

Neonates with hypoplastic left heart syndrome and their fate after staged palliation

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Abstract

Hypoplastic left heart syndrome (HLHS) is a rare congenital heart defect in which the left side of the heart is severely underdeveloped. Etiology of this condition remains unknown. After the labour, three-stage cardio-surgical treatment is necessary, however all of the procedures run a significant risk of complications.

Depending on the general condition of the newborn, the first operation – Norwood procedure – may be carried out in different modifications. Complications are most common after this stage of palliation, and may include morbidities of both cardiogenic and non-cardiogenic etiology. First procedure is also characterized by the highest mortality rate. It is followed by Glenn procedure, usually performed on patients at the age of 3 to 6 months. Finally, HLHS patients undergo the Fontan operation, which is a method used commonly in cardiosurgical management of many single-ventricle lesions. A heart transplantation is an alternative method of treatment.

Development of cardiac surgery significantly increased survival rate of children born with congenital heart defects, hypoplastic left heart syndrome among them. Nowadays, a high percentage of those patients may have hope to reach adulthood. Nevertheless, the surgical treatment still bears a great risk of complications and continually is considered to be mere palliation, as HLHS remains a lethal condition.

Keywords: Hypoplastic left heart syndrome, HLHS, Norwood procedure, Glenn procedure, Fontan procedure

Introduction

Hypoplastic left heart syndrome (HLHS) is the most common variant of single-ventricle defects. HLHS is a frequent cause of death among infants born with congenital heart diseases under the age of twelve months. Until the 1970s, single-ventricle lesions were lethal. A new method of cardiac surgery – the Fontan procedure – and its further modifications made it possible for the infants with HLHS to survive. Before the introduction of this strategy, 95% of newborns with HLHS did not make it through the first month of life [1].

Development of such fields of medicine as anaesthesiology, cardiac surgery, intensive care medicine and pediatric cardiology has also influenced the prognosis for children born with this syndrome.

Nowadays patients undergo a three-stage surgical treatment, which enables the optimal development of the central nervous system. However, it is important to emphasize that the surgery is still considered as palliative treatment.

Comparison of Physiological and Pathological Heart Function- In postnatal life, the left ventricle of the heart

Manuscript received: 24th April 2017
Reviewed: 2nd May 2017
Author Corrected: 11th May 2017
Accepted for Publication: 18th May 2017

is filled with oxygenated blood from the left atrium and then pumps it under high pressure through the aortic orifice. In that way the blood is delivered to the systemic circulation, thus providing all of the tissues and organs with oxygen, which is essential for fundamental life processes. Oxygen-poor blood from the tissues flows through the veins to the right atrium and then enters the right ventricle. Next, the blood is transported to the lungs by the pulmonary artery. There the gas exchange takes place.

The oxygen-rich blood returns to the left atrium by the pulmonary veins. However, during the prenatal development there are many differences in heart anatomy and function. One of the most important difference is the presence of ductus arteriosus, also called ductus Botalli, a vessel which connects the pulmonary artery to the descending part of the aorta.

It allows the blood to bypass the pulmonary circulation. Soon after birth the ductus arteriosus closes and is transformed into ligamentum arteriosum. In this way, the connection between the systemic and pulmonary circulation is lost.

Hypoplastic left heart syndrome (HLHS) is a congenital heart disease, in which the left side of the heart is severely underdeveloped. Atresia or stenosis or hypoplasia of aortic and/or mitral valve could also be present in HLHS. Moreover, hypoplasia of the ascending part of the aorta or the aortic arch is possible as well. As the left ventricle is unable to function properly, the right ventricle takes over and is forced to deliver blood both to the systemic and the pulmonary circulation.

During the antenatal period most fetuses with HLHS develop normally, as the oxygenated blood is provided by the mother through the umbilical vessels. The presence of the ductus arteriosus allows the blood to bypass the lungs – during pregnancy the child receives sufficient amount of oxygen. Body weight and anthropometric measurements of neonates with HLHS may be within normal limits at the moment of birth, in addition to this the newborns may get a high score when evaluated by the Apgar scale. Soon after labor the ductus arteriosus closes. From this moment, blood pumped by the right ventricle remains in the pulmonary circulation, resulting in ischemia of the tissues, which leads to systemic hypoxia.

The clinical symptoms, including tachycardia, prolonged capillary refill, oliguria/anuria, metabolic acidosis and dyspnea, are observed within 24 hours and aggravate in time. The condition is lethal unless cardiocirculatory treatment is initiated. Otherwise multiple organ failure develops.

Norwood Procedure- Norwood procedure is the first stage of the reconstructive surgical treatment. It can be performed in different modifications, depending on the general condition of the patient. The Norwood procedure is carried out usually within the first week of the infant's life (as soon as the child's condition is stabilized). In general the aim of this stage is to create a connection between the systemic and pulmonary circulation. This method requires the use of hypothermia and extracorporeal circulation [1].

Sternotomy along with pericardiectomy are done in order to gain access to the heart [1]. To secure the proper level of oxygenation of the blood pumped into the systemic circulation vessels, the interatrial septum is removed. The ductus arteriosus (whose closure is until this moment prevented by pharmacotherapy) is ligated at first, and then cut. The next step is the transection of the pulmonary artery (proximally to its bifurcation) and a longitudinal cut of the aortic arch. The incision on the aorta is then joined with the proximal part of the pulmonary artery with a prosthesis [1].

The last step can be carried out in one of two possible modifications, which use different vessels to provide blood flow to the lungs. In the first variant, so called Blalock-Taussig (BT), the innominate artery or the subclavian artery is connected to the right pulmonary artery by a duct made of polytetrafluoroethylene. The other variant, Sano modification (RV-PA) - includes the usage of conduit joining the right ventricle to the pulmonary artery. There is a significant difference in diastolic blood pressure values that can be achieved in the systemic circulation – higher values in the Sano modification result in increased perfusion of the coronary arteries.

In the BT variant a constant blood flow to the pulmonary artery is assured (both in systole and diastole) due to lower resistance of the pulmonary veins in comparison to the systemic circulation. Unfortunately, this may lead to the so called “coronary steal”, which may trigger cardiac ischemia [2].

Some sources claim that mortality rate is lower if the Sano modification is used [2], whereas other insist there is no such difference between those two methods [2,8,9].

Generally, the risk of cardiogenic shock is higher for neonates with single-ventricle lesions before as well as after the first stage of palliation [2]. Mortality rate for Norwood procedure is estimated to be about 2-16% [2]. Factors influencing this rate directly include: low birth weight, necessity of extracorporeal membrane oxygenation (ECMO) support, genetic disorders, prematurity, total time of hypothermic circulatory arrest, comorbidities and additional abnormalities in heart anatomy [6,7].

Delayed sternal closure is sometimes used in order to minimize the frequency of complications after this stage of palliation, as it provides hemodynamic and respiratory stability. Nevertheless, no significant reduction in number of complications has been noticed in those cases, since the incidence of infections during the postoperative period grows higher [10]. As prematurity is an important factor of the prognosis, it is beneficial to avoid preterm delivery [14]. One of the studies identified three main causes of early postoperative mortality as inappropriate prosthesis size, heart failure and massive haemorrhage during the procedure [1].

As compared to healthy neonates, patients with HLHS have additional risk factors, such as reduced volume of myocardium, which is the source of mechanical energy driving the circulation; moreover, abnormalities in the anatomy of the cardiovascular system lead to lower levels of arterial blood oxygenation, because the right ventricle is forced to double its stroke volume [2].

Circulatory insufficiency combined with cardiac arrest and multiple organ failure are also observed among children with HLHS after the Norwood procedure. The postoperative period is characterized by high morbidity of cardiogenic and non-cardiogenic etiology, induced by reduced cardiac output. Possible complications that may develop are different types of arrhythmia (the most frequent is supraventricular tachycardia), complete heart block, tricuspid insufficiency and kidney failure. The most common of the neurological complications is convulsion [2]. Blood creatinine level is increased in 13% of children that underwent the procedure, whereas

1 to 18% of this population develops necrotizing enterocolitis (NEC) [2]. The most significant factor influencing the prognosis is the 24-hour care of multidisciplinary team, which deals with comprehensive treatment of such patients.

In addition to those findings, an improvement in general condition of patients after Norwood procedure has been noticed after the use of breathing gas containing low oxygen partial pressure and high carbon dioxide partial pressure. Although such composition lowers saturation, hypercapnia increases the amount of oxygen supplied to the tissues, including the central nervous system [2].

Another technique used to improve the survival rate and reduce the risk of complications is the measurement of mixed venous oxygen saturation (SvO₂). Value of SvO₂ above 50% correlates with higher degree of neurological development (at the age of both 4 and 6) [2]. It is important to highlight that the reduction of SvO₂ is not necessarily linked with changes in SaO₂, blood pressure or heart rate [2]. Arterial and venous blood pressure measurements, electrocardiography, capnography, urine volume test and biochemical evaluation of tissue perfusion should all be routinely parts of postoperative monitoring of the patient [2]. It is believed that closure of the chest should be carried out several days after the operation to lower the probability of cardiac tamponade [2].

Extracorporeal membrane oxygenation (ECMO) is a life-saving procedure, inevitable in certain critical cases. The therapy and especially its prolonged duration (7 days or more), considerably increases the mortality rate. Among complications related to ECMO are following: need of renal replacement therapy, blood coagulation disorders, convulsion, stroke, NEC and bacteremia [15].

One of the studies evaluated the survival rate of children with HLHS supported with ECMO after the first stage of palliation, comparing them with patients with no need for ECMO. Three checkpoints were established: hospital discharge (after the Norwood procedure), Glenn procedure and Fontan procedure. Survival rate for ECMO-supported population was 43, 8%, 35, 9% and 25,4%, respectively [15]. Another study assessed a 2-year survival of those patients at 26% [6]. Hybrid procedure is an alternative for the classical Norwood procedure. During the hybrid

procedure the surgeon performs bilateral banding of the pulmonary arteries and places a stent in the ductus arteriosus. The advantages of this technique include avoiding the use of cardiopulmonary bypass and hypothermic circulatory arrest, although a positive effect of those factors has not yet been proven [11].

Severe aortic coarctation, aortic arch hypoplasia (<2mm), oval foramen stenosis and impaired pulmonary venous drainage rule out the possibility of hybrid procedure. However, the research has shown that 1-year survival does not differ significantly between hybrid and Norwood procedure [12].

Home surveillance program, which has been introduced in some centers where Norwood procedure is performed, turned out to be a tactic which managed to reduce interstage mortality from 15% to 0% [13]. Venous oxygen saturation, pace of growth and brain activity were measured, the last parameter by near infrared spectroscopy (NIRS) [7]. Unfortunately, despite excellent results, it is still not a widespread strategy.

Glenn Procedure- The second stage of the cardiosurgical treatment of HLHS is Glenn procedure. It is performed at the age of 3 to 6 months – during which period a relatively large amount of blood streams down from the superior vena cava, making the operation more effective. The idea of the procedure is to create a partial cavo-pulmonary connection. Just like the first stage of palliation, Glenn procedure includes hypothermia and extracorporeal circulation. The way of reaching the heart is similar to the one used in Norwood procedure (sternotomy, pericardiotomy).

The vessels, especially the superior vena cava, the pulmonary arteries and the left brachiocephalic vein must then be dissected. The superior vena cava is cut above its orifice in order to connect its distal part to the right pulmonary artery. Sometimes double superior vena cava is present - in such cases bilateral Glenn is performed. The BT shunt, created during the previous operation, may be eliminated now, nevertheless it is believed the shunt ensures pulsatile pulmonary blood flow if it remains in its position.

Blood pressure in the inferior vena cava needs to be continuously monitored, as it directly influences the preload. The method described above is known as

classical bidirectional Glenn procedure with a partial cavo-pulmonary connection. Over the years, however, different modifications have evolved. The most popular is Kawashima procedure, carried out when the inferior vena cava is interrupted. Via the azygos vein, the drainage of blood returning from the lower parts of the body to the superior vena cava is assured. In such situations the Glenn shunt becomes the so called total cavo-pulmonary connection (TCPC).

The estimated survival rate after the second stage of palliation reaches 95% [2]. Complications are observed less frequently and they result mainly from the procedure itself and anatomical abnormalities (cavo-pulmonary connection) – the venous blood streaming down from the brain, head, neck and arms drifts into the pulmonary circulation [2].

Possible complications after the Glenn procedure include: arrhythmia, cyanosis, phrenic nerve injury (sustained during the transection of the superior vena cava) and embolism [2]. Children suffering from single-ventricle lesions, especially hypoplastic left heart syndrome, have a considerably higher risk of pericardial, pleural and peritoneal effusion, so the perioperative care focuses on avoiding those dangers [2].

Fontan Procedure- The aim of the Fontan procedure is to form a complete cavo-pulmonary connection. It was first carried out by Francois Fontan in 1971. It is commonly used in cardiosurgical treatment of many single-ventricle defects. In most cases, the child undergoes this stage under the age of 5. The Fontan procedure is performed in two modifications. The first one is the de Leval procedure, in which the cavo-pulmonary connection is created by an interatrial tunnel.

Through this tunnel the blood from the inferior vena cava flows to the superior vena cava and then enters the pulmonary arteries. In a variant called fenestrated Fontan, a fenestration remains between the tunnel and the atrium to ensure a left-right shunt, resulting in an increase in cardiac output. The side effect of this method is lower arterial blood oxygen saturation. In contrast to the extracardiac modification of Fontan (described below), this technique does not require the use of a graft to join the vessels, so it is better for younger patients.

A total cavo-pulmonary connection is performed in order to reduce the speed of blood flow into the pulmonary artery and to minimize the loss of kinetic energy. In this way the probability of embolism is lowered.

In 1990s, the de Leval procedure was modified and evolved into extracardiac total cavo-pulmonary connection (extracardiac TCPC), first performed by Marcelletti. As extracardiac TCPC requires no intervention inside the heart, circulatory arrest is not necessary, which means that the coronary flow is preserved. Intraoperative myocardial damage of the single ventricle or sinoatrial node is less frequent, thanks to which the number of postoperative arrhythmias is smaller. Another great advantage is the absence of surgical sutures in the right atrium [2].

In extracardiac TCPC the surgeon uses an avaluvar graft circumventing the heart to connect the inferior vena cava with the pulmonary arteries. Similarly to classical de Leval procedure, a fenestration may be created between the right atrium and the extracardiac graft, which brings down the risk of complications such as circulatory collapse, pleural and pericardial effusion and ascites. At the same time, fenestration makes embolism and lower systemic blood oxygen saturation more likely.

The survival rate after Fontan procedure is very high – 10-year survival is estimated at 72-91% [2]. However, it is worth mentioning that such impressive results have been achieved only recently – one of the studies determined post-Fontan mortality rate as 9,3% from 1992 to 1996, and merely 1,2% from 2003 to 2009 [17]. The frequency of both early and late complications has been reduced since extracardiac TCPC was introduced. 50-70% of newborns suffering from HLHS survive all stages of palliation and live to the age of 5 [2].

Potential complications after Fontan procedure are arrhythmia, protein-losing enteropathy (PLE) and pleural effusion. In the following years, children who had undergone the treatment may develop systolic and diastolic dysfunction, progressive hypoxia, higher pulmonary vascular resistance, arrhythmia or liver failure. Exercise intolerance is quite common in these patients [2]. In recent years the Fontan procedure has been much refined, and the survival rate has increased. Nonetheless, we still have to cope with serious late

complications, for example PLE or heart failure (in which cases reoperation may have to be considered). According to recent studies, 10-, 20- and 30-years survival rates are estimated at 74%, 61% and 43%, respectively [18].

Nevertheless, the study focused not only on infants with HLHS, but also on patients who had undergone Fontan procedure for different reasons. It has not been long since HLHS can be successfully treated with Fontan procedure, with the result being that there is a small group of such patients to study. All the same, there is no proof that mortality rate is higher for HLHS patients when compared to other Fontan patients. Still, it is believed that the procedure itself is more likely to fail when the patient suffers from HLHS [16].

In spite of three-stage surgical treatment, the longevity of a single-ventricle heart is still below average. However, the treatment is introduced in order to improve the quality of life and to extend the lifespan, as well as to enable the most optimal psychomotor development possible. There exists one alternative to the staged palliation – heart transplantation.

Heart Transplantation- When we consider the population of children with HLHS, a heart transplant seems to be the best choice of treatment. Neurological dysfunctions are considered to be less frequent in those cases. The greatest limit is the small number of organs available for transplantation. For this reason, patients are divided into two groups: children selected for Norwood procedure undergo three-stage palliation, whereas newborns diagnosed with severe stenosis of the ascending aorta, severe regurgitation of atrioventricular valve or right ventricle dysfunction are selected for heart transplantation.

1-year survival rate after a heart transplant stands at 76% [2]. The most common cause of death are infections (30%) [2]. Kidney, liver or respiratory failure is also observed [2]. Some patients with single-ventricle lesions may produce anti-HLA antibodies specific for the donor's HLA as a result of earlier blood transfusions or as a reaction to the graft [2]. In such situation desensitization (for example plasmapheresis) is advised.

Older sources claim that transplantation performed after any other procedure described previously is not as effective as the one carried out immediately [5].

This was believed to be caused by massive production of antibodies (described above) and comorbidities – PLE and kidney/liver failure [4]. Nonetheless, more recent studies indicate no significant difference in post-transplantation survival rate between children who had undergone staged palliation for HLHS and patients who were selected for transplantation for other reasons. When the HLHS group was compared with group of patients with acquired cardiomyopathy, both 30-day (100% vs 87.5%, respectively) and 5-year survival rate (98.1% vs 88.9%, respectively) are similar [3].

In the same study, right ventricular failure combined with aortic regurgitation was the main indication for the transplant in 94% of HLHS cases. 25% of patients with HLHS developed this failure for the second time after the transplantation, but none of these cases was lethal. No statistically significant difference in frequency of right ventricular failure has been proven between the two groups [3].

Life after the Staged Palliation- Patients with Fontan procedure have a tendency to develop characteristic complications: endothelial dysfunction, reduced cardiac output and high venous pressure. With the passage of time, the risk of complications increases [2]. Cardiac care needs to be permanent and should include ECG, pulse oxymetry and four-limb blood pressure measurement. Use of cardiac MRI is controversial in those situations – although the quality of the MRI images is very high, the test itself includes sedation [2].

HLHS may coexist with conditions like PLE (if the two are combined, survival rate is determined at 46%) or plastic bronchitis [2]. Apart from the perioperative period, arrhythmia is the most common cause of death, however its incidence is about 30% lower if the extracardiac variant had been performed (when compared to the lateral tunnel method) [2]. 20 years after the procedure, 23% of patients require a cardiac pacemaker [2].

There is no available database concerning adults with HLHS. The results presented above relate to a broader population of patients who underwent Fontan procedure. All the same, in some centers patients with HLHS make up even 50% of the group qualified for Fontan procedure [17], so the mentioned data can be considered as valid. Average life expectancy of men with univentricular heart is estimated as below 30 years

[2]. One study claims 98% of the patients develop progressive neo-aortic root dilatation and neo-aortic valve regurgitation [2]. It is possible for a woman with a Fontan circulation to go through a full-term pregnancy and a physiological labor, but there is a great risk of embolism and atrial arrhythmia. The pregnancy does not affect the circulatory system, but it increases the probability of stroke during and after the labor [2]. Miscarriages and infertility are more common among these women [2].

Psychomotor dysfunctions are often observed in children with HLHS. Impulsive behavior, difficulties with studying, cognitive disorders, problems with psychosocial functioning are the most frequent conditions [2]. Motor functions are within the normal range, but exercise intolerance is present. According to the parents, children with HLHS suffer from low self-esteem and do not function correctly in their peer group. Speech therapy may be necessary [2].

All these problems may result from abnormal prenatal brain development [2]. According to some studies, duration of hypothermia >40 minutes is a risk factor for neurological complications [2]. Duration of hospitalization and low birth weight also negatively affect the prognosis [2]. Cardiac care must be continued lifelong. Sources suggest even 70% of patients born with HLHS may reach adulthood [2]. It is still worth highlighting that HLHS remains a lethal condition and palliation is still considered as a method of therapy.

Conclusions

Infants born with hypoplastic left heart syndrome require specialist care from the first moments after the labor. Presence of a multidisciplinary team, experienced in treatment of HLHS is essential. Complications are less common after the following stages of palliation. The future development of transplantology might one day make it possible to replace the presently used method of treatment with one procedure of heart transplantation.

Funding: Nil, **Conflict of interest:** None initiated, **Perission from IRB:** Yes

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How to cite this article?

Katarzyna Baran, Justyna Gilewska, Michalina Gałuszka, Piotr Surmiak, Małgorzata Baumert. Neonates with hypoplastic left heart syndrome and their fate after staged palliation. *J PediatrRes*.2017;4(05):295-302.doi:10.17511/ijpr.2017.i05.02

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