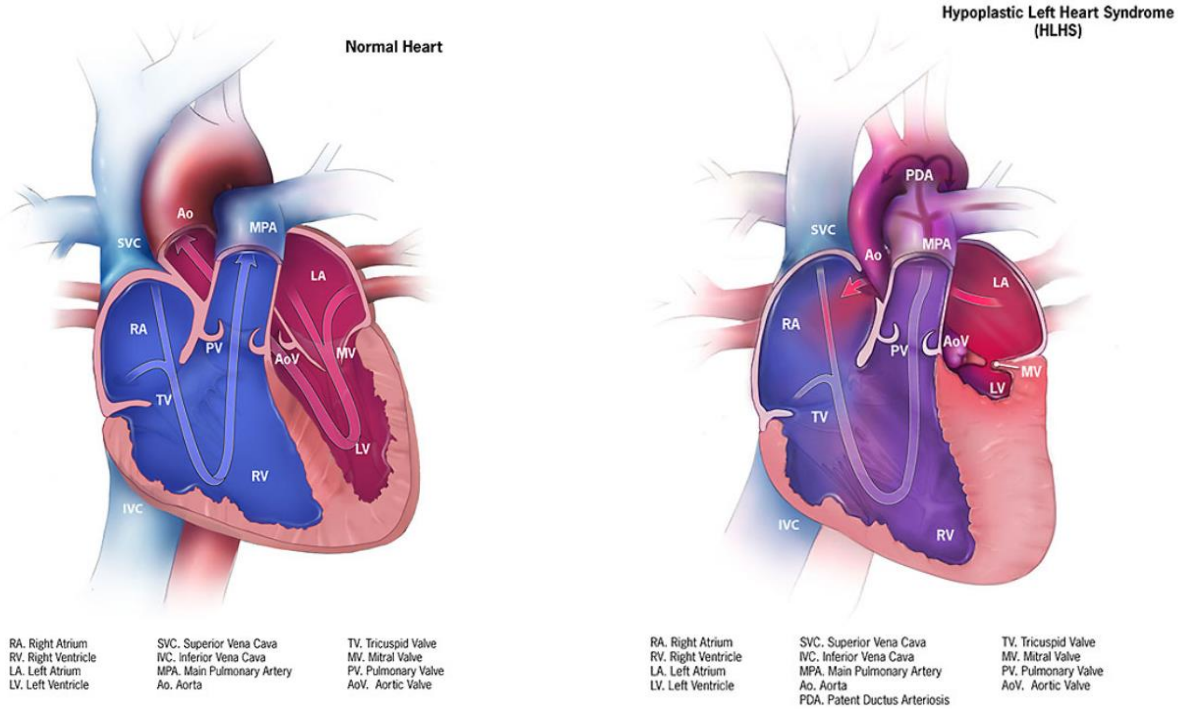

Figure 3 - Hypoplastic left heart syndrome affects a number of structures on the left side of the heart that do not fully develop. Source: Center for Disease Control and Prevention (2022).

Heart Transplantation in Children:

The first pediatric heart transplant in Brazil took place in 1991. The procedure was carried out by InCor (the Heart Institute of the Faculty of Medicine at USP's Hospital das Clínicas). The first patient, a 13-day-old baby, had been born with hypoplastic left heart syndrome, a severe irreversible congenital heart disease (ARAGÃO, et al. 2013).

One of the major complications in pediatric transplantation is the compatibility between donor and recipient. For example, the donor's weight cannot be less than 20% or more than twice the weight of the patient on the waiting list. In neonates, this is even more complicated, as the variation in weight and height changes rapidly over the course of days (ROELEVELD, 2019).

Heart Transplant Surgical Procedures in Neonates:

According to Rivera et.al (2007), performing heart transplant surgery on neonates depends on a large healthcare team, consisting of cardiovascular surgeons, cardiologists, intensivists, anesthesiologists, nurses, instrumentation specialists, perfusionists, psychologists and social workers. According to Di Carlantônio et.al (2015), the multidisciplinary team analyzes each case from the preoperative consultation, as well as assisting in the selection of the organ that the child will receive and in the surgical procedure, in addition to the care after the heart transplant is completed. Due to the complexity of the surgery and the young age of the patients, two teams of professionals are formed. One team is responsible for removing the donor's heart, while the other prepares the recipient simultaneously. All with the aim of reducing the ischemia time (time when the heart's blood flow is interrupted) of the transplanted heart, so that it is as short as possible (FARIA BASTOS et. al, 2013). According to Kindel et. al (2017), after surgery, the transplanted child is monitored continuously and needs immunosuppressive therapy, with medication that acts on their immune system, preventing the inflammatory process that can lead to organ rejection. After discharge from hospital, which varies between 15 and 30 days, the child or adolescent is monitored by the Cardiovascular Surgery and Cardiology Service.

Final Considerations:

Heart transplantation is the most effective form of therapy for prolonging the lives of patients with severe, advanced heart disease whose quality of life has been greatly reduced. As mentioned throughout this review article, transplantation is indicated when clinical and surgical measures to treat heart failure have been exhausted and the patient's life expectancy is low. Complex congenital heart diseases can be treated with heart transplantation, at some stage of their evolution, without increasing mortality or morbidity, a fact that we have seen in the medical complications and post-transplant survival discussed. The complications encountered after pediatric heart transplantation are, for the most part, medically manageable and are not a limiting factor for patient survival. This survival has improved in the medium term and can currently be considered very good, as the research points out. The greatest benefit expected from

a transplant is that life expectancy is better than the disease that prompted the procedure, even if it is treated with all the available treatment options. Many transplant recipients have no physical limitations in their day-to-day activities. Heart transplantation in children has been an option in complex importance for congenital heart diseases and
cardiomyopathies refractory to conventional therapy. Diagnostic research into the etiology of heart disease has advanced in the last decade, significantly increasing the chances of survival for children with congenital heart dysfunction. The shortage of organ donors is still a major obstacle to transplants in Brazil. Even in cases where the organ can be obtained from a living donor, the number of transplants is small compared to the demand from patients waiting for surgery. Lack of information and prejudice also limit the number of donations obtained from brain-dead patients. With effective public awareness, the number of donations could increase significantly. For many patients, organ transplantation is the only way to save their lives. There is a shortage of pediatric donors and the origin of this problem is multifactorial and can be found in the lack of notification, the lack of structure in the hospital of origin, weight incompatibility and family refusal. When dealing with children, the emotional factor of the family is even more present. Especially in Brazil, a country of continental dimensions, it is also difficult to obtain organs in places that are very far away or with difficult access. In this case, the challenge is biological: respecting the maximum ischemia time to keep the organ viable.

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