To Never Know Heartbreak – Fetal Cardiac Intervention to Treat Hypoplastic Left Heart Syndrome

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> "Fetal cardiac intervention modifies the course of cardiac growth, function and/or development in utero sufficiently to alter the postnatal outcome."

Abstract

Within the last three decades, no congenital heart defect has undergone a more dramatic change in management and outcome than hypoplastic left heart syndrome (HLHS), which is an invariably lethal heart defect without treatment. During this time, we have seen a change from a fatal diagnosis to a successful treatment where 70% of those diagnosed with HLHS will reach adulthood, albeit with a single ventricle system or "Fontan circulation". As the pathogenesis of HLHS is being elucidated, fetal cardiac intervention (FCI) is becoming a real possibility. It has been hypothesised that FCI could potentially halt the development of HLHS and consequently create a biventricular system. Two predominant research groups have shown promising results and have achieved biventricular circulation as a postnatal outcome in 30–67% of neonates. It is believed that with further research, improved instrumentation and more advanced imaging, we will see significant progress not only in treatment of HLHS but of congenital cardiac defects overall.

Introduction

Congenital heart disease is the most common inborn defect, occurring in 19/1000 live births[1]. Over 20 years ago, the idea of fetal cardiac intervention (FCI) was put forth to treat congenital heart defects (CHD). The idea arose due to the observations that some forms of cardiac malformations progressed in severity as the pregnancy progressed[2]. Fetal cardiac intervention modifies the course of cardiac growth, function and/or development *in utero* sufficiently to alter the postnatal outcome[3]. There is also evidence that prenatal intervention may allow the fetus to recover in the supportive environment found *in utero* that encourages enhanced wound healing and myocyte proliferation[4,5]. Fetal cardiac intervention is most effective in cases where intervention may alter the evolution of the condition or if the fetus is at risk of

death. It is therefore indicated if the severity of postnatal disease may be substantially reduced[3] (Table 1 includes examples of such conditions in which FCI is feasible).

Of the CHDs, none has been researched more for FCI than hypoplastic left heart syndrome (HLHS). This syndrome is a lethal congenital heart defect that is associated with obstruction to left ventricular outflow[6], leaving the left heart complex underdeveloped[7]. The degree of hypoplasia is proportional to the severity of obstruction, except in circumstances where there is an alternative route of blood flow such as with a ventricular septal defect. If the hypoplasia is severe, the left ventricle (LV) cannot support systemic circulation[6], which can lead to development of right heart compression and severe hydrops *in utero*[8] or demise soon after birth.

Fetal echocardiography has allowed for prenatal diagnosis and assessment of HLHS, demonstrating that LV hypoplasia severity evolves throughout gestation. This implies that normal cardiac morphogenesis requires blood-flow-directed remodelling in addition to intrinsic patterning. Therefore, abnormal blood-flow streaming may lead to HLHS[6].

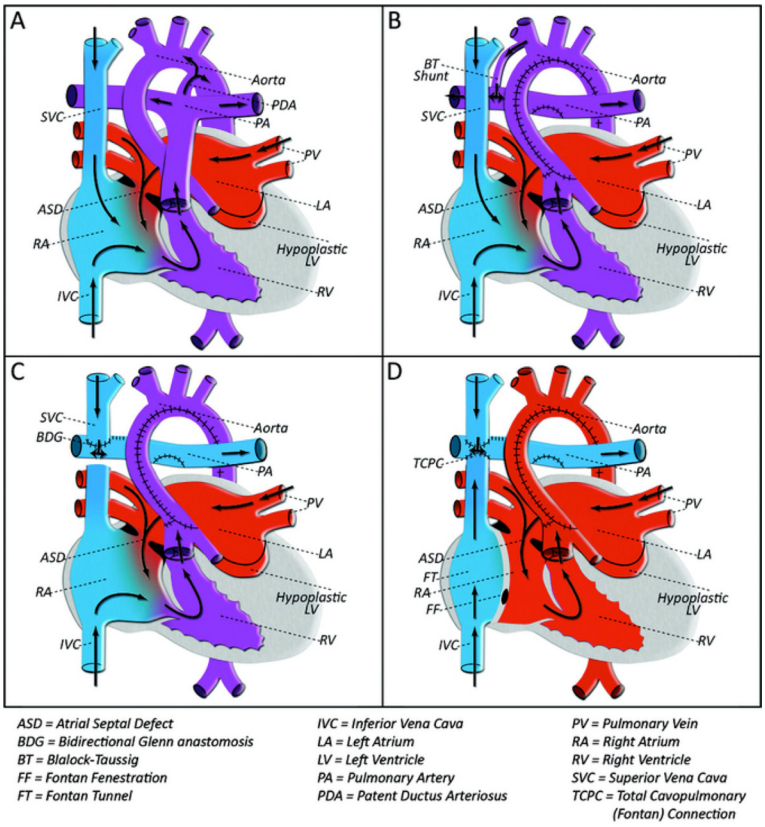

Figure 1. *3-stage palliative repair of a neonate diagnosed with HLHS. Heart with HLHS (A), Norwood Procedure (B),Glenn Operation (C), Fontan Procedure (D)[26].*

Current Treatment for HLHS

Newborns with HLHS (Figure 1A) may be asymptomatic, but as soon as the ductus arteriosus closes they become severely ill and, without treatment, almost invariably die[7]. The current treatment of HLHS that allows a 70% survival rate into adulthood includes a three-stage palliation procedure beginning with the Norwood procedure shortly after birth[9]. This procedure converts the right ventricle into the main systemic ventricle while

Table 1. Congenital Cardiovascular Anomalies Potentially Amenable to FCI

Condition	Actual or Possible FCI
Fetal tachycardia with hydrops	Maternal antiarrhythmic pharmacology
Structural anomalies causing hydrops	Maternal digoxin
Congenital heart block	Pacemaker
Severe Ebstein malformation	Tricuspid valve repair
Severe congenital MR or AS	Balloon or surgical valvuloplasty
HLHS with intact atrial septum	Creation of atrial septal defect
Evolving hypoplastic right heart	Pulmonary valve perforation and dilation
Premature closure of ductus arteriosus	Ductal stenting
Absent pulmonary valve syndrome	Pulmonary arterioplasty

McElhinney et al.[3]

Clinical Points

1. Hypoplastic left heart syndrome (HLHS) is a lethal congenital heart abnormality that usually occurs due to left ventricular outflow obstruction.

2. In the past 30 years, the only treatment option for HLHS has been a sequence of complex open-heart operations that lead to a univentricular "Fontan circulation".

3. Potential long-term outcomes of Fontan circulation include increases in the development of arrhythmias and coagulopathies and poor exercise tolerance' leading to heart failure and neurological disability.

4. Fetal cardiac intervention is theorised to perhaps prevent the development of HLHS by making the stenotic aortic valve patent and allowing fetal cardiac flow dynamics to run their natural course.

5. Postnatal outcomes of FCI and aortic valvuloplasty that resulted in biventricular circulation for HLHS vary between 30 and 67%.

6. Advancement in instrumentation and imaging will lead to improved outcomes of FCI and a potential to prevent HLHS before it manifests.

the aorta and pulmonary trunk are joined together[10]. The pulmonary arteries are cut away from the pulmonary trunk and a Blalock Taussig (BT) shunt is created to allow blood flow from the innominate artery to the pulmonary arteries (Figure 1B)[11].

Six months after the Norwood procedure, the bi-directional Glenn operation[10] (Figure 1C) occurs. The superior vena cava (SVC) is connected to the pulmonary artery and the BT shunt is disconnected. This will send blood directly to the lungs without its having to pass through the univentricle.

Lastly, the Fontan procedure occurs between 18-36 months and connects the inferior vena cava (IVC) to the pulmonary artery. Consequently, all the systemic venous blood will flow directly into the lungs[10,12], become oxygenated, then enter the univentricle to be distributed to the systemic blood supply (Figure 1D).

This procedure has demonstrated success, but numerous complications can arise. Following the Norwood procedure, supra-ventricular tachycardia occurs in about 15% of cases, infection affects about 10% and bleeding and coagulopathy are almost universal. Lastly, seizures occur in 17-22% of patients and are associated with developmental delay[9].

Long-term complications can occur as well. As the original Fontan operation was performed in 1971, the first cohorts of adult patients are now being looked at for evidence of long-term complications. Arrhythmias, thrombosis, protein-losing enteropathy, and increasing exercise intolerance leading to heart failure after 15-30 years are a few examples[12]. Once this ventricle fails, transplant is the only option[2]. Van den Bosch et al. studied a cohort of patients who underwent the Fontan procedure with a mean follow up period of 15 years. They demonstrated that 28% had died at a mean age of 10 years old while 58% of patients underwent a reoperation to revise the Fontan connection. Supraventricular tachycardia was observed with an increased incidence of arrhythmias in 56% of patients, and finally, 25% experienced thromboembolic events that resulted in fatalities of three patients[12]. It should be noted that this three-stage palliation procedure is life-saving for many neonates who would otherwise succumb to their condition. These results reflect a procedure that took place about 30 years ago[6]. Since then, it can be postulated that experience and new research have improved the technicalities of the procedure and that future cohorts may show improved long-term outcomes. However, it can also be inferred that there is room for an improved technique in treating HLHS and perhaps an intrauterine approach (FCI) will prove to be just that.

Fetal Cardiac Intervention

Despite improved surgical outcomes achieved with the three-stage palliation procedure, the question

Figure 2. *Ultrasound images in the Arzt trial in 2011 showing: (a) favorable position of the fetus while introducing the needle into the left ventricle, (b) catheter with balloon in left outflow tract and (c) dilatation of aortic valve by balloon insufflation.*[15]

remains. What if HLHS doesn't have to develop at all? It has been observed that anatomic cardiac obstructions that lead to ventricular dysfunction by diverting fetal blood flow in utero can result in cardiac chamber hypoplasia. Therefore, severe aortic stenosis (AS) in midgestation may lead to myocardial damage[8]. The abnormal flow dynamics and shear stresses appear to result in poorly orchestrated ventricular growth and development. As gestation continues, the cardiomyocytes undergo a switch in myogenic potential that lose the ability to undergo mitosis, meaning ventricular hyperplasia can no longer occur. Consequently, remodeling of the ventricular tissue is confined to muscular hypertrophy[6]. Therefore, due to faulty flow dynamics during development, a fetus progressively develops HLHS. This is possibly oversimplifying the pathogenesis as another likely cause could be a primary genetic disorder that affects the myocardial and valvular development[6]. There is some evidence of a link between HLHS and bicuspid aortic valve disease, as bicuspid aortic valves are the most common cardiac abnormality in first-degree relatives of children with HLHS[13]. Reports of bicuspid aortic valves in otherwise normal first-degree relatives to those with HLHS is as high as 11%[14], whereas bicuspid valves in the overall population is only 1-2%[6].

Thus it is theorised that if there can be early relief of AS then left-heart function may be preserved and HLHS could potentially be prevented[8]. This theory has been tested in clinical trials using FCI and has made tentative progress. One of the first larger clinical trials was done in 2004 by Tworetzky et al. in Boston. They performed balloon dilation in fetuses with severe AS in order to prevent HLHS. Twenty fetuses between 21 and 29 weeks gestation underwent the procedure. After both the mother and fetus were anaesthetized, a cannula was manually passed through the maternal abdomen and uterine wall and into the fetal chest under ultrasound guidance. The cannula then punctured the fetal LV and a coronary balloon was dilated while in the aortic valve (aortic valvuloplasty). Out of the 20 cases, 14 were considered technically successful; however, two of those babies died *in utero*. Of the 12 that survived, three went on to develop biventricular circulation at birth[8], meaning the LV was able to support systemic circulation, which is the optimal outcome[15].

Data collected from 2000 to 2009 demonstrated that 70 fetuses underwent the above procedure; 74% were considered to be a technical success, 29% of those were able to achieve biventricular circulation at birth[16] and another 8% were converted to a biventricular circulation after initial univentricular palliation[3].

In 2011, a trial done by Arzt et al. demonstrated that aortic valvuloplasty achieved technical success in 70% of the 24 procedures and biventricular circulation in 67% of those fetuses[15]. At a median follow-up of 27 months, 40% of those newborns had only AV balloon dilation in the first postnatal week and no further surgery. The remaining 60% had to undergo a Ross-Konno procedure, which is a

Table 2. Current Selection Guidelines for Fetal Aortic Valvuloplasty

Unequivocal AS (vs aortic atresia)
LV long axis Z score >−2
Threshold score ≥4 of the following
LV long axis Z score >0
LV short axis Z score >0
Aortic annulus Z score > −3.5
MV annulus Z score > −2
MR or AS maximum systolic gradient ≥20 mmHg

McElhinney et al.[16]

pulmonary valve autograft that is used to replace a diseased aortic valve[17].

Overall, these clinical trials have demonstrated not only improved outcomes throughout the years, but also that HLHS can indeed be prevented with the correct intervention. Makikallio et al. demonstrated that after successful FCI, the physiological parameters that lead to the development of HLHS were improved[18], indicating that progression to HLHS could be avoided. These parameters included improved aortic and mitral valve growth relative to control fetuses, as well as a clear increase in LV ejection fraction, anterograde flow in the transverse arch, and bidirectional flow across the foramen ovale[19]. However, there was no difference in growth velocity of the LV short or long axis[3]. Even if biventricular circulation is not achieved after FCI for AS, there is still improvement by the left side of the heart in contributing to the univentricular circulation, improving the heart's efficiency and durability[3].

Fetal Cardiac Intervention for HLHS with IAS

An area that needs special attention is a subset of infants who have HLHS, as well as a highly restrictive intact atrial septum (IAS). These neonates develop profound cyanosis and pulmonary oedema immediately after birth and resuscitative measures are often unsuccessful. Those who undergo emergency Norwood procedures have a mortality rate of 83% at 6 months[20]. Even neonates who underwent early transcatheter procedures to relieve atrial septal obstruction had a neonatal mortality of 48%[20].

The neonates who have HLHS with IAS suffer from high mortality rates due to intrapulmonary anatomic abnormalities, including "arterialization" of the pulmonary veins and lymphatic dilation due to left atrial (LA) hypertension *in utero*, subsequently suffering from severe cyanosis and pulmonary oedema[20]. It is thought that if prenatal LA hypertension causes these changes, the best form of management would be a procedure that creates an atrial septal defect *in utero*[20]. However, there are marked technical limitations to creating a large atrial communication. Recently, FCI was reported in 21 HLHS fetuses with IAS where the interatrial communication was created with either balloon dilation or placement of a stent. In two of the cases, the fetus died due to significant hemopericardium and those that were delivered had a surgical survival of only 58%[21]. However, there does seem to be some benefit to this procedure in terms of preoperative management, as these neonates with an atrial septal defect ≥3mm after FCI had higher oxygen saturation at birth and were less likely to need urgent postnatal left atrial decompression[22]. FCI may indeed be a useful procedure for this cohort of patients too, but more research is needed to refute or confirm this assumption.

Complications of FCI

FCI for aortic valvuloplasty is not without its complications. Almost half of all fetuses experience a combination of bradycardia and right ventricular dysfunction of variable severity[3]. Other complications include pericardial effusions, ventricular thrombosis and fetal death[23]. However, most of these complications are manageable. The bradycardia is treated with epinephrine administration into the left ventricle[23] or prophylactic administration of epinephrine and bicarbonate through the balloon catheter at the time of the intervention[3]. The thrombosis does not usually have any further consequences[23].

Furthermore, a concerted postnatal evaluation to determine if there are adverse neurological consequences of FCI has yet to be completed. However, a recent study illustrated that there is no evidence to suggest that prenatal aortic valvuloplasty significantly affects cerebral arterial flow parameters[24]. It should also be noted that no maternal complications requiring treatment have arisen during these trials[3,15].

Future considerations to improve FCI

One of the most important prerequisites for success is implementing the proper inclusion criteria to increase the chances of having an optimal biventricular outcome. The new inclusion criteria can be seen in Table 2. It was conceded that the loose entry criteria in the Boston 2004 study, including patients with heterogeneous cardiac anatomy[8], may have contributed to the poor outcomes reported for the procedure.

Gestational age at the time of the procedure should also be considered. The Arzt et al. group in 2011 had better success than the group in Boston in terms of optimal outcome since their cohorts had a higher gestational age and therefore a larger LV at the outset. A key factor in predicting success is the size of the LV at the time of the intervention[23]. Ultimately, safety and success rates are dependent on patient selection and the level of experience of the interventional team[15].

Other limitations in FCI include instrumentation and imaging techniques. Currently, with the exception of the 18-gauge curved tip cannula that was developed specifically for FCI, the instruments that are used are used off-label, which may hamper procedural feasibility and limit technical options[3]. As for imaging, ultrasound is used to manually guide the needle into the maternal abdomen through the chest cavity of the fetus and into the LV[15]. This poses a major barrier to technical success. It is a considerable challenge to accurately and rapidly deliver a needle across multiple tissue planes without damaging vital structures[25].

Emery et al. have begun to improve upon this technical limitation by creating a computer-assisted navigation (CANav) system that allows for the targeting of small structures during robotic surgery with minimally invasive interventional procedures. CANav system provides the user with an ultrasound image of the target structures but with the additional feature of visualizing the trajectory of the medical instrument before it is introduced into the body. That way, the needle's point of entry and trajectory can be adjusted prior to entering the body cavity of both the mother and the fetus. It also allows the operator confidence that the needle trajectory will target the desired structure and avoid any vital structures that could cause fetal complications[25].

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