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# Tiny hearts, great solutions:
## a Literature Review about the surgical therapeutic approaches for Hypoplastic Left Heart Syndrome

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«Dá-se a volta ao medo, dá-se a volta ao mundo»
- Sérgio Godinho

# Resumo

A síndrome do coração esquerdo hipoplásico (SCEH) é uma malformação congénita complexa, caracterizada pelo subdesenvolvimento do lado esquerdo do coração na presença de um ventrículo esquerdo hipoplásico, normalmente com hipoplasia ou atresia da aorta e/ou das válvulas aórtica e mitral. A SCEH é umas das cardiopatias congénitas mais severas e, na ausência de tratamento, apresenta uma mortalidade superior a 90% no primeiro ano de vida. Há cerca de cinco décadas o tratamento convencional incluía apenas medidas de conforto e o curso natural da doença culminava na morte precoce destas crianças. Atualmente, há duas modalidades cirúrgicas reconhecidas, a reconstrução paliativa e a transplantação cardíaca. A terapêutica convencional envolve o recrutamento do ventrículo direito para a circulação sistémica e a separação da circulação pulmonar da sistémica, em três fases. Consiste na cirurgia de Norwood durante o período neonatal, seguido do procedimento bilateral de Glenn ou um Hemi-Fontan entre os 4 e os 6 meses, terminando com a cirurgia de Fontan entre os 18 e os 48 meses de idade. Mudanças na seleção dos doentes, gestão pré- e pós-operatória, e melhoria das técnicas cirúrgicas contribuíram para a diminuição da mortalidade peri-operatória para 10%. Contudo, os sobreviventes apresentam várias complicações e alguns doentes evoluem para falência circulatória. A transplantação cardíaca foi estabelecida com uma opção terapêutica primária para crianças com SCEH, sendo que a principal vantagem é a substituição de um coração univentricular por um coração normal, numa única cirurgia. Apesar da sobrevivência ser excelente, a reconstrução paliativa tem sido favorecida face à limitada disponibilidade de órgãos. Com os avanços do diagnóstico pré-natal, na segunda metade do século XXI, procedimentos in útero foram propostos para alterar curso natural da doença. O racional por detrás destas intervenções é o restabelecimento do fluxo e a redução da pressão intraventricular, promovendo o crescimento e a função do ventrículo esquerdo. A valvuloplastia aórtica fetal requere numerosos recursos e experiência nas áreas do diagnóstico fetal, obstétrica e imagem cardiovascular, bem como técnicas percutâneas avançadas. Poucos centros o detêm para o fazer com sucesso, sendo os resultados cada vez mais encorajadores. A presente revisão da literatura tem como objetivo avaliar o papel das diferentes opções cirúrgicas existentes para a SCEH, procedimentos, otimizações, sobrevivência e melhoria da qualidade de vida, bem como efeitos adversos, *outcomes* a longo prazo e morbilidade. Pretende ainda explorar algumas perspetivas de futuro quantos à gestão destes doentes.

# Palavras-chave

Cardiopatias congénitas; Síndrome do Coração Esquerdo Hipoplásico; Cirurgia de Norwood; Procedimento Híbrido; Cirurgia Bidirecional de Glenn; Procedimento Hemi-Fontan; Cirurgia de Fontan; Transplantação Cardíaca; Valvuloplastia Aórtica Fetal.

# Resumo Alargado

A síndrome do coração esquerdo hipoplásico (SCEH) é uma malformação congénita complexa, caracterizada pelo subdesenvolvimento do lado esquerdo do coração na presença de um ventrículo esquerdo hipoplásico, normalmente com hipoplasia ou atresia da aorta e/ou das válvulas aórtica e mitral. A SCEH é umas das cardiopatias congénitas mais severas e, na ausência de tratamento, apresenta uma mortalidade superior a 90% no primeiro ano de vida. Alguns autores admitem que distúrbios hemodinâmicos intracardíacos levem à diminuição do fluxo através de válvula mitral, impedindo o crescimento das estruturas esquerdas do coração. Outros autores implicam fatores genéticos na origem desta síndrome.

Há cerca de cinco décadas o tratamento convencional incluía apenas medidas de conforto e o curso natural da doença culminava na morte precoce destas crianças. Atualmente, há duas modalidades cirúrgicas reconhecidas, a reconstrução paliativa e a transplantação cardíaca. A terapêutica convencional envolve o recrutamento do ventrículo direito para a circulação sistémica, direcionamento do retorno venoso sistémico para a rede vascular pulmonar e a separação da circulação pulmonar da sistémica, em três fases. Consiste na cirurgia de Norwood durante o período neonatal, seguido de uma anastomose bidirecional cavopulmonar, na forma de um procedimento de Glenn ou um Hemi-Fontan entre os 4 e os 6 meses, terminando com a cirurgia de Fontan entre os 18 e os 48 meses de idade.

A cirurgia de Norwood consiste numa conexão aortopulmonar e construção de um neoarco aórtico, e os seus princípios incluem uma comunicação permanente entre o ventrículo direito e a aorta, limitação do fluxo sanguíneo pulmonar e uma comunicação interatrial capaz de dar resposta às necessidades fisiopatológicas destas crianças. Esta cirurgia é bastante desafiante, e várias otimizações ao longo dos anos contribuíram para melhoria das taxas de sobrevivência. A sobrevivência livre de transplante é melhor do que inicialmente esperada, superando os 80% 5 anos após a cirurgia. Contudo, há complicações importantes, taquicardias, bloqueio atrioventricular e eventos trombóticos, bem como alterações do neurodesenvolvimento.

Inicialmente, a anastomose bilateral cavopulmonar integrava a cirurgia de Fontan, contudo, com significante mortalidade e morbilidade. Assim, introduziu-se uma etapa intermédia na forma de um procedimento bilateral de Glenn ou um Hemi-Fontan, aumentando para três as etapas da reconstrução paliativa. Esta etapa, com uma taxa de

mortalidade de 1%, contribui para a redução da mortalidade associada ao procedimento de Fontan. Alguns autores consideram que o procedimento de Hemi-Fontan oferece uma anastomose cavopulmonar mais favorável, diminuindo o potencial desenvolvimento de fibrilação ou flutter atrial. Contudo, este procedimento requer paragem cardíaca.

A cirurgia de Fontan, inicialmente proposta para a reparação da atresia tricúspide, restabelece o fluxo sanguíneo pulmonar fisiológico através da transmissão do sangue das veias cavas diretamente para os pulmões e assegurando que apenas chega ao coração sangue oxigenado. Dilatação arterial progressiva, arritmias e complicações tromboembólicas levaram ao desenvolvimento das técnicas: túnel lateral e condutor extracardíaco. Outra modificação projetada para manter o output cardíaco é a fenestração. Mudanças na seleção dos doentes, gestão pré- e pós-operatória, e melhoria das técnicas cirúrgicas contribuíram para a diminuição da mortalidade operatória para 10%. Contudo, os sobreviventes exibem várias complicações e alguns evoluem para falência circulatória.

A transplantação cardíaca proposta por Leonard Bailey foi estabelecida com uma opção terapêutica primária para crianças com SCEH, sendo que a principal vantagem é a substituição de um coração univentricular por um coração normal, numa única cirurgia. As crianças transplantadas durante o período neonatal apresentam o potencial de chegar à idade adulta com necessidades mínimas de reintervenção. Apesar da sobrevivência ser excelente, a reconstrução paliativa tem sido favorecida face à limitada disponibilidade de órgãos. Ainda assim, independentemente da abordagem cirúrgica escolhida, doentes com SCEH começam a sobreviver até à adolescência e mesmo idade adulta.

Com os avanços do diagnóstico pré-natal, foi proposto que a estenose da válvula aórtica poderia estar na origem da hipoplasia do ventrículo esquerdo durante o desenvolvimento fetal e, sob determinadas condições fisiológicas, poderia induzir-se o crescimento das estruturas hipoplásticas. Assim, na segunda metade do século XXI, procedimentos in útero foram propostos para alterar curso natural da doença. O racional por detrás destas intervenções é o restabelecimento do fluxo e a redução da pressão intraventricular, promovendo o crescimento e a função do ventrículo esquerdo. A valvuloplastia aórtica fetal requere numerosos recursos e experiência nas áreas do diagnóstico fetal, obstétrica e imagem cardiovascular, bem como técnicas percutâneas avançadas. Poucos centros o detêm para o fazer com sucesso, sendo os resultados cada vez mais encorajadores.

Otimizações devem continuar a ser empregues, uma vez que ainda há grandes variações na gestão pré-, intra- e pós-operativa entre centros. Critérios de seleção e protocolos mais ajustados permitem que diferentes fenótipos recebem diferentes e mais adequadas abordagens, quer cirúrgicas, quer não-cirúrgicas. Não existe uma abordagem cirúrgica superior à outra, existe apenas uma abordagem cirúrgica superior para um paciente específico. Os médicos devem, à luz das evidências científicas mais atuais, e considerando fatores morfológicos e funcionais, recomendar um caminho ajustado ao doente, e oferecer às famílias a oportunidade de tomar decisões informadas sobre a vida de seu filho.

# Abstract

Hypoplastic left heart syndrome (HLHS) is a complex congenital malformation characterized by underdevelopment of the left heart with significant left ventricle hypoplasia, including atresia, stenosis, or hypoplasia of the aortic and mitral valves. It is one of the most severe forms of congenital heart disease and, without surgical treatment, the mortality rate for infants with HLHS exceeds 90% in the first year of life. About five decades ago, comfort care was the only therapeutic option available, resulting in premature death of infants with this syndrome. Nowadays, there are two recognized surgical modalities, palliative staged reconstruction, and cardiac transplantation. Conventional surgical therapy involves recruiting the right ventricle to the systemic circulation and separating the pulmonary and systemic circulations, in three stages. It consists of an initial Norwood operation during the neonatal period, followed by a bidirectional Glenn or a Hemi-Fontan procedure performed at 4 to 6 months of age, and a Fontan operation between 18 and 48 months of age. Changes in patient selection, pre- and postoperative management, and improved surgical techniques, have contributed to minimize perioperative mortality to 10%. However, the surviving cohort presents with multiple early and late complications, with some patients evolving to the “failing” Fontan. Cardiac transplantation has been established as a primary treatment option in infants with HLHS. The main advantage is the replacement of a functionally univentricular heart with a normal heart in a single surgery. Although survival is excellent, the multistage palliation has been favored due to limited number of available donors. With prenatal diagnosis advancements in the second decade of the 21st century, in-utero procedures were proposed to change the rules of the game. The rationale for in-utero interventions is restoration of onward flow and reduction of intraventricular pressure, hence promoting left ventricle growth and function. Fetal aortic valvuloplasty requires numerous resources and expertise in fetal diagnosis, obstetric and cardiovascular imaging, catheter techniques, and maternal care. Few centers have the capacity to do so successfully, nevertheless its results are more and more encouraging. This literature review aims to assess the role of different surgical therapeutic options for HLHS, procedures, optimizations, survival, and improvement in quality of life, adverse effects, long-term outcomes, and burden of disease in these patients. It also wants to shed light and explore future perspectives regarding the best approach to these patients.

# Keywords

Congenital Heart Diseases; Hypoplastic Left Heart Syndrome; Norwood operation; Hybrid procedure; Glenn operation; Hemi-Fontan procedure; Fontan operation; Cardiac transplantation; Fetal Aortic Valvuloplasty.

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# List of abbreviations

| | |
|---|---|
| APBF | Accessory pulmonary blood flow |
| Ao | Aorta |
| ArchAo | Aortic arch |
| AV | Aortic valve |
| AA | Aortic valve atresia |
| AS | Aortic valve stenosis |
| AscAo | Ascending aorta |
| ASD | Atrial septal defect |
| BCPA | Bidirectional cavopulmonary anastomosis |
| BDG | Bidirectional Glenn operation |
| bPAB | Bilateral pulmonary arterial banding |
| BiV | Biventricular |
| BVR | Biventricular repair |
| BTS | Blalock-Taussig shunt |
| CO | Cardiac output |
| CTx | Cardiac transplantation |
| CPB | Cardiopulmonary bypass |
| CoA | Coarctation of the aorta |
| CHD | Congenital heart disease |
| CAS | Critical aortic stenosis |
| DescAo | Descending aorta |
| DA | Ductus arteriosus |
| EC | Extracardiac conduit |
| ECMO | Extracorporeal membrane oxygenation |
| FAV | Fetal aortic valvuloplasty |
| FO | Foramen ovale |
| HFP | Hemi-Fontan procedure |
| HLHC | Hypoplastic left heart complex |
| HLHS | Hypoplastic left heart syndrome |
| IVC | Inferior vena cava |
| LT | Lateral tunnel |
| LA | Left atrium |
| LV | Left ventricle |

| | |
|---|---|
| LVOT | Left ventricular outflow tract |
| MPA | Main pulmonary artery |
| MeSH | Medical Subject Headings |
| MV | Mitral valve |
| MA | Mitral valve atresia |
| MS | Mitral valve stenosis |
| NYHA | New York Heart Association functional classification |
| PDA | Patent ductus arteriosus |
| PFO | Patent foramen ovale |
| PTFE | Polytetrafluoroethylene |
| PLE | Protein-losing enteropathy |
| PA | Pulmonary artery |
| PBF | Pulmonary blood flow |
| PVR | Pulmonary vascular resistance |
| RAA | Right atrial appendage |
| RA | Right atrium |
| RV | Right ventricle |
| RVPAS | Right ventricle-to-pulmonary artery shunt |
| RVOT | Right ventricular outflow tract |
| SV | Single ventricle |
| SVR | Single ventricle reconstruction |
| S1P | Stage 1 palliation |
| S2P | Stage 2 palliation |
| S3P | Stage 3 palliation |
| SVC | Superior vena cava |
| SBF | Systemic blood flow |
| TV | Tricuspid valve |
| UVH | Univentricular heart |

# Introduction

Worldwide each year around 1.35 million children are born with congenital heart disease (CHD), which are the most common types of birth defects with a prevalence of 9 per 1000 live births. (1) Hypoplastic left heart syndrome (HLHS) is a complex congenital malformation ranging in severity from aortic valve stenosis (AS) to the most severe form in which both the aortic (AV) and mitral valves (MV) are atretic and the left ventricle (LV) is underdeveloped or even absent. It is one of the most severe forms of CHD and, without surgical treatment, the mortality rate for infants with HLHS is 25% in the first few weeks of life and exceeds 90% in the first year of life. (1,2)

About five decades ago, the natural course of HLHS culminated in premature death, with comfort care being the only therapeutic option available. In the early 1980s, two surgical approaches were proposed, palliative staged reconstruction developed by Norwood (3) and orthotopic cardiac transplantation (CTx) pioneered by Bailey (4). Ever since, surgical therapeutic approaches have undergone an enormous evolution. The Norwood procedure has been favored as outcomes improved, instead of primary CTx due to limited number of available donors, nonetheless there continues to be a debate as to the optimal therapeutic approach. Regardless of the approach, survival has vastly improved, and current expectations are that up to 70% of infants born today are surviving not only through the Fontan procedure, but also into adolescence and adulthood. (5)

Conventional surgical therapy involves recruiting the right ventricle (RV) to the systemic circulation and directing the systemic venous return to the pulmonary vascular network, separating the pulmonary and systemic circulations, in three stages. (6) First (S1P) and second stage palliation (S2P) attempt to improve symptomatology, provide optimal pulmonary artery (PA) architecture and low pulmonary vascular resistance (PVR), relieve systemic ventricular outflow tract obstruction, and provide the anatomy required for Fontan circulation, the third stage (S3P). (7) Although this procedure increases the survival of children with HLHS, its mortality is still one of the highest among treated CHD, and the natural evolution of this type of circulation is not without complications.

With prenatal diagnosis advancements, it was proposed that AS could at some stage of fetal development be associated with underdevelopment of the LV. Therefore, in the second decade of the 21st century, in-utero procedures were proposed to alter the natural history of the disease. However, some authors (8–12) have demonstrated the role of genetics in cardiomyocyte proliferation and differentiation, and in the penetrance of cardiac abnormalities, questioning the effectiveness of this innovative procedure.

This literature review aims to assess the role of different surgical therapeutic options for HLHS, procedures, optimizations, survival, and improvement in quality of life, adverse effects, long-term outcomes, and burden of disease in these patients. It also wants to shed light and explore future perspectives regarding the best approach to these patients.

# Methods

Literature searches were conducted in PudMed and Google Scholar, identifying relevant publications related to surgical approaches in patients with HLHS. Eligible studies were randomized controlled trials, multicentric and observational studies, and expert opinion papers. This paper focuses on surgical treatment for patients with HLHS, staged palliation, primary CTx and in-utero intervention, from the prenatal period until the Fontan procedure, and when available through the follow-up period. Primary outcomes are survival and improvement in quality of life, whereas secondary outcomes are pos-operative adverse effects, long-term outcomes, and burden of disease.

Both Medical Subject Headings (MeSH) terms – "Hypoplastic Left Heart Syndrome" [Mesh], "Univentricular Heart"[Mesh], "Heart Bypass, right"[Mesh], "Norwood procedures"[Mesh], "Fontan procedure"[Mesh], "Heart Transplantation"[Mesh], "Aortic Valve Stenosis/therapy"[Mesh] – and free text – “Fetal Aortic Valvuloplasty" – were employed. No past date was imposed and searches for this review were run between October 2021 and April 2022. Only English studies were considered. The most relevant studies in the reference lists of retrieved studies were also included.

After a first selection based on abstracts, 163 studies were included in the present review, categorized into: staged palliation, primary CTx, and in-utero procedures. Additional articles were included to contextualize the subject in study. One limitation found was regarding the design of the publications researched. There are few randomized controlled trials in pediatric cardiac literature, especially relating to HLHS, therefore more observational studies and expert opinion papers were used.

# Background

## Definition, morphology, and classification

Bardeleben, a German pathologist, first described, in 1851, the pathologic-anatomic characteristics, pathophysiology, and clinical features of HLHS. (13) The term "Hypoplastic Left-heart Syndrome" was proposed by Noonan and Nadas (14), in 1958, for obstructive lesions on the left side associated with LV hypoplasia and RV hypertrophy, and the anatomic findings to define the syndrome were grouped together. The Congenital Heart Surgery Nomenclature and Database Project (15) has defined HLHS as "a spectrum of cardiac malformations with normally aligned great arteries without a common atrioventricular junction, characterized by underdevelopment of the left heart with significant hypoplasia of the LV including atresia, stenosis, or hypoplasia of the AV or MV, or both valves, and hypoplasia of the ascending aorta (AscAo) and aortic arch (ArchAo).".

This complex syndrome exhibits various cardiac phenotypes. On the one hand, the severe end of the spectrum, patients with aortic (AA) and mitral valve atresia (MA) with an almost non existing LV (Figure 1). On the other hand, patients with AS and LV hypoplasia or those without intrinsic valvar stenosis or atresia (Figure 2), defined by Tchervenkov et al. (15) as hypoplastic left heart complex (HLHC).

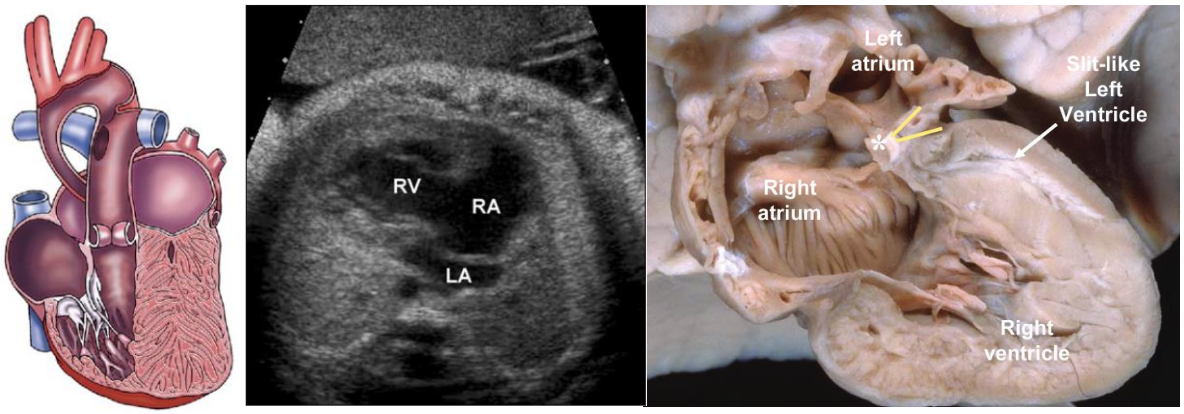


Figure 1: Aortic and mitral atresia complex (A) the hypoplastic LV model shows the severe end of the spectrum, with MA/AA, and a minute Ao [Hickey et al., 2012, p.S45 (16)]; (B) a transverse fetal echocardiogram shows enlargement of the right atrium (RA) and RV. Whereas the left atrium (LA) is small, and no LV is visible because of severe hypoplasia. [Allen et al., 2005, p.1201 (17)] (C) phenotype of MA/AA in the autopsy of a mid-term fetus. In most fetuses evaluated by Sedmera et al., the left atrioventricular junction (yellow lines) had joined the muscular base of the atrial septum (*) [Sedmera et al., 2005, p. 58 (18) ].

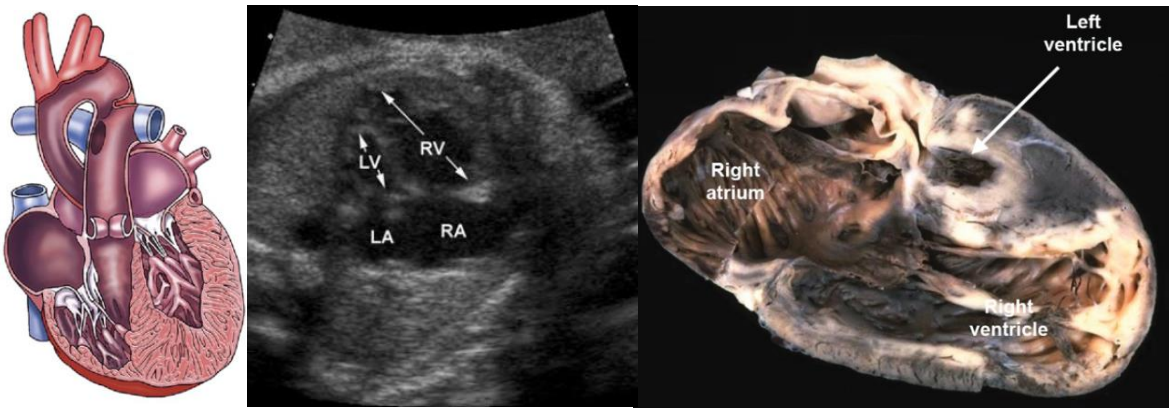


Figure 2: Severe aortic stenosis or atresia with mitral stenosis complex (A) the hypoplastic LV model shows an abnormal left ventricular outflow tract (LVOT) development, at a milder spectrum, with mitral valve stenosis (MS), and a larger Ao [Hickey et al., 2012, p.S45 (16)]; (B) a transverse fetal echocardiogram shows a LV, and an enlarged RV [Allen et al., 2005, p.1200 (17)]; (C) four-chamber views of fetal and newborn heart showing small size and thick wall of the hypoplastic chamber [Sedmera et al., 2005, p. 57 (18)].

Bharati and Lev (19) conducted a study of 230 hearts with HLHS. There were 105 cases of AA/MS, 95 cases of AA/MA and 30 cases of severe AS/MS, as described below:

Every heart was enlarged with the RV forming the apex. The RA was always hypertrophied and enlarged, with a focally thickened and whitened endocardium. An atrial septal defect (ASD) was found in 105 cases. The tricuspid orifice was enlarged in all cases, and, in 143 cases, the tricuspid valve (TV) exhibited an increased hemodynamic change. The RV was always hypertrophied and enlarged. Both the pulmonary orifice and the pulmonary trunk were enlarged in all hearts. The two PAs were smaller than normal in some cases and large for the age of the individual in others. The ductus arteriosus (DA) was widely patent in most cases. A minute AscAo was in normal position. Left side of the heart differed considerably between those specimens with AA/MA and those with AS/MS or AA/MS.

### Aortic and mitral atresia complex

The LA was small in 90 cases, with a thick-wall in 47, and a thin-wall in 43, hypertrophied and enlarged in 4 and normal in 1. The endocardial lining was often thicker. The mitral orifice was replaced by either a puckered or a membranous area. Frequently, the LV did not possess a lumen, and in some cases, a small lumen with a thin endocardial lining could be detected. In both complexes, as stated earlier, the AscAo was a minute structure. The transverse Ao was larger than the AscAo but smaller than normal. In some cases, the isthmus presented with a coarctation of the aorta (CoA) just before the entry of the DA.

### Severe aortic stenosis or atresia with mitral stenosis complex

The LA was smaller with a thick-wall in 67 cases, thin-wall in 61, and normal in the remainder. Its endocardium was often thickened and whitened. The mitral orifice was smaller in all cases and the MV leaflets were thickened with short thick chordae. In cases

of atresia, the aorta (Ao) had either no valve or a fold soft tissue resembling valvular tissue. In the cases in which the Ao orifice was open, the valve was small, thickened, and either bicuspid, tricuspid, unicuspid, incompletely divided, or a curtain of tissue. The LV consisted of a much smaller than normal chamber. Its wall was relatively thick, and the endocardial lining showed luxuriant fibroelastosis.

## Etiology, genetics, and embryology

Two contrasting theories have been proposed to explain the etiopathology of HLHS. The first rests on the argument «no flow, no grow». In support of this theory, the evolution of fetal echocardiography has highlighted the progressive nature and the importance of abnormal flow patterns in its evolution (Figure 3). AS is one of the earliest defects to be observed during fetal development, suggesting that in some patients AV dysfunction decreases flow across the MV and in consequence decreases growth of the distal left-sided structures. Moreover, studies in zebrafish have shown that diminished LV function results in underdevelopment of the AV and MV, indicating that the loss of endocardial function might be a critical early step in its etiopathology. (5,20) DeAlmeida et al. (21), using a chick model, surgically ligated the embryonic LA, restricting blood flow into the LV, which gave rise to LV hypoplasia. By subsequent clipping the RA and forcing more blood flow across the atrial communication, the hypoplastic LV was “rescued”, indicating that the LV growth was a physiologic response to volume overload. This study demonstrated that at least under some circumstances, an embryonic hypoplastic LV can be salvaged, and that myocyte proliferation can be induced under the appropriate physiologic stimulus.

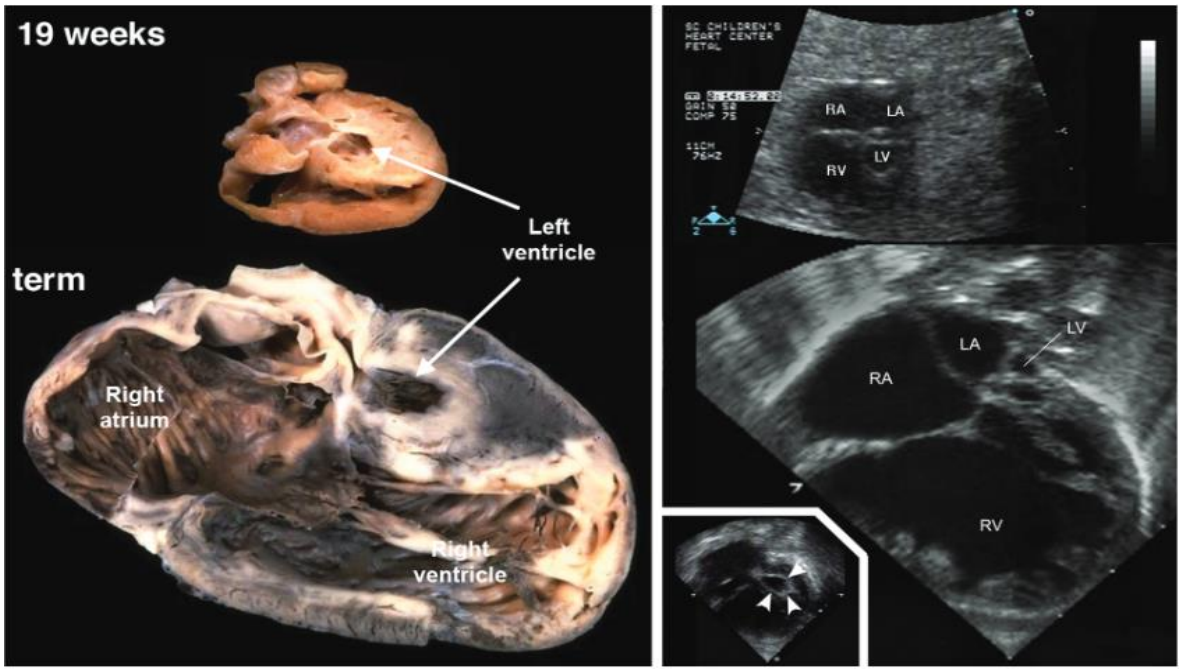


Figure 3: Progressive nature of HLHS (A) four-chamber views of a 19-week fetus and a newborn heart show the progressive nature of LV hypoplasia, with a smaller size and thicker wall of the hypoplastic chamber at

term; (B) matching ultrasound pictures show the progression of a prenatal MS to a postnatal MA and no demonstrable flow in the LV. [Sedmera et al., 2005, p. 57 (18)].

The second theory implicates HLHS as a primary mechanism caused by genetic factors, as some patients have LV hypoplasia in the absence of valvar stenosis. (20) Moreover, a high concordance for LVOT malformations among families has been documented, as well as its association with various syndromes such as Turner and Jacobsen, and trisomy 9, 13, and 18. (9) Consistent with this hypothesis, in 2009, Hinton et al. (10) estimated that HLHS was almost entirely heritable, and that same year, identified two significant loci on10q22 and 6q23. (11) McBride et al. (12) offered evidence of linkage to chromosomes 2p23, 10q21, and 16p12 for the combined LVOT malformation phenotype and for the individual phenotypes of AS, CoA, and HLHS. And in 2017, Liu X et al. (8) coupled mouse chemical mutagenesis with ultrasound phenotyping of 100,000 fetal mice to yield eight HLHS mutant lines (Figure 4) and, unlike other CHD phenotypes, it exhibited nonmendelian segregation. Mice and zebrafish modelling identified mutations in Sap130[1] as LV hypoplasia mediators by perturbing cardiomyocyte proliferation and differentiation, with increased apoptosis and mitotic cell cycle arrest restricted to LV cardiomyocytes, and in Pcdha9[2] to increase penetrance of AV abnormalities.

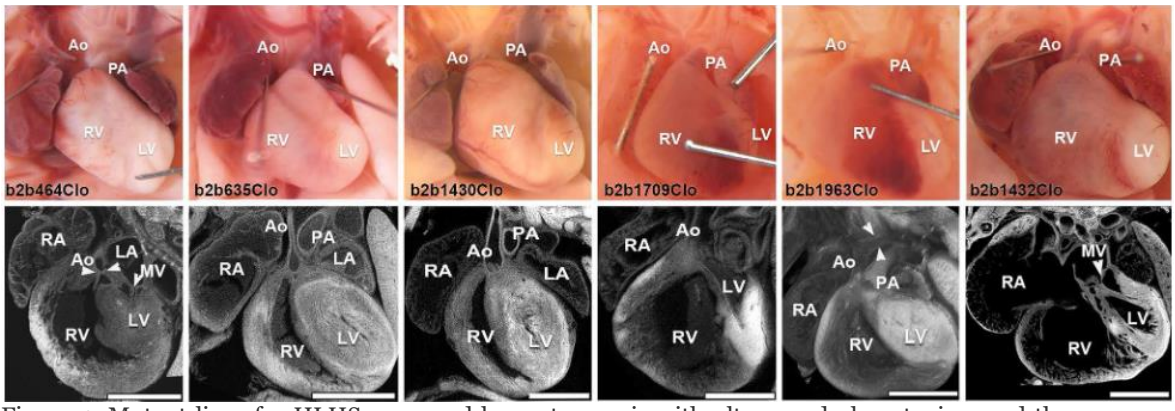


Figure 4: Mutant lines for HLHS recovered by mutagenesis with ultrasound phenotyping, and the necropsy and confocal histopathology above show the wide spectrum of disease associated with HLHS in six of the eight mutant lines. [Yagi et al., 2018, p. 1072 (9)].

Together these findings suggest a multigenic and heterogeneous genesis, rather than a valvar disease. If HLHS is not hemodynamic disturbance dependent, then neither in-utero procedures nor restoration of normal antegrade blood flow should be effective. And the incomplete penetrance observed in animal models might reflect epigenetic effects. There are important therapeutic implications around the etiology of HLHS, whether it is hemodynamic dependent, associated with genetic factors or has both components. (8,9)

[1] encodes a Sin3A-associated protein in the histone deacetylase complex
[2] encodes the cell-adhesion protein protocadherinA9

## Pathophysiology

When one ventricle is underdeveloped, the contralateral ventricle can compensate, allowing for normal growth and development of the remaining organs. In patients with HLHS, the RV supports both systemic and pulmonary circulations, and depending on the spectrum might partial or completely replace the physiological role of the LV. In mild cases, systemic circulation is partially dependent on the RV, as antegrade flow from the LV secures flow to the AscAo and the various portions of the ArchAo. While in patients with more severe forms, systemic circulation is completely dependent on the RV, as flow passes retrogradely through the DA into the AscAo and ArchAo. (5,22)

The pulmonary venous return crosses the atrial septum into the RA, either through an ASD or a patent foramen ovale (PFO). When the interatrial communication at birth is mildly restrictive, pulmonary resistance[3] balances systemic (SBF) and pulmonary blood flow (PBF). In contrast, severe restriction leads to an important hypoxemia at birth and represents a hemodynamic emergency. A small amount the mixture blood enters the MPA, and the remaining travels through the DA. Systemic output, delivered via the DA, depends on ductal patency, which without intervention involutes during the first days of life, and systemic circulation fails. Neutze et al. (23) introduced, in 1976, the use of prostaglandin-E infusions to increase ductal patency in cyanotic heart disease, which continues to be used today. (5,22)

There is growing interest regarding the pathophysiology of neurodevelopmental anomalies in patients with HLHS. McElhinney et al. (24) found that cerebral blood flow characteristics in mid-gestation fetuses with evolving HLHS were abnormal, with low pulsatility and resistive, similar to fetuses with established HLHS. Proposing that abnormal delivery of oxygen or energy substrate to the brain, as well as abnormal cerebral arterial hemodynamics resulting from an impaired left cardiac output (CO), is at the essence of poor postnatal neurodevelopmental outcomes in this population.

## Diagnosis, clinical presentation, and management

The structure of the fetal heart, either normal or abnormal, can be defined from 12 to 14 weeks of gestation onwards (25). High-resolution fetal echocardiography has become the diagnostic procedure of choice in structural heart defects as it details fetal cardiac anatomy and function, and its improvements have led to increasing prenatal diagnosis. Pulsed doppler is accepted as an important addition to this two-dimensional procedure,

[3] For any CO the flow given to each circulation is inversely proportional to the resistance of the circulation. The neonate has a high PVR, which decreases only after the first weeks of life, and balance of the competing vascular resistances has been a focal point in surgical approaches. (22)

and cardiac catheterization might also be needed to evaluate the PVR or accessory pulmonary blood flow (APBF) sources. This technology combined with medical experience minimizes the risk of misdiagnosis. (22,26) Despite advancements in the field, recent multicenter data (27) indicates that prenatal diagnosis rates vary from 39 to 75%.

Despite encouraging surgical outcomes, HLHS can place an enormous burden on families, as these patients require lifelong medical attention, numerous hospitalizations, and countless expenses. (28,29) Prenatal diagnosis allows the healthcare team to provide detailed information about staged palliation, primary CTx, in-utero procedures, and the potential for unplanned cardiac interventions, and should include discussion of pregnancy termination and comfort measures only. Comprehensive parental education and counselling gives families the opportunity for more informed decisions. (26) After secondary evaluation at a pediatric cardiac center, reported (27) termination of pregnancy rates varies from 12 to 48%.

Perinatal survival is dependent on systemic circulation through a patent ductus arteriosus (PDA). Death in the first few days of life is generally due to closure of the DA and the consequent decrease in systemic perfusion, which result in a rapid progression to acidosis, cyanosis, and cardiopulmonary collapse. (30) Whereas neonates with restrictive atrial septum, or restrictive/closed FO present after birth with severe respiratory distress, acidosis, and cyanosis. Interventions designed to enlarge the atrial communication might be required in the neonatal period, and even considered throughout fetal development. Infants with unobstructed PBF can develop congestive heart failure or pulmonary vascular disease. Rapid intervention is mandatory in patients with CoA, severe obstruction to PBF or extreme acidosis at first examination. Symptoms might also deteriorate with falling pulmonary resistance in the first weeks after birth. (5,7,22,31)

The anatomic complexity of HLHS, has been considered prohibitive of long survival with or without surgery, and five decades ago comfort care was the only option. (32) Since Fontan revolutionized the treatment of patients with UVH, there are now more options available, multistage palliation, primary CTx and even in-utero interventions. Regardless the preferred approach, early postnatal intervention with administration of prostaglandin-E1 infusion has been associated with improved outcomes. (33) And, when CTx is the intended primary treatment, prenatal diagnosis provides additional time to find a donor and to relocate the family to an appropriate facility for delivery and postnatal surgery. A precise anatomic diagnosis, information on the size of the PAs, degree of PBF, and presence of accessory lesions, as well as assessment of cardiac function is also essential to surgical planning. (5,26)

# Staged palliation

Around five decades ago, in 1970, when reported surgical experience was limited to case reports, the first palliative operation for patients with HLHS was described by Cayler et al. (34) It consisted of an anastomosis between the right PA and the AscAo, along with a right and left branch bilateral pulmonary arterial banding (bPAB). Litwin et al. (35) placed a non-valved conduit from the main pulmonary artery (MPA) to the descending aorta (DescAo) and banded the MPA distal to the conduit. Whereas Doty et al. (36) attempted to connect the partitioned RA to the PAs through a conduit, and in order to provide balance between the SBF and PBF, connected the proximal pulmonary trunk to the Ao with another conduit. None of these techniques presented with encouraging results.

Considering the work of Fontan during the 1970s, Norwood et al. (3) proposed, in 1979, the placement of a valved conduit from the RV free wall to the DescAo, and a PA band on the MPA. Norwood set the stage for a multistage approach, and physiologic correction was achieved by separating systemic and pulmonary circulations using a Fontan-type procedure. It has become accepted to perform an intermediate stage, in the form of a bidirectional cavopulmonary anastomosis (BCPA) or a Hemi-Fontan procedure (HFP), before the Fontan operation, increasing the number of surgeries to three. (15) The first patient with HLHS to successfully undergo the Fontan operation, in 1983, offered hope for infants born with this malformation. (30) However, the gradual decline of patients' functional status indicated the palliative nature of the multistage reconstruction. (37)

Staged palliation is based on the knowledge that an effective circulation is possible in the absence of a pulmonary ventricle and allows the body to adapt progressively to changes in PVR and to vessel size, which reduces operative morbidity and mortality. (38,39) Nowadays, it consists of an initial Norwood operation during the neonatal period, with either a systemic arterial or ventricular source of PBF, followed by a bidirectional Glenn operation (BDG), through the conversion to a superior cavopulmonary source of PBF, or a HFP, undertaken at 4 to 6 months of age, and a Fontan operation completed between 18 and 48 months of age with the addition of inferior caval blood to the pulmonary inflow. (6,40) Since the early 1980s, there have been several optimizations, hoping to better prepare infants to become optimal candidates for the Fontan operation. (15) Moreover significant improvements in preoperative diagnosis, intraoperative technique, and postoperative care, have resulted in a dramatic increase in survival.

# Stage 1: Norwood operation

## Historic perspective

The earliest first-stage operation proposed by Norwood et al. (3) involved the placement of a non-valved conduit between the proximal MPA and the DescAo, together with the ligation of the PDA and banding around the MPA distal to the graft. Then, in 1980, Norwood et al. (32) proposed the placement of a valved conduit between the right ventricular outflow tract (RVOT) and the DescAo. This approach was abandoned in favor of direct anastomosis of the proximal MPA to the AscAo and ArchAo (Figure 5). PBF was established with an aortopulmonary shunt of 4 mm via a polytetrafluoroethylene (PTFE) tube graft from the newly constructed AscAo to the confluence of the PAs. The palliation was completed with creation of a large interatrial communication and ligation of the DA. This approach is recognized as the earliest «Norwood operation», and is considered preferable, as it reduces the length of the suture lines, the likelihood of excessive postoperative hemorrhage, and distortion of the branch vessels of the Ao. (30)

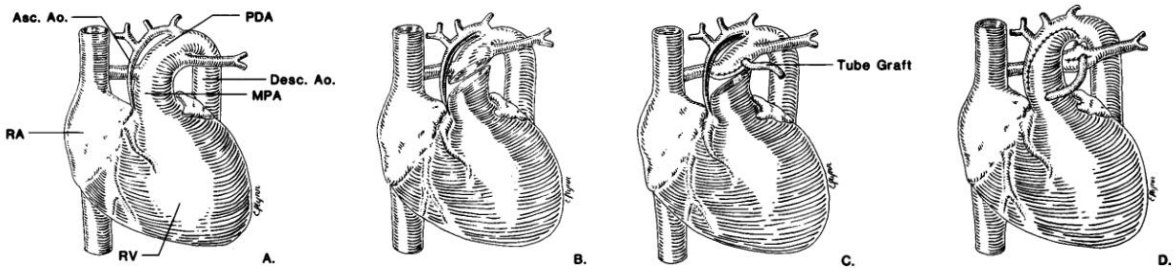


Figure 5: The Norwood operation (A) the MPA is transected, and an incision is made in the AscAo and ArchAo; (B) the distal MPA is oversewn, and the anastomosis of the 4-millimeter shunt established; (C) the MPA is anastomosed to the AscAo and ArchAo, the DA is ligated, and the shunt is completed [Norwood et al., 1983, p. 25 (30)]

The principles of S1P were brought forward by Norwood et al. (3), and are the establishment of a permanent communication between the RV and Ao, limitation of PBF to attenuate the pulmonary vascular changes secondary to elevated PBF and pressure, and insurance of a satisfactory interatrial communication in the presence of MV hypoplasia or atresia. These have been recognized ever since, and continue to apply today, even though the techniques by which they are achieved continue to evolve. Recently, guarantee of adequate coronary arterial perfusion has been recognized as a crucial fourth principle. (15)

## Procedure

The Norwood operation is defined as an aortopulmonary connection and neoaortic arch construction resulting in a univentricular physiology. (15) As a result, this operation leaves the pulmonary and systemic circulations in parallel and the RV to undertake both circulations. The indications for the Norwood operation include AA and MA, as well as anatomic variants characterized by underdevelopment of the left-sided structures in which

survival with the establishment of a biventricular (BiV) heart seems improbable. (41) The individual pathophysiology of patients is crucial to determine whether it is possible successfully to achieve a BiV circulation as opposed to a functionally univentricular repair.

To obtain optimal results and avoid the development of pulmonary vascular disease, S1P should be performed during the neonatal period. Constant infusion of prostaglandin-E1 is required prior to surgery to inhibit physiologic closure of the DA, which decreases the risk of apnea and the rapid decrease of PVR. This procedure entails a systemic-to-PA shunt, a RV-to-PA shunt (RVPAS), or seldom a cavopulmonary connection, and transection of the PA. With the patient cooled and on cardiopulmonary bypass (CPB), the dissection of the ductal remnant and the reconstruction of the ArchAo follow, and a side-to-side anastomosis of the PA to the reconstructed Ao is performed. The use of autologous valvular and vascular tissue in the systemic circulation maximizes both technical simplicity and the potential for growth and development of the reconstructed heart and great vessels. (15,30,40,42,43)

The aim of the Norwood operation is an unobstructed pulmonary venous return across the atrial septum, unobstructed SBF from the morphologic RV to the Ao, nonrestrictive coronary blood flow and adequate PBF with minimal volume overload. (3) As volume overload from excessive PBF lead to a dilated RA, poor coronary perfusion, low CO, and hypotension, which can result in death. (41) This operation is a technical challenge with several complications possible – impairment of coronary perfusion, excessive or obstruction of PBF, neoaortic obstruction, RV failure and bleeding. (44) The original operation has not ceased to evolve since its early days, and some modifications have been incorporated resulting in improvements to survival.

## Optimizations

The classic Norwood procedure entails a modified Blalock-Taussig shunt (BTS) of 3 to 4 mm in diameter from the innominate or subclavian artery to the PA. As PA resistance is lower than systemic, there is a decreased diastolic blood pressure in the aortic root and decreased coronary arterial perfusion, which is considered a risk factor for post-operative mortality. (43,45) Some nonrandomized studies (46–48) began reporting better maintenance of diastolic blood pressure with a non-valved conduit directly from the RV-to-PA, a RVPAS. The RVPAS, also referred to as a Sano shunt, ensures a stable systemic circulation by eliminating pulmonary overcirculation and coronary arterial steal, in contrast, it requires a ventriculostomy, with increased risk to ventricular function and dysrhythmias. (49,50) The Pediatric Heart Network (45) designed, in 2005, a landmark randomized clinical trial which compares outcomes of Norwood procedure with either a

modified BTS or a RVPAS, and randomly assigned 555 patients to one or the other shunt. At the 12-month primary endpoint, infants in the RVPAS group had a 74% transplant-free survival while the BTS group had a 64%. (51) At 3-years, the RVPAS was no longer associated with a superior transplant-free survival. This group required in fact more unplanned surgical and catheter-based interventions. (52) The 6-year results favored the RVPAS with a 5% higher transplant-free survival, but there was no statistical significance. These data support the importance of tailoring the choice of shunt to the experience level of the surgeon. (53)

Shunts have also become smaller over the years, from a standard of 4 to a 3 mm shunt. It is well accepted that optimal results are obtained when smaller shunts are employed. (54) Improved tailoring of the pulmonary allograft patch used for the arch augmentation and reconstruction is also of great importance to maximize results. (40) Vitanova et al. (55) used either a homograft, autologous pericardium, or equine pericardium for ArchAo reconstruction, with a freedom from recoarctation of 85%, 86%, and 30% at 2-years, respectively.

Since the outcomes of the Norwood operation exponentially improved, the concerns have shifted to minimize burden of the disease, and postoperative cerebral damage has been one of the major concerns. Hypothermic circulatory arrest has been a used method for the surgical repair of LV hypoplasia; however, it has been suggested that it might result in neurologic injury. Asou et al. (56) developed a selective cerebral perfusion technique, using a PTFE tube graft, which serves as a systemic-pulmonary shunt after weaning from the bypass, and for patients who weigh less than 3 Kg a specially designed thin-walled, metal-tipped aortic cannula, is used.

## Primary outcomes

Functionally univentricular palliation remains one of the highest-risk and costliest operations performed among CHD. As establishing a stable circulation that is dependent on a single, volume-overloaded RV with altered endothelial function and limited reserve poses a surgical challenge. (40,57) Neonatal death usually results from inadequate coronary and systemic perfusion secondary to high pulmonary to systemic flow ratios. Less commonly, death results from hypoxemia and pulmonary venous congestion secondary to a restrictive interatrial communication. (3)

Between 1984 and 1999, among 840 patients who underwent S1P at the Children's Hospital of Philadelphia, Mahle et al. (58) estimated that the 1-, 2-, 5-, 10-, and 15-year survival rate was 51%, 43%, 40%, 39%, and 39%, respectively. From 1995 to 1998, early

survival improved dramatically, due to introduction of hypoxemia and hypercarbia to balance the systemic/pulmonary flow ratio. Bove et al. (59) reported 158 patients operated from 1990 to 1995, post-operative survival was 76%, and 86% among standard risk patients. Tweddell et al. (57) analyzed 115 patients at the Children's Hospital of Wisconsin, from 1992 to 1996 hospital survival was 53%, whereas from 1996, when continuous venous oxygen saturation monitoring was introduced, to 2001, it improved to 93%. Age >14 days at the time of operation and weight <2.5 Kg were associated with a higher mortality.

Furck et al. (60), evaluated data from 157 patients, who were treated at the University Hospital of Schleswig-Holstein from 1996 to 2007, 30-day mortality after S1P decreased from 21% to 2.5%. Overall actuarial survival was 74% at 1-year and 68% at 5-year. The anatomic subgroup MS/AA and female gender tended to show an increased early mortality. Considering the 549 subjects included in the single ventricle reconstruction (SVR) trial, from 2005 to 2008, Tabbutt S et al. (61) and Tweddell JS et al. (62) reported a 30-day mortality was 12%, and the 1- and 3-year mortality rates were 29% and 33%. Tanem et al. (63) reviewed 177 patients operated between 2006 and 2016, transplant-free survival for standard risk patients – low birth weight, ventricular dysfunction/MV regurgitation, intact or restrictive atrial septum/obstructed anomalous pulmonary venous return, and multiple factors – of 89% at 1-year and 81% at 5-years.

## Secondary outcomes

Some centers have found aortic diameter <2 mm, MA/AA, preoperative acidosis, obstruction to pulmonary venous return, non-cardiac congenital conditions, age >1 months at operation, and weight <3 Kg to predict a higher risk of death. (64) Among patients included in the SVR trial, factors associated with death or transplant included smaller pre-operative TV diameter, the presence of an aberrant right subclavian artery, longer CPB time, longer deep hypothermic circulatory arrest time, higher pre-Norwood lactate value, postoperative ECMO, and steroid use. (61,65) Tweeddell et al. (62) added that early death factors included lower socioeconomic status, and smaller AscAo. Constant factors included genetic syndrome and lower gestational age. Ohye et al. (66) assessed the SVR trial participants, the most common cause was cardiovascular – myocardial failure and low CO –, then multisystem organ failure, with the highest number of deaths occurring during the post-operative period.

Gist et al. (67) showed that postoperative tachyarrhythmias were common, occurring in 34% among 98 patients who underwent S1P at Children's Hospital Colorado, nonetheless conferred no increase in overall mortality. Also, among patients included in the SVR trial (68), 20% presented with tachyarrhythmias, also not associated with interstage mortality,

and 4% with atrioventricular block after S1P, which showed worse short- and mid-term outcomes. 14% met the criteria for heart failure, and after the first 12 months, the risk of developing heart failure was approximately 3% per year. Among 549 infants included in the SVR trial, White et al. (69) reported that 10% experienced a first-time thrombotic event during the interstage period, and 61% of all thrombotic events occurred during the Norwood operation hospitalization period. According to a systematic review (70) published in 2016, including 15 cohort studies, incidence of thrombosis ranged from 0% to 40% with an overall mortality ranging from 4.5% to 31% across studies.

Following the SVR trial (40), neurodevelopmental outcomes were analyzed at 14-months and again at 3-years for the SVR trial. Using the Psychomotor Development Index and Mental Development Index of the Bayley Scales of Infant Development-II at 14 months, overall, the average scores were below normal means. The Ages and Stages Questionnaire was used for 3-years, all domains for the study subjects demonstrated means lower than the reference population, and at least 51% of the cohort demonstrated delay in at least one domain. The Functional Status, 2nd Edition Revised, demonstrated lower total and lower activity scores than the reference population. These neurocognitive abnormalities, among patients with HLHS, are common, and likely associated with structural brain abnormalities or may be acquired due to circulatory insufficiency inherent to the univentricular physiology, and not necessarily a consequence of surgical trauma. (71,72)

## Alternatives

The Hybrid procedure was proposed, in 1993, by Gibbs et al. (73) as a less invasive approach to palliate neonates with HLHS. The procedure would begin with the stenting of the arterial duct combined with bPAB and atrial septostomy. However, based on eight unsuccessful experiences, the authors (74) no longer recommended ductal stenting as a palliation. Later a successful surgical-interventional approach was achieved by performing bPAB via a brief open-chest procedure, with a mortality rate <1%, followed by a second elective percutaneous transcatheter arterial duct stenting, with or without atrial septum manipulation. (75) A Hybrid Stage I would be followed by a comprehensive S2P, also referred to as combined Norwood 1 and 2 with reconstruction of the ArchAo and BCPA, and later completion of the Fontan. (76)

Between 1998 and 2000, 11 newborns had ductal stenting performed with a balloon-expandable peripheral stent, followed by bPAB. Both procedures were performed with no mortality. Akintuerk et al. (77) showed that a Hybrid operation allows the combination of neoaortic reconstruction with a BCPA, as well as the chance for CTx with the extension of the waiting period. Gallantowicz et al. (76) conducted a retrospective review on all patients

undergoing a Hybrid operation, divided into pre-protocol, from 2002 to 2010, and post-protocol – age >3 months and avoidance of emergent comprehensive S2P –, from 2010 to 2014. Care modifications instituted resulted in a significant decrease in mortality from 19% to 4%. A retrospective study conducted by Schranz et al. (78) between 1998 and 2013 reported a hospital mortality following initial Hybrid palliation around 1%, interstage mortality was 7% and for comprehensive S2P was 9%. At 1-year, the survival rate of HLHS and variants was 84%, and at 15-year was 77%.

The early success with the Hybrid operation have prompted the increasing use of this strategy in patients with high-risk factors. This approach avoids the Norwood procedure in the newborn period entirely and allows postponement beyond the newborn period before committing to one versus two-ventricle repair. This form of palliation may also have a place in stabilizing the neonate who is on a transplant trajectory, and whose wait for a donor heart is prolonged. Following the comprehensive S2P, the completion of Fontan circulation can be performed with low mortality, however, it requires more intensive follow-up and more frequent interventions in the period between S1P and S2P. (40)

## Stage 2: Glenn operation

### Historic perspective

Diversion of blood from the SVC to the right PA was experimented by Carlon in 1951, and clinically used by Glenn (79) (Figure 6) to increase PBF in cyanotic congenital cardiac lesions. (80) An anastomosis was performed between the distal end of the right PA and the side of the SVC at the level of its junction with the azygos vein. The SVC was then ligated at its entrance into the RA. Significant improvement in arterial oxygen saturation and exercise tolerance was achieved since operation. Modifications by Haller et al. (81) were made in 1966 to include a bidirectional SVC-to-PA anastomosis without PA division and allow bidirectional pulmonary arterial distribution after the Fontan operation.

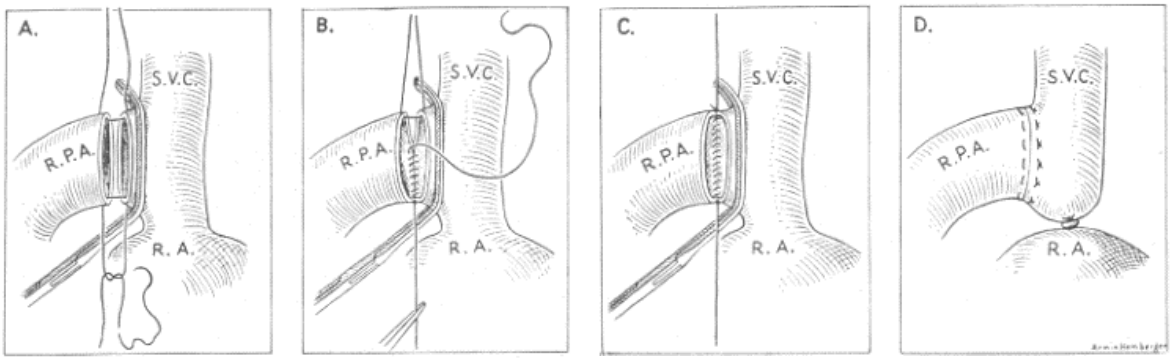


Figure 6: The bidirectional Glenn operation. Drawing illustrates the anastomosis technique between the SVC and the right PA to achieve a BCPA. [Glenn., 1958, p.119 (79)]

The original Fontan operation included a classic SVC-to-right PA shunt and survivors of the Norwood operation were staged directly to the Fontan operation, with significant morbidity and mortality. Hopkins et al. (80) concluded, in 1985, that this bidirectional shunt provided excellent relief of cyanosis, and could be done before, with, or after a Fontan operation. An intermediate stage was introduced in 1988, in the form of a superior BCPA, or a HFP, increasing to three the number of operations in the multistage palliation. It was an important step in reducing mortality from the Fontan procedure, as patients generally remain well palliated, until they reach an age when they are more suitable candidates for last stage palliation. (22,59)

## Procedure

Progression to the BDG is possible at 3 to 6 months, with clamping of the SCV at its insertion into the RA, above the sinoatrial node, and transection. Following the atrial orifice being oversewn, the pulmonary remnant of the arterial shunt/conduit is excised. A pulmonary arteriotomy is performed to accommodate the SVC. The BCPA represents a fundamental part of the Fontan circulation as much more desaturated venous blood enters the PA, and therefore a higher uptake of oxygen per mL of blood is achieved. Systemic venous return is diverted to the lungs, thus eliminating the existing, high-pressure, arterial, or ventricular source of PBF and reduces the volume load on the SV. This helps prevent ventricular hypertrophy, subendocardial ischemia, and eventual diastolic dysfunction, which impact long-term ventricular function, and accounts for higher arterial saturations. The second stage reconstructive procedure is an optimal time for correction of additional risk factors, including TV regurgitation, PA hypoplasia, residual obstruction to pulmonary venous return, and systemic outflow tract obstruction. (22,41,65,82,83)

## Optimizations

Evidence regarding the optimal timing of S2P was limited. Jaquiss et al. (84) divided 85 patients undergoing BCPA into group I and group II, <4 and >4 months respectively. No deleterious outcomes prior to multistage palliation completion, nor after, were however, younger patients were more cyanotic post-surgery and required more resources. Petrucci et al. (85) lowered the age limit to <3 and >3 months and, although younger patients also required higher resource use, S2P was proved feasible and safe in patients as young as 2 months old. Lee et al. (86) reported that age younger than 3 months was associated with worse outcomes, whereas Viegas et al. (87), in a cohort divided in median age for BCPA of 79 days and of 107 days, there were no differences in late mortality rate. Meza et al. (65) analyzed the SVR trial data set, and the interval of 3 to 6 months after Norwood for patients with minimal risk factors was associated with maximal calculated 3-year, risk-

adjusted, transplant-free survival. As for patients with multiple risk factors, transplant-free survival was severely compromised, regardless of the timing of S2P.

From 1986 through 1998, among 149 patients undergoing BDG, 93 patients had elimination of all sources of APBF, whereas 56 patients had either a shunt or a patent RVOT. The operative mortality rate was 2% without APBF and 5% with APBF, whereas the late mortality rate was 4% without APBF and 15% with APBF. These results suggest that the elimination of APBF at the time of BDG may confer a long-term advantage for patients with a functional SV. (88)

## Primary outcomes

Among infants who underwent some form of bidirectional cavopulmonary shunt at the Children's Hospital in Boston between 1983 and 1993, the actuarial survival rate at 3-years for patients undergoing a BCPA was 86%, superior to other second-stage approaches. (89) From 1989 through 1992, 50 consecutive infants underwent the BDG at C.S. Mott Children's Hospital in Michigan, 21 with HLHS. Actuarial survival was 92% at 1-month. PA distortion and higher PVR were indicated as significant risk factors for death. (82) Jaquiss et al. (84) reported a hospital survival of 100%, and an actuarial survival at 1-year of 96% for both patients under and above 4 months. Scheurer et al. (90) analyzed pre- and post-operative characteristics of 167 patients, and after BCPA freedom from death or transplantation was 96% at 1-year and 89% at 5-years. From a 14-year experience at the Children's Hospital of Pittsburgh (87), there were no operative mortalities in the cohort, and overall interstage mortality rate was 4%. In a large cohort of patients undergoing S2P over a 30-year period (91), mortality has decreased to only 1% in the most recent era. The results of the S2P procedure as an intermediate stage of single ventricle (SV) physiology have been reproducibly excellent, exceeding 95% survival rates in various reports. (22,80,92) Mendelsohn et al. (93) also reviewed infants and children who underwent the BDG at C.S. Mott and found a significant decrease in mean PA pressure and ventricular end-diastolic pressure, a significant increase in systemic arterial saturation after the BGD.

## Secondary outcomes

Despite impressive results with the Glenn anastomosis, Hopkins et al. (80) recognized some difficulties, such as the development of collateral venous channels from SVC to IVC, pulmonary arteriovenous fistulas, abnormalities in regional pulmonary perfusion, and difficulty in dismantling the shunt. Mendelsohn et al. (93) was the first to describe changes in PA size, and these findings raised concerns, as PA stenosis or hypoplasia was regarded as a risk factor for poor outcome after the Fontan operation. Scheurer et al. (90) analyzed preoperative characteristics of 167 patients with preoperative atrioventricular

valve regurgitation being appointed as an important risk factor for death or transplantation after 1-year. Moderate or greater TV regurgitation and low weight z-score at the time of BDG were considered by Carlo et al. (94) important risk factors for death or CTx. Kogon et al. (92) highlighted the adverse effect of prolonged CPB time, elevated central venous pressure and transpulmonary gradient. Lower weight z-score was also associated with an increased risk of postoperative BDG complications.

## Alternatives

Introduced by Norwood and Jacobs (95) in 1998, to tackle low CO posterior to the original Fontan operation, the HFP (Figure 7) involves associating vena cava venous return to the central PAs. Separate patches are used to augment the central PAs and allow for a connection between the RA-to-SVC junction and the PAs with elimination of other sources of PBF. By making use of normal growth potential of the surgical pathways, HFP allows early normalization of ventricular function, eliminates prosthetic valves, avoids artificial conduits, and avoids a large high-pressure systemic venous reservoir. Lee et al. (86) presented routine augmentation of the proximal branch PAs as one advantage of the HFP.

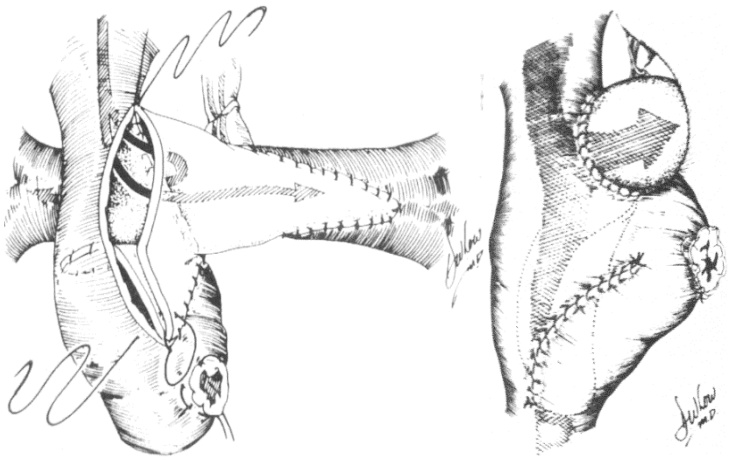

Figure 7: The Hemi-Fontan procedure. Drawing illustrates (1) the PAs are opened anteriorly and augmented with a homograft, and the same graft is used to create a roof over the anastomosis of the SVC-to-PAs, and to close the junction of the RA with the SVC; (2) completion of the Fontan operation with a LT [Norwood et al., 1993, p.549-550 (95)]

Some surgeons have reported better survival for the Fontan procedure after the HFP than the BDG. Norwood and Jacobs (95) reported a substantial difference in early mortality for a primary-Fontan operation when compared with a completion-Fontan operation, the latter achieving superior survival rates. Marshall et al. (96) obtained similar low operative mortality rates, as did Douglas et al. (97). This procedure simplifies the posterior Fontan operation in cases using a lateral tunnel (LT) Fontan. Centers which prefer the LT, have optimal outcomes in the progression to the Fontan circulation.

Some authors agree that HFP provides a more favorable total cavopulmonary connection, sparing more energy, as well as minimizing the potential for late development of atrial fibrillation or flutter. On the other hand, HFP involves some technical difficulties, and

requires CPB with cardioplegic arrest. Cohen et al. (98) also reported a higher incidence of sinus node dysfunction post-surgery in patients undergoing HFP, no differences were reported by the time of hospital discharge. Avoidance of the sinus node during HFP has not altered the early development of sinus node dysfunction. Understanding the hemodynamic performance of surgical operations, allowed Bove et al. (99) to consider the HFP and BDG procedures outcomes similar, with equivalent energy losses and almost equal flow distributions to the lungs. Further follow-up might be necessary to understand whether these differences have implications for long-term outcomes.

## Stage 3: Fontan operation

### Historic perspective

Fontan and Baudet (38) introduced, in 1971, a new surgical procedure to repair tricuspid atresia (Figure 8), designed to restore physiological PBF by transmitting the whole vena caval blood to the lungs and ensuring only oxygenated blood would return to the left heart. The RA directs the IVC blood to the left lung and the right PA receives the SVC blood through an atriopulmonary anastomosis. This technique was experimented in three patients, being successful in two of them. Its success demonstrated that it is possible to use the RA as a pumping chamber to maintain a normal pulmonary circulation and adequate CO both at rest and on effort. (100)

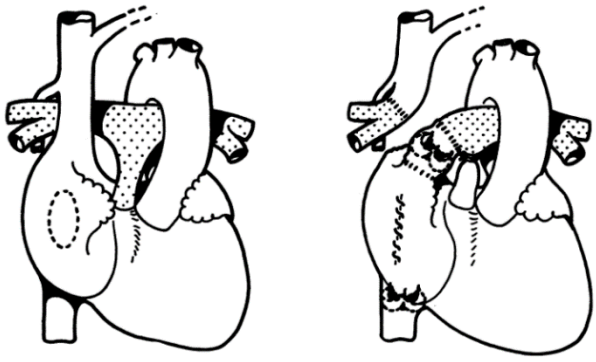

Figure 8: The Fontan operation. Drawing illustrates steps in surgical repair: end-to-side anastomosis of distal end of right PA to SVC, end-to-end anastomosis of RAA to proximal end of right PA by means of an AV homograft, closure of ASD, insertion of a pulmonary valve homograft into IVC, and ligation of MPA. [Norwood et al., 1983, p. 25 (38)

Since its introduction, the Fontan operation has undergone a steady evolution. Kreutzer et al. (101) described an end-to-end anastomosis between the right atrial appendage (RAA) and the PA, with a pulmonary homograft or patient's own pulmonary annulus. Björk et al. (102) attempted to anastomose the RAA to the RV with an autologous pericardial patch, avoiding foreign materials. Two patients were reported by Stanford at el. (103) after correction of tricuspid atresia with insertion of an aortic allograft conduit between the RA

and PA with additional placement of a pulmonic valve allograft at the IVC-RA junction. Leval et al. (104) developed an approach to exclude most or all the RA, a total cavopulmonary connection, and suggested it would avoid damage to the atrioventricular node. The Fontan procedure with its various modifications currently is the treatment of choice for children with SV physiology. The ultimate success of the Fontan operation depends on suitably low PVR and adequate PA architecture. Advances over the past decade have improved both early and late outcomes. (105)

## Procedure

During the last stage of palliation, the Fontan operation, which is usually performed between 18 and 48 months of age (6). IVC desaturated blood return is connected to the PAs without the interposition of an adequate ventricle. To complete the separation of the pulmonary and systemic circulations, a conduit is placed in the lateral wall of the RA, or an extracardiac conduit (EC). The absence of ventricular pump and creation of passive venous flow through the cavopulmonary circuit results in an elevated central venous pressure. (106) It also leads to a relatively low CO state, and chronic ventricular volume depletion. A fenestration can be created between the medial wall of the conduit and RV, to allow decompression of the atrial conduit pathway into the systemic atrium. This technique depends on the size of the PAs, therefore, younger children or those with smaller PAs would be treated by palliative surgical procedures. Small size of the PAs is a risk factor for death or takedown after the Fontan operation, and the smaller the PAs the greater the risk. For a successful Fontan operation, characterized as having a good CO at an acceptable systemic venous pressure, there are some cardiac and pulmonary requirements, which have evolved along the years. It requires unobstructed ventricular inflow, reasonable ventricular function, and unobstructed outflow, as well as non-restrictive connection from systemic veins to the PAs, which must have a good size and no distortion, normal PVR, and unobstructed pulmonary venous return. Advantages of the Fontan circulation include normalization of the arterial saturation, and abolishment of the chronic volume overload, however chronic hypertension, congestion of the systemic veins, and decreased CO might arise. (22,28,38,39,107)

## Optimizations

Progressive atrial dilatation, and arrhythmias and thromboembolic complications of the original atriopulmonary have led to modifications of the original atriopulmonary connection, with the LT technique and the EC (Figure 9). (22,108) The LT provides a path between the IVC and the PA, consisting of a prosthetic baffle and the lateral atrial wall. This circuit has potential for growth, but multiple atrial suture lines and part of the atrium being exposed to high venous pressure, allowed the EC to gain acceptance. The EC conduit

consists of a tube graft between the transected IVC and the PA, that leaves the entire atrium at low pressure. With minimal atrial suture lines, performed without aortic cross clamping, or even without CPB, it optimizes early postoperative outcomes, and maintains a stable hemodynamic state. (39)

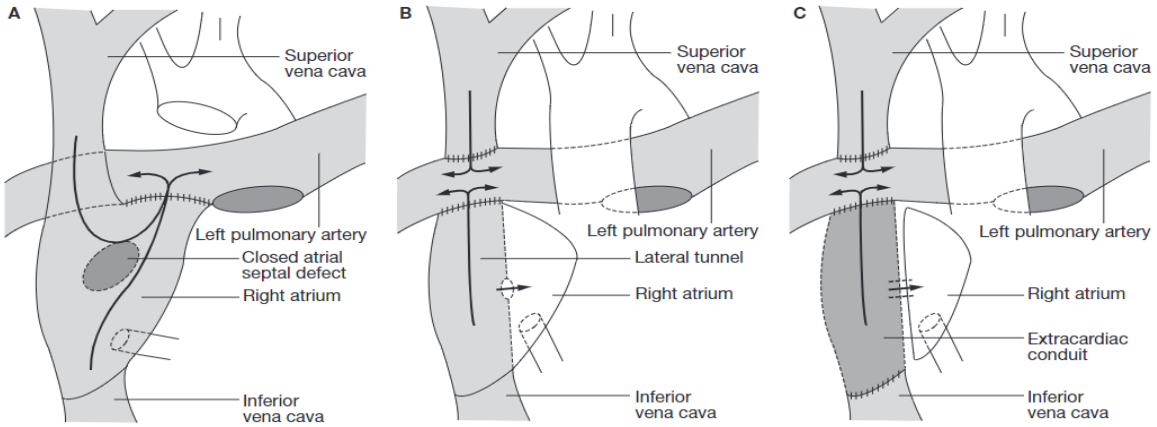


Figure 9: Modifications to the original atriopulmonary connection. Drawing illustrates (A) the original atriopulmonary connection; (B) the LT; and (C) the EC. [Leval 2005, p. 203 (109)]

Authors have conflicting outcomes between approaches. On the one hand, d'Udekem et al. (110) reported a 15-year survival of 94% after a LT, compared to an 81% after an atriopulmonary connection. Undergoing a LT predicted a 15-year freedom from supraventricular tachyarrhythmias superior to the atriopulmonary connection. Fiore et al. (111) exhibited an operative mortality of 2%, and survival at 5-years was 95% for a LT compared to 90% for an EC. Robbers-Visser et al. (112) reported that at 6-year, freedom from Fontan failure was 83% for the LT and 79% for the EC patients, freedom from late reoperations was similar in both groups, and freedom from arrhythmias was inferior to the EC. Stamm C et al. (113) estimated a survival with the LT of 93% at 5-years and 91% at 10-years, with low evidence of atrial tachyarrhythmia. Kumar et al. (114) reported comparable early and mid-term results, and having a LT with a prior HFP, required fewer intra-atrial interventions. Stewart et al. (115) concluded that the LT Fontan might be associated with superior early outcomes in freedom from revision, Fontan failure, and shorter postoperative hospital stay. Azakie et al. (116) reported a significantly higher incidence of postoperative sinoatrial node dysfunction, supraventricular tachycardia, and need for temporary postoperative pacing.

On the other hand, Azakie et al. (116) reported an operative mortality of approximately 5%, which did not differ between conduits, and survival was 94% at 1-month, 92% at 1-year, and 92% at 5-years. The total cavopulmonary connection using the EC is considered easier to perform, especially in patients with extensive prior surgery. (117) There are several advantages to the EC cavopulmonary anastomosis, including the ability to

complete the Fontan circulation without cardioplegic arrest of the heart and with minimal duration of CPB. In some cases, McElhinney et al. (118) and Yetman et al. (119) consider EC possible without CPB altogether in selected patients. Another promising advantage is its potential to reduce supraventricular arrhythmias, which are an important cause of morbidity and mortality after the Fontan operation. The EC prevents elevated systemic venous pressure in the RA, extensive atrial incisions, and suture lines, intracardiac prosthetic material, and ventricular dysfunction. There are also potential disadvantages related to the EC, including lack of growth potential, conduit stenosis, and thromboembolism. (117,120) Iyengar et al. (121) half the patients undergoing EC will suffer a late adverse event by the age of 14 years.

Bridges at el. (122) raised the question of whether ventricular dysfunction, elevated PVR, and residual distal PA distortion were transient or reversible, and proposed the surgical creation of a baffle fenestration. The fenestration, allowing right-to-left shunting, maintains CO, limits RA pressure, and diminishes the risk of a low output state and its consequences. Patients with a baffle fenestration had shorter hospitalizations, decreased pleural drainage, lower postoperative RA pressure, and better outcome when compared to patients without a fenestrated baffle. Fenestration was not associated with post-Fontan stroke, ventricular dysfunction, thrombosis, PLE or arrhythmia. Most fenestrations were later closed in the catheterization laboratory, nonetheless, a significant percentage had spontaneous closure. (98,122–125) After 20 years of follow-up, Ono et al. (126) highlighted that fenestrated patient had significantly lower incidence of late tachyarrhythmias, and higher cardiac index than other types of Fontan procedure. Yet, Lemler et al. (123) suggested that not every patient requires a fenestration to achieve a good outcome. Some authors (120,127) prefer performing fenestration only in selected cases, who demonstrate objective evidence of poor or marginal postpump hemodynamics.

## Primary outcomes

Fontan et al. (37) estimated the survival rate after the Fontan operation under optimal conditions between 1968 and 1988 to be 88%, 86%, 81%, and 73% at 1-, 5-, 10- and 15-years, respectively, with a perioperative survival of 92%. From 1975 through 1984, Laks et al. (128) reported an overall survival of 89% with a mean follow-up of 2 years. In early survivors, Khairy et al. (129) estimated an overall actuarial freedom from death or CTx at 1-, 5-, 10-, 15-, 20-, and 25- years was 97%, 94%, 90%, 87%, 83%, and 70%, respectively. Between 1980 and 2000, d'Udekem et al. (110) reported a 3% mortality rate, with no deaths after 1990, and a 20-year survival of 84%. Authors suggested these results to be related with improved patient selection, better adjustment of PBF, and to staging with BDG. Hirsch et al. (83) reported a hospital survival of 96%, and the 5-, 10-, and 14-year

survival was 95%, 93%, and 91%, respectively. 98% of long-term survivors presented with a New York Heart Association functional classification (NYHA) I or II and a normal or mildly reduced ventricular function. Over an 18-year period, Rogers et al. (130) estimated a perioperative mortality rate similar to d'Udekem et al. (110), with mortality decreasing 1% from 1996 to 2009. Ventricular dysfunction, elevated PVR, and residual distal PA distortion contribute to early mortality with death occurring in the clinical setting of a low output state, and elevated RA pressure. (124,131)

The outcomes after conversion to the Fontan circulation are better than initially expected. Changes in patient selection, pre- and postoperative management, along with improved surgical techniques, have contributed to minimize perioperative mortality to 1%. (39,110,132) Current expectations point towards the current cohort of patients performing better than the early series. These outstanding results include all patients palliated with a Fontan operation, pulmonary atresia, LV hypoplasia and other congenital heart malformations, therefore must be interpreted with caution. Patients diagnosed with a single morphological RV have been associated with higher perioperative mortality rates, poorer ventricular and valvular function, and higher risk for heart failure. (83,105,130,133–135) d'Udekem et al. (108) described HLHS as the primary predictor of Fontan failure and reported a 10-year freedom from failure of 79% for patients with HLHS compared to 92% for other morphologies. Authors have indicated that the structure of the RV is suboptimal for a systemic ventricle. (134)

## Secondary outcomes

Evidence that chronic elevated venous pressure and decreased CO associated with the Fontan physiology contributes for the functional progressive decline of patients palliated has become indubitable, as survivors grow into adulthood. (71) During the first months of life, the volume overload in the SV leads to dilation and spherical reconfiguration, cardiac overgrowth, and hypertrophy. Post-Fontan operation, some normalization might occur, however, manipulation of atrial tissue can result in impaired chronotropy, which further limits CO and proper response to demand. Overall vascular resistance and ventricular afterload are increased, and an increase in the mesenteric vascular resistance might be a response to low CO and a compensatory attempt to redistribute blood flow to vital organs. (39,106,136,137) The surviving cohort presents with multiple early and late complications such as: tachycardia, palpitation, transplantation, reoperation, stroke, tachy- and bradyarrhythmia, as well as thromboembolic events, bleeding, protein-losing enteropathy (PLE), and poor functional status. In a cohort in Australia and New Zealand (121), 47% of survivors experienced an adverse event within 15 years.

Some studies have reported poor exercise performance and decreased peak oxygen consumption at ventilatory anaerobic threshold after the Fontan procedure. Others demonstrate that exercise capacity is well preserved, with normal peak oxygen consumption. Paridon et al. (138) reported that only 28% had a normal peak oxygen consumption, and d'Udekem et al. (139) that cardiopulmonary performance would increase up to a certain level, after which the Fontan circuit became too restrictive to allow any further increase in CO. Patients with patent fenestrations have a higher CO than those with no right to left shunting. In these patients, low stroke volume index at maximal exercise was proposed as the most important factor limiting exercise capacity. Male subjects going through puberty become unable to meet the metabolic demands of the increased muscle mass during exercise. (138) Training programs in patients with a stable hemodynamic status result in improved aerobic capacity, ventilatory anaerobic threshold, and respiratory indices, and can be performed without adverse effects. (140,141)

The development of intra-atrial reentrant tachycardia is one of the most prevalent complications and might be the first sign of deterioration of the Fontan circulation. (142) Carins et al. (143) found atriopulmonary Fontan, higher immediate postoperative right atrial pressures and reduced ventricular function to be predictors of developing arrhythmias. Pundi et al. (132) reported a freedom from arrhythmia at 10-, 20-, and 30-years after the Fontan operation was 71%, 42%, and 24%, respectively. In a cohort from Australia and New Zealand (143), within 10 years after onset of any arrhythmia approximately half of patients experienced failure of Fontan circulation. In a population of patients with Fontan physiology who survived to adulthood (144), the presence of atrial arrhythmia was significant, 40% of patients having a previous atrial arrhythmia, higher than studies in pediatric populations. Among patients with tachyarrhythmias, 86% were prescribed at least one antiarrhythmic medication. Electric cardioversion was performed in 50% at a median of 5 years after the initial onset, and radiofrequency ablation in 34% of the patients with tachyarrhythmias. A pacemaker was implanted in 89% of patients with bradyarrhythmias. (142,143)

Thrombi are an important complication after a Fontan operation, and its incidence is often underestimated. (145) Lack of a subpulmonic pump, venous stasis and low CO, factors inherent to the Fontan physiology, and an imbalance in coagulation proteins might explain thrombus formation. Deficiencies in protein S, protein C, factor VII, and antithrombin III have been described, possibly related to poor hepatic function. (144,146) The use of synthetic material in the operation, and the presence of cardiac arrhythmias were also credited for the development of such events. (147)

Rosenthal et al. (147) estimated an overall occurrence rate of 20% in a cohort without early postoperative heparin therapy. Thrombotic events were seen as early as the perioperative period, and the risk for such events persisted during the follow-up period. Coon et al. (146) detected intracardiac thrombi in approximately 9% of patients after Fontan operation, while Balling et al. (145) in 33%. Thrombus occurred in patients both on aspirin therapy and on warfarin therapy, occurred similarly in atriopulmonary or LT type Fontan modification, and in patients with or without fenestration. Despite awareness surrounding thromboembolic events, optimal preventive measures are unclear, particularly when patients on aspirin or warfarin are also at risk. (144,146) Routine transesophageal echocardiography might be beneficial to exclude eventual thrombi. (145,147)

PLE is defined as the abnormal loss of serum proteins into the lumen of the gastrointestinal tract, with hypoalbuminemia and hypoproteinemia. Elevated central venous pressure increases lymphatic fluid and at the same time impedes drainage, as result intravascular oncotic pressure reduces and fluid steps into the interstitium. (136,148,149) Mesenteric chronic low flow has also been found in patients with PLE. (136,137) The incidence of PLE, in a cohort of 3029 patients (149), was almost 4%, with a median age at diagnosis of 12 years. Fedt et al. (150) estimated a risk by 10 years of 13%. Incidence seems to increase throughout the years post-Fontan operation. Common symptomatology includes peripheral edema, diarrhea or steatorrhea, abdominal bloating or pain, and effusions within the pleural and pericardial spaces. (148,149) Imaging is possible using MRI, and techniques of direct cannulation of lymphatic channels and lymphangiography. (106) Once the diagnosis is established, medication is focused on symptomatic relief, optimizing hemodynamics, or to prevent further complications. Dietary changes are also recommended. (39) When these strategies fail, the patient is considered for circuit fenestration. If both these strategies fail, or the patient is at particularly high risk for mortality, CTx should be considered. Continued follow-up is necessary to identify those in whom PLE may develop in the late follow-up period.

Elevated systemic venous pressure and the impedance to hepatic venous flow imposed by the Fontan physiology leads to a state of chronic hepatic congestion, and over time hepatic dysfunction might develop. It has been suggested that all post-Fontan patients have some form of hepatic fibrosis, from mild centrilobular changes to cirrhosis. Some cases of hepatocarcinoma have also been described. (71,106) The pathophysiology is thought to share some similarities with cardiac hepatopathy, and its evaluation and management requires a biopsy. (151) Clinical presentation is often subclinical and can be disguised by symptoms and signs of right-sided heart failure. (152) In the case of failing Fontan

circulation, there might be changes in drug clearance and hepatic encephalopathy. (106) Hepatic chronic passive congestion, which is usually a consequence of right-sided heart failure, and centrilobular necrosis, usually a consequence of severe hypotension or shock, are common findings in autopsy. Prolonged chronic congestion can also lead to the development of cardiac cirrhosis, approximately 11 to 15 years after a Fontan procedure, which could result in a hepatocellular carcinoma and be fatal. Patients who undergo the Fontan procedure must be carefully followed. Careful surveillance might be needed in these patients. (152,153)

Pathophysiologic interactions between the cardiovascular system and advanced non-cardiovascular end-organ dysfunction play an important role in the "failing" Fontan circulation. The concept of this failing phenotype remains unclear, and can include postoperative complications, high central venous pressure, low arterial blood oxygen saturation, systolic and diastolic SV dysfunction, hepatorenal dysfunction, glucose metabolism abnormalities, and even bone and nutritional problems. (154)

## Final considerations

From a 0% survival rate to an exponential increase in the number of patients who become adolescents and adults, the multistage reconstruction has revolutionized the fields of pediatric cardiology and cardiac surgery. The Norwood operation outcomes have exceeded all expectations with continuous improvements in the surgical techniques and can now be performed with low mortality rates. Optimizing the outcomes of the comprehensive S2P has allowed a smoother transition to the last stage palliation, the Fontan circulation. Improvements in management, from preoperative diagnosis, patient selection criteria to intraoperative technique and postoperative care, have contributed to a substantial improvement in survival rates. AT the same time, technical optimizations have aimed at the morbidity associated with the Fontan physiology. Even so, some infants and children do not respond to these operations, and CTx has become a salvage therapy.

These series of palliations offer infants born with HLHS improved quality of life with increased exercise tolerance, and good intermediate- and long-term outcomes. Nonetheless, with a growing number of patients surviving into adolescence and adulthood, the unique long-term challenges associated with the Fontan circulation have become more and more evident. As long as the multistage palliation represents the paradigm of care for patients with HLHS, focus must be placed on identifying modifiable variables that contribute to end-organ consequences, and consequent circulatory failure. Physicians must continue exploring preventative and therapeutic strategies to optimize the Fontan circulatory state and minimize the burden of the disease.

# Transplantation

## Historic perspective

Cardiac replacement in newborns with HLHS was first attempted by Magdi Yacoub in 1984, however, only became recognized as a possible alternative therapy to multistage palliation after the clinical trial of cardiac xenotransplantation. (155) During the trial, Leonard Bailey performed more than 200 experimental animal transplantations, then proceeding to investigate potential animal donors for humans. (156) Baboons were the animal donors chosen, and in October 1984, Leonard Bailey and his team (4) transplanted the heart of a 7-month baboon into a baby girl, “Baby Fae”, who had been born with LV hypoplasia. She died 21 days after CTx, when her body rejected the baboon heart, later it became known that her blood type did not match the baboon’s.

In November 1985, Bailey performed the first successful transplant of a human heart into a human baby, “Baby Moses”. He was still alive in 2019 with the same transplanted heart and remained the longest living recipient of an infant heart transplant. Bailey went on to transplant 376 human hearts, earning a global reputation as a pioneer in infant CTx. (156) These groundbreaking contributions established CTx as a primary treatment option in infants with HLHS. The main advantage is the replacement of a functionally univentricular heart (UVH) in which the RV is fulfilling a systemic role with a normal heart possessing four chambers and normal physiology. Although survival is excellent, the approach has been limited by the inadequate availability of donor hearts. (15)

## Procedure

Infants awaiting a suitable donor are palliated with continuous prostaglandin E1 to maintain ductal patency. Bourke et al. (157) also highlighted the benefits of maintaining a PBF:SBF ratio ≤1:1, minimal fraction of inspired oxygen, and avoidance of elective atrial septostomy. CTx should optimally be performed in the neonatal period to decrease waiting-associated mortality and the deleterious effects of prolonged low CO. The arterial duct can be stented, and the branches of the pulmonary trunk banded, to stabilize blood flow prior to transplantation. Infants with restrictive FO tend to experience progressive hypoxemia, heart failure and even systemic organ dysfunction during the waiting period and might require enlargement of the interatrial communication. (155,158,159)

Orthotopic CTx remains a challenging procedure and requires an experienced team, as it involves some important steps from recipient preparation to graft harvest and actual transplantation. The procedure begins with a midsternal incision, followed by isolation of the ArchAo branches. Extracorporeal perfusion is established, and the patient is cooled.

Follows ligation and excision of the DA. The recipient heart is excised, the MPA transected at the bifurcation into right and left PAs, and the AscAo transected proximal to the brachiocephalic trunk. The donor heart, intermittently bathed with 4°C saline, is inserted and anastomosed. The patient is rewarmed, and spontaneous cardiac contractions begin early and progress to regular sinus rhythm. Residual defects that cannot be corrected by implantation of a normal heart should also be addressed during CTx. (160)

## Primary outcomes

Transplantation procedures were performed in 84 at Loma Linda University from 1985 to 1991, 32% died awaiting a donor heart, operative mortality was 13% and 5-year survival was 61%. Chiavarelli et al. (159) reported a 5-year survival of 81% and freedom from reoperation was 89% in transplant recipients. Among 176 infants with HLHS in a CTx-protocol from 1985 to 1995, survival at 1-month and at 1, 5, and 7 years improved to 91%, 84%, 76%, and 70% respectively. (158) Chrisant et al. (155) accessed data from the 20 institutions between 1993 and 1998. About 25% of infants with HLHS died while waiting for transplantation, the primary cause of death being cardiac failure, and 9% underwent Norwood or Fontan-type surgeries. Post-transplant survival was 72% at 5-years, with most deaths occurring within 3 months primarily caused by graft failure. Stackhouse et al. (161) revealed that between 1994 and 2000, survival after primary CTx was better than after surgical palliation with fewer symptoms, and equivalent health-related quality of life. The institutional pediatric heart transplant database (162), from 1985 to 2017, revealed a survival at 10 years and 25 years of 74% and 56%, respectively. Freedom from retransplantation was 81% at 20 years.

Survival after CTx has significantly improved over the years. 1-year survival in the 1980s was around 70%, and contemporary 1-year survival is over 90%. (163) Jenkins et al. (64) reported that patients with atresia of one or both valves had worse 1-year mortality in the staged palliation, therefore being considered better candidates for CTx. Children transplanted in the newborn period have the potential to reach adulthood with long-term survival and minimal need for reintervention. Although CTx offers the potential for a normal cardiovascular physiology as opposed to the limitations of the Fontan circulation, pediatric CTx waiting list mortality remains too high in the current era due to shortage of heart donors. (158,164)

## Secondary outcomes

Early death is usually related to technical issues, graft failure, infection, or rejection, which are recognized as the major cause of death in pediatric recipients, also represent a major

concern following CTx because early diagnosis is often challenging. Excessive CO and systemic hypertension associated with larger donor hearts might contribute to recipients' cerebral edema, and visceral and renal vasospasm. However, due to the severe shortage of pediatric donors, size matching the donor heart with the infant recipient is not a straightforward assignment. (158) Infants transplanted present no limitations on physical activity and only 1% required total assistance in daily activities. (163)

Moreover, this procedure requires lifelong immunosuppression, with the chance of rejection, infection, graft atherosclerosis, malignancies, and side effects of its lifelong use. Common side effects of immunotherapy such as mild hirsutism and gingival hyperplasia are minimal beyond the first 6 to 12 post-transplant months. Delayed bone age maturation and growth impairment have also been described in children taking corticosteroids, however, after its discontinuation, growth velocity normalized, and most infants have ultimately shown normal growth. (15,158,159) Razzouk et al. (158) outlined that most infants present a normal mental development index and psychomotor developmental index after CTx.

## Final considerations

Transplantation in infants diagnosed with HLHS provides a BiV circulation, associated with excellent early and long-term outcomes. Infant recipients present little limitations and are expected to reach adulthood. Although survival rates in the beginning of the century encouraged primary CTx as a superior approach to multistage palliation, these results were obtained in an era when pre- and post-operative management were still being optimized. Despite better pediatric heart allocation over the past decade, shortage of heart donors continues resulting in waiting list mortality rate unacceptably high and children listed for CTx face the highest waiting list mortality in transplantation medicine.

The American Heart Association Council on CHD (165), the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group issued a consensus pointing out the decrease in CTx as a primary option for patients with LV hypoplasia, as a result of improvements to the multistage palliation, and in the face of scarcity of donor organs, and of an appropriate size. In the end, the decision belongs to healthcare professionals and their assessment, and institutions' experience. Jenkins et al. (64) suggested a practical solution to this dilemma, Fontan circulation should be recommended for neonates with fewer risk factors, reserving transplantation for infants at higher risk in staged surgery. However, it begs the question: are there sufficient donor hearts for higher risk patients?

Cardiac xenotransplantation was investigated in neonatal animals, and there were favorable results in animal models, with data suggesting variable homology between baboons and humans. Recent advances in genetic engineering and xenotransplantation have provided the potential to eliminate waitlist-associated mortality with successful outcomes, through genetically modified pig-to-human neonatal cardiac xenotransplantation. Considering the impressive results associated with CTx, but the imitation imposed by lack of donor hearts, should cardiac xenotransplantation be reconsidered? (4,166,167)

# Fetal aortic valvuloplasty

## Historic perspective

Fetal echocardiography provides detailed imaging for evaluation of cardiovascular structure and function during gestation, and its development has allowed the opportunity for changing the rules of the game. Case reports began demonstrating the impairment growth of left-side cardiac structures during prenatal development in the presence of CAS, leading to inadequacy at birth. (71) Hornberger et al. (168) suggested that HLHS could develop or progress during second and third trimesters in the presence of structural and hemodynamic abnormalities that result in a reduction in blood flow through the left-side structures. The Department of Fetal Cardiology at Guy's Hospital (169) examined 7021 fetuses of which 27 presented with AS. The median gestational age at presentation was 22 weeks, and those with AS showed a reduced rate of growth of left ventricular length and width. Among fetuses with AS and normal LV length at 30 weeks gestation, Mäkikakkio et al. (170) demonstrated that all progressing to HLHS had retrograde flow in the transverse ArchAo, 94% had significant LV dysfunction, 91% had monophasic MV inflow, and 88% had left-to-right flow across the FO.

Although hypoplasia of the left-sided structures was considered irreversible, and preventive of a BiV approach for most patients, there is evidence that growth of the hypoplastic structures might be possible under certain physiologic conditions. (21,42,171) Maxwell et al. (172) attempted, in 1991, intrauterine balloon dilatation of the AV in two fetuses with CAS. Balloon dilatation was already well established for the relief of pulmonary or AS in children, and the balloon catheters used were a modification of those used in children. Allan et al. (173) in a report published in 1995 described the performance of a balloon aortic valvuloplasty and, subsequent, improvement in the LV function with an EF of 55% at 3 weeks of age. Although a second aortic valvuloplasty was required at 2 months, the infant was thriving at the age of 4 years. Prolonged time of gestation after the procedure was credited for the successful postnatal result. Technical advances in creating the percutaneous operative setup for minimally invasive fetoscopic in-utero interventions encouraged experiments in fetal sheep. Kohl et al. (174) demonstrated that fetoscopic and open transumbilical fetal cardiac catheterization are viable and carry important potential for dilatation of severe valvar obstructions in human fetuses.

The rationale for in-utero interventions (Figure 10) is restoration of onward flow and reduction of intraventricular pressure, hence promoting LV growth and function, improving coronary perfusion, and minimizing ischemic damage. (25) Early clinical experience in human fetuses with severe AV obstruction was poor, due to defective selection criteria, technical problems, and high postnatal operative mortality in those surviving through gestation. (175) Since its introduction, results have become more and more encouraging, and percutaneous fetal balloon valvuloplasty has become well recognized in some specialized centers.

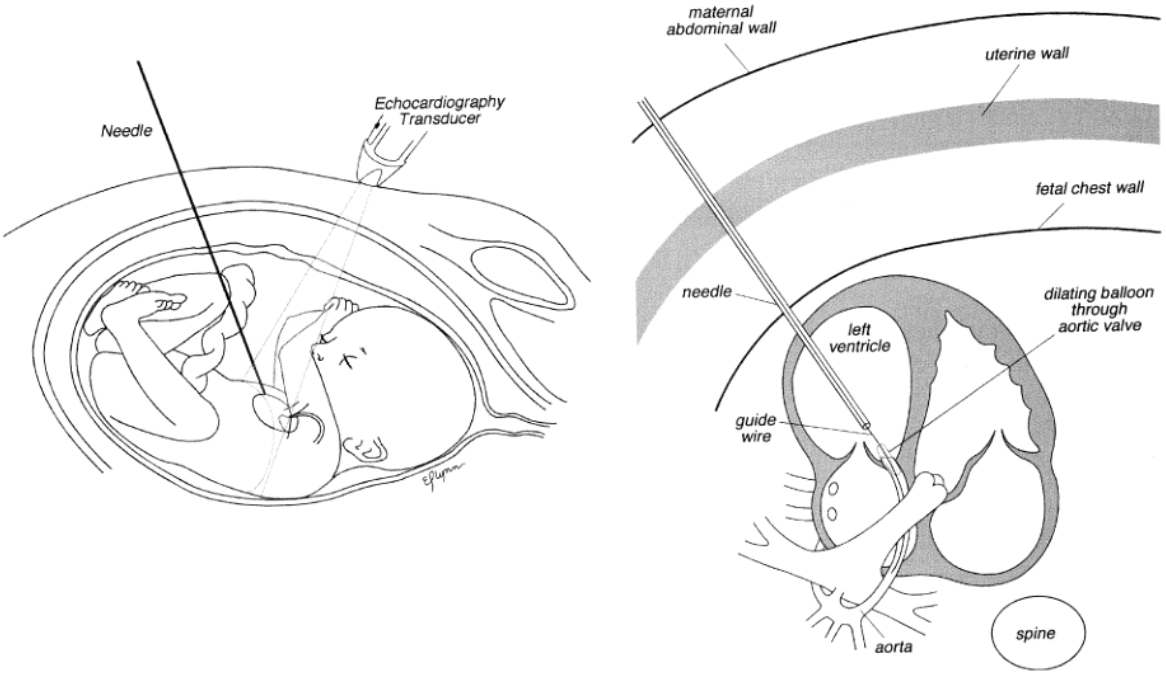


Figure 10: Fetal aortic valvuloplasty. For the cannula to achieve the AV, fetal left chest must be anterior, and pathway from maternal abdomen to LV apex unobstructed. [Tworetzky et al., 2004, p. 2127 (176)]

## Procedure

Over the years, to successfully alter the natural history of the disease, careful selection of patients suitable for in-utero intervention has become more important, and candidacy more selective. Prenatal echocardiography has a significant role to play in this selection as left-to-right shunting at the atrial level with retrograde flow in the ArchAo, a dilated LV and evidence of AS are obligatory findings. This significantly narrows the potential candidates for fetal aortic valvuloplasty (FAV), and it is safe to say that most patients presenting with HLHS in utero have some form of AA, MA, or severe MV hypoplasia, which precludes LV recruitment. Hence, fetal intervention as a therapeutic strategy can only be applied in a relatively small subset of patients with HLHS. (71,169,172,177)

Performance of FAV requires numerous resources and expertise in fetal diagnosis, obstetric and cardiovascular imaging, catheter techniques, and maternal care. All these elements must be in place to offer a safe and effective intervention of this nature, and few centers have the capacity to do so successfully.

## Optimizations

Criteria for successful BiV circulation have changed considerably since the introduction of FAV for patients with CAS. Preintervention anatomic and physiological features can indicate fetuses with and without the potential for a postnatal BiV outcome. CAS as the dominant lesion, retrograde flow in the transverse ArchAo, left-to-right shunt across the FO, LV long-axis Z-score of >2 and LV/RV ratio of >0.8 are good predictors of a successful BVR. (178) Fetuses with salvageable left hearts are likely to undergo successful intervention and thrive with a BiV circulation after successful in-utero intervention. AA has been associated with inevitable technical failure at the time of intervention, and significant morbidity and mortality. (179) Considering the technical aspects, the wire passage across the AV should be quick and automatic to avoid progressive fetal bradycardia and the need to manipulate catheters in a collapsed LV. Optimal fetal positioning and angle of cannula entry, improved cannula, catheter and wire configurations, ultrasound imaging, and maternal-fetal management are fundamental pieces to achieve a successful outcome. (176) Efforts should also be moved to develop fetoscopic and open interventional techniques that allow fetal cardiac intervention prior to 20 weeks of gestation. (180)

## Primary outcomes

Between 2000 and 2004, Tworetzky et al. (176) diagnosed 24 fetuses with CAS in the second or early third trimester, and 20 were subjected to in-utero intervention 1 to 6 weeks after initial diagnosis. All 14 surviving fetuses experienced improvement of antegrade flow and growth of the MV and AV, and 3 fetuses achieved a BiV circulation at birth. Following a 4-year experience and technique improvement, technical success improvement from 25% to 90%. (177) Freud LR et al. (181) attempted FAV in 100 patients, from 2000 to 2013, at a median gestational age of 24 weeks. The procedure was technically successful in 77 cases, and 38 achieved a BiV circulation with volume and systolic function within the normal range, although more than one-third had ventricular dilatation. 10-year survival rate was 72%. Arzt et al. (178) estimated technical successful in 70% fetuses with a success rate increasing to 79% after an initial learning curve, leading to BiV postnatal outcome in 67% and a low in-utero mortality. Since 2001, 103 fetuses have undergone FAV (182) with a technical success of 87%. BiV outcome at 28 days was

achieved in 71% patients and 55% at 1-year. Gardiner et al. (183) documented 107 fetuses with AS from 2005 to 2012 and showed that a substantial proportion of fetuses that met the criteria for emerging HLHS and were candidates for FAV achieved a BiV circulation without fetal intervention. Finer selection criteria might increase the likelihood of a successful BiV outcome.

On the one hand, McElhinney et al. (179) described success in 74% fetuses, with technical failures associated with unfavorable fetal position, difficulty puncturing the LV, suboptimal cannula trajectory, inability to cross the valve with the wire, and fetal hemodynamic instability. Equivocal AA and a shorter LV long-axis dimension score were also associated with technical failure. On the other hand, larger left-side heart structures and higher LV pressure at the time of intervention have been associated with a better likelihood for a BiV circulation. In fetuses with CAS, Tierney et al. (184) found that technically successful FAV resulted in significant changes in physiological properties of the left heart complex – LV systolic and diastolic function improved, flow across the ArchAO and the PFO also increased. FAV also facilitated a modest restoration of the cerebral:placental balance, and there was a tendency for the middle cerebral artery pulse and resistant to increase modestly. (185)

## Secondary outcomes

Complications were prevalent, occurring in almost 50% of the attempted interventions, and occurred commonly during or shortly after the intervention. Higher rates of complications were seen in procedures with more than one cardiac puncture and larger cannula sizes. (186) Among 15 patients undergoing FAV, Tworetzky et al. (176) reported 15 cases of intraoperative bradycardia, 2 of pericardial effusion, 1 of maternal respiratory compromise, 2 intrauterine deaths, 1 previable delivery and 2 ruptured balloons. Bleeding complications, or high rates of preterm rupture of membranes, premature delivery and maternal complications were also reported. (175,187)

There were significant abnormalities in LV diastolic function indexes post-FAV throughout the neonatal and follow-up period, increasing risk for left atrial and pulmonary hypertension. Diastolic function indexes improved after relief of LV pressure load. Patients with BiV circulation post-FAV presented with MV and AV disease, LV endocardial and myocardial damage, and fibrosis. Endocardial fibroelastosis, myocardial fibrosis and myocyte hyperplasia are thought to be significant contributors to diastolic dysfunction. (188,189)

Infants who have undergone FAV exhibit significant impairment in their general adaptive functioning, reflecting difficulties achieving age-appropriate skills. Infants with BVR despite having worse general adaptive functioning, were comparable with those with SV physiology in all domains of behavior and development. (190) Individual patient factors are probably involved and might be irreversible by the time of in-utero intervention. Postintervention neurologic hemodynamics might be inadequate to allow normalization of cerebral vascular impedance. (185)

## Final considerations

Although multistage palliation has endured a functional right-sided univentricular circulation, this strategy involves significant long-term cardiovascular and systemic morbidity, and transplantation is not possible for every patient. In-utero interventions appear with the purpose of altering the natural history of HLHS and enhancing quality of life. FAV has the potential to achieve a BiV circulation in selected fetus with CAS and evolving HLHS, however, selection criteria must be carefully met. So far results have been encouraging, nonetheless, critical evaluation of longer-term outcomes associated with FAV are essential. Cooperation between specialists in prenatal medicine, pediatric cardiologists and cardiac surgeons is paramount for success.

Some authors have described a genetic etiology to LV hypoplasia, raising questions about the advantage of the in-utero interventions, other consider it a flow-related phenomena. Since several pathogenic processes might play a role in the evolving HLHS, modifications to in-utero procedure require a better understanding of the genesis and biological processes involved in left-sided hypoplasia throughout gestation. This innovative and important attempt should continue further, the era of fetal treatment is here, and fetal cardiac intervention went from idea to reality.

# Conclusion

Functional single ventricles are one of the most severe forms of CHD, and in the absence of surgical intervention, account for an important mortality rate in the neonatal period. Five decades ago, palliative care was the sole therapeutic option available, since then remarkable progress has been made in the care of patients with HLHS from multistage palliation to transplantation, and now the window of opportunity for in-utero interventions has been opened. Patients have grown into adolescence and young adulthood, so the emphasis has shifted from the overall survival toward quality of life, burden of the disease, and brain neurodevelopmental outcomes. The present papers is a thorough review of the existing literature aimed to explore the surgical therapeutic approaches for patients with HLHS, as well as understand the reason for staged palliation being the preferred surgical approach in most centers.

Staged reconstruction aims to achieve a Fontan circulation, through a multistage separation of systemic and pulmonary circulations. Prenatal diagnosis allows a better understanding of the individual anatomy and pathophysiology and enables a more adequate surgical planification. During the neonatal period, the Norwood operation unobstructs the RVOT and allows pulmonary venous return to flow into the RA, and the systemic circulation. Then follows a BDG or a HFP, depending on center preference and experience, undertaken at 4 to 6 months of age. To conclude the Fontan physiology, between 18 and 48 months, inferior caval blood is channeled to the pulmonary inflow. There have been several improvements in pre- and postoperative management, and surgical optimizations, resulting in a perioperative mortality <1%, and infants with LV hypoplasia born today are expected to live beyond 30-year. Nevertheless, there are several mid- and long-term complications described in the literature, which evolve to an entity, the Failing Fontan, which prevent survival into late adulthood.

Transplantation entails the replacement of an incompetent UVH with a normal heart, preserving a BiV circulation. Survival after CTx has significantly improved over the past years, complications occur predominantly during the first months after transplantation, and current expectations point toward a 1-year survival over 90%. Infants transplanted in the newborn period may reach adulthood with a good quality of life, and minimal need for reintervention. Numerous authors have attempted to compare the multistage surgical outcomes to those of transplantation, but both strategies present with good early- and long-term outcomes. The great differential is the scarcity of donor hearts, which prevents most patients from receiving one transplant. Therefore, some authors have suggested

leaving this option to neonates with higher risk factors, expected to be worse candidates for staged reconstruction.

Fetal echocardiography has highlighted the progressive nature of LV hypoplasia, giving rise to the concept «no flow, no grow». Some studies have demonstrated that under some circumstances, an embryonic hypoplastic LV can be salvaged, proving the rationale behind in-utero interventions, and offering the chance to alter the natural history of HLHS, and enhancing quality of life. FAV success rate has increased substantially, with a BiV circulation being achieved in over 50%. This procedure was met with a different set of complications, such as fetal demise, and premature rupture of membranes, and also infants with a BVR presented with adaptive malfunctioning. Although these drawbacks, results of FAV seam encouraging. Nevertheless, some researchers have dismissed the hemodynamic disturbance theory, in favor of a multigenic and genetically heterogeneous genesis, which may have important therapeutic implications.

Despite increasing surgical success and improvements in overall outcomes, the palliative nature of staged reconstruction, the shortage of donor hearts, and the genetic component of HLHS with documented negative intrinsic neurodevelopmental outcomes, has led some physicians to advocate for a non-surgical management. With prenatal diagnosis, parents should be offered the opportunity to make informed decisions. Kane et al. (191) reported a decreased percentage of patients undergoing non-operative discharge to home over the years, nevertheless, given the progressive reduction in mortality, better understanding of possible early- and long-term complications, further dialogue about ethical justification of non-operative palliative or comfort care is imperative.

Limitations include the nature of the included studies, as randomized controlled trials on congenital heart disease are scarce in the literature, therefore more observational studies and expert opinion papers were used. Another limitation concerns the data in those studies as several studies included provide data on surgical therapeutic approaches for various cardiac malformations, and not only for patients with HLHS. Similar to the SVR trial, in the future more randomized clinical trials should be dynamized to better understand the early- and long-term impact of the optimizations proposed so far, optimize patient selection and surgical protocols around the globe, and maximize outcomes. Large-scale studies should also be conducted to produce stronger evidence on the biomarkers and imagiological features present on early stage Failing Fontan, to allow prompt intervention, and to prevent its progression to circulatory failure.

Optimizations must be continuously made as there is still a wide variation in preoperative, intraoperative, and postoperative management between centers around the world. Finer selection criteria and protocols enable different phenotypes to receive different and more adequate surgical and non-surgical approaches. There is no surgical approach superior to the other, there is only a superior surgical approach to an individual patient. One size does not fit all, physicians must, in light of the most current scientific evidence, and considering morphologic and functional factors, propose an optimal pathway, in addition to offering families the opportunity to make informed decisions regarding their child's life.

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