Hypoplastic left heart syndrome

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Hypoplastic left heart syndrome is a rare congenital heart defect in which the left side of the heart is underdeveloped. Surgical management of hypoplastic left heart syndrome has changed the prognosis of the condition that was previously regarded as fatal. We discuss surgical strategies based on staged procedures, with the right ventricle supporting both systemic and pulmonary circulation. We also discuss other management options, such as neonatal transplantation and the recent innovation of hybrid techniques. Surgical techniques and the understanding of the pathophysiology of this condition have been at the forefront of neonatal cardiac surgery and intensive care. The management of the syndrome remains a challenge because affected children grow into adolescence and adulthood posing various new problems and demands.

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Introduction

Hypoplastic left heart syndrome is characterised by a variable degree of underdevelopment of the left ventricle and its components, so that it is unable to support systemic circulation. The condition is fatal without intervention, usually within the first few days of life. No definitive treatment existed for the condition until the 1980s when the use of the right ventricle to support systemic circulation was first proposed. Treatment of the condition in the UK was first undertaken in the early 1990s, and now several established surgical programmes manage this complex syndrome. Management involves multidisciplinary teams for antenatal diagnosis and counselling, specialist fetal medicine centres, neonatal intensive care, paediatric cardiac surgical and cardiology teams, and lifelong surveillance by adult congenital heart disease specialists and transplant teams.

At present, two main treatment modalities exist: primary cardiac transplantation and staged functionally univentricular palliations. In the UK, neonatal transplantation is not available, therefore discussion is limited in this article. Functionally univentricular palliation treatment consists of three stages: (i) the Norwood operation on neonates; (ii) stage II at 6–8 months of age; and (iii) stage III between 18 months and 5 years of age (most commonly around 4 years). Hypoplastic left heart syndrome is still one of the most high-risk lesions in children with congenital heart disease and, although surgical outcomes continue to improve, survival is currently around 65% at 5 years of age and 55% at 10 years of age.[1–3] Counselling is essential for parents to make an informed decision and should include discussion of comfort care only. Despite the encouraging surgical outcomes, affected children require lifelong medical attention, and many have substantial developmental issues and health problems later in life that can place an enormous strain on families.

Epidemiology

Hypoplastic left heart syndrome is rare, accounting only for 2–3% of all congenital heart diseases and occurring in about 2 in every 10 000 livebirths (studies vary from 1·5 to 6·7 per 10 000 livebirths), which equates to 200–260 babies per year in the UK. Data from a census of serious congenital heart disease on behalf of the British Paediatric Cardiac Association (BPCA) in 1993–95[4] showed 228 cases of hypoplastic left heart syndrome registered in the UK. Despite this low incidence, the natural history of the condition is so serious that without treatment it would be responsible for 25–40% of all neonatal cardiac deaths[5] because it is fatal within a few weeks from birth in 95% of cases.[6] The syndrome is recognised worldwide and no evidence exists of any ethnic or geographical association, but it is slightly more common in male than in female children.[7] No association exists between the syndrome and maternal age or parity.

Genetics

No gene is specific to hypoplastic left heart syndrome. However, several genetic associations have been identified but without any consistent marker. Associations with sporadic cases of the syndrome include connexin protein 43 (also known as gap junction protein α1 or GJA1), a lesion at 11q23.3,[8] and a cardiac homeobox transcription factor NKX2.[9]

Chromosomal anomalies have also been linked to the syndrome in up to 5–12% of cases, with monosomy X (Turner's syndrome) and trisomy 18 or 13 being common,[10,11] but the most common is in terminal 11q deletion (Jacobsen's syndrome) in which 10% of all children born have hypoplastic left heart syndrome.[12] Hypoplastic left heart syndrome has been described as one of at least 32 syndromes, some of which have a known genetic cause—as in Holt-Oram syndrome (caused by a mutation in TBX5) and Rubinstein-Taybi syndrome (caused by cAMP-element binding protein

Search strategy and selection criteria

We searched PubMed and Medline library databases for publications with the term "hypoplastic left heart syndrome" over the past 30 years. We preferred systematic reviews of prospective studies when available. For clinical presentation, management, and outcome data, we relied on large case series. Information about pathogenesis was compiled from animal, in-vitro, and clinical studies.

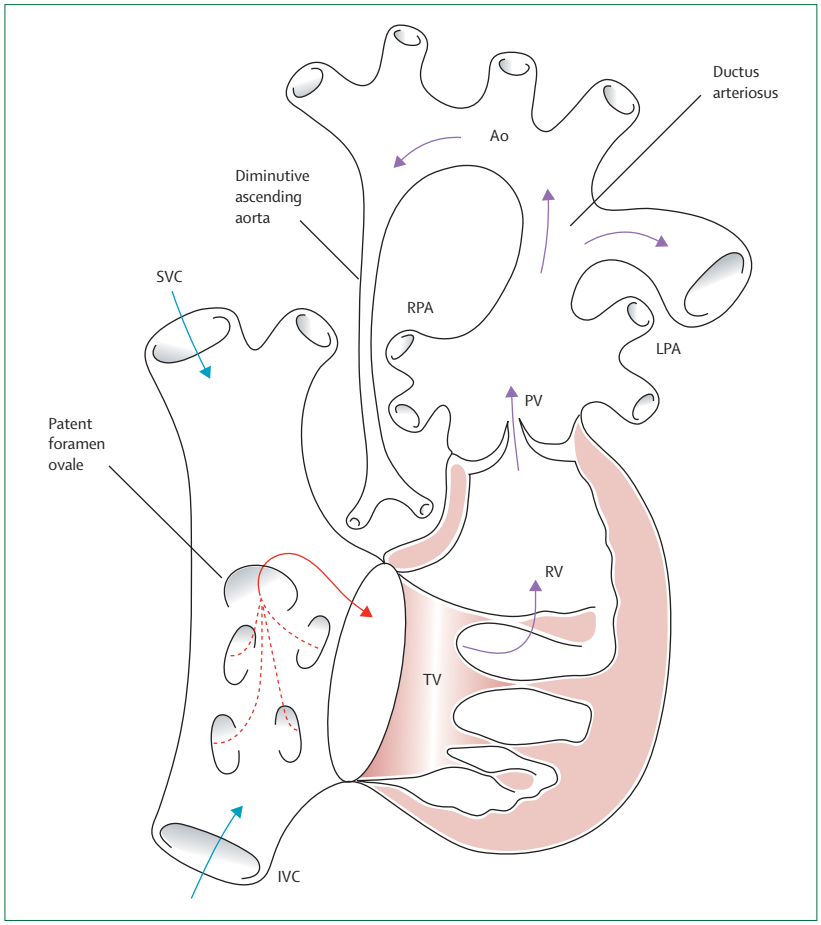

Figure 1: **Schematic representation of hypoplastic left heart syndrome**
Blue arrows represent systemic venous (deoxygenated) blood, the red arrow oxygenated blood returning from the lungs, and purple arrows mixed blood. Ao=aorta. IVC=inferior vena cava. LPA=left pulmonary artery. PV=pulmonary valve. RPA=right pulmonary artery. RV=right ventricle. SVC=superior vena cava. TV=tricuspid valve.

[CBP] mutations).[13] Physical examination should focus on dysmorphic facial, eye, and ear abnormalities, limb defects, polydactyly, various skeletal defects, and gastrointestinal and urological anomalies. Genetic consultation is recommended in the presence of multiple congenital anomalies, facial dysmorphia, or if the standard karyotype is normal despite clinical suspicion of a genetic defect. In this situation, high-resolution banding or more-advanced cytogenetic techniques might be needed (fluorescence in-situ hybridisation [FISH] for specific defects or telomeric and subtelomeric probes). Consultation with a clinical geneticist is recommended in the presence of chromosomal abnormality so that appropriate counselling and assessment of family members can be undertaken.

Although no single genetic basis for the condition has been established, a well recognised risk of recurrence in future pregnancies, albeit small, exists. This is estimated at around 2–4%, although in families that have had two affected children the recurrence risk is 25%.[14] This risk suggests that at least some genetic component exists; overall, however, hypoplastic left heart syndrome is regarded as having multifactorial causes that are poorly understood. Embryonic alterations in blood flow patterns through the fetal heart might also be important, preventing expansion and development of the left ventricular chamber. Attempts to improve flow through the fetal left heart are the basis of research into fetal intervention.

Morphology and pathophysiology

By definition, the left side of the heart is unable to support systemic circulation. Hypoplastic left heart syndrome is, therefore, only viable because of the presence of the patent ductus arteriosus at birth. Systemic circulation is supported by the right ventricle, via right-to-left flow through the ductus (figure 1), and so is a duct-dependent circulation. Similarly, pulmonary venous return can only reach systemic circulation by traversing the atrial septum (via a patent foramen ovale) to reach the right side of the heart. This precarious situation implies obligate mixing of pulmonary venous and systemic venous return, creating a cyanotic condition. Without intervention, the duct naturally closes during the first few days of life and, as the duct closes, the insufficiency of the left heart is exposed and systemic circulation fails.

Morphological diagnosis is not uniform, and various malformations that fall within this definition exist. The term itself acknowledges that the condition is too complex to be simply called left ventricular hypoplasia. The term hypoplastic left heart syndrome recognises that the components that make up the left heart are all inter-related in their function and development, so that no single component can be considered in isolation. Thus, the mitral valve, the left ventricular cavity, the outflow tract, the aortic valve, the ascending aorta, and the aortic arch are all involved in the condition and more than one—frequently all—components are underdeveloped. The anatomical subtype can be important, especially in the case of aortic atresia and mitral stenosis, in which there is inflow but no outflow into the small, hypertensive left ventricular cavity. This subgroup frequently has poor outcomes, possibly related to abnormal coronary patterns associated with it.[15]

Various more complex morphological features might occur together with hypoplastic left heart syndrome—such as transposition of the great vessels, atrial isomerism, and total anomalous pulmonary venous drainage—in about 7·5% of all cases.[16] Although these might affect outcome and require additional surgical procedures, hypoplastic left heart syndrome remains the dominant lesion and management is fundamentally the same.

In most cases, diagnosis is unequivocal and, regardless of the precise morphological subtype, the central premise is based on the fact that the left heart is unable to support systemic circulation. Inevitably, few patients have borderline morphology and decision making can be very difficult. In borderline cases, biventricular repair might

be achieved, but this can be high risk, requiring multiple procedures to achieve adequate sized left-sided structures and leave patients with the burden of pulmonary hypertension. Although pursuit of biventricular repair is welcome, survival is frequently better with the Norwood strategy.[17]

Presentation and diagnosis

Babies are commonly in good condition at birth. The ductus is open and thus the systemic circulation is supported. If the patent foramen ovale and the ductus are widely open, then the baby might not be noticeably cyanosed and initial examination might be normal other than evidence of a large patent duct (continuous murmur and wide pulse pressure). These patients have uncontrolled pulmonary blood flow and a large volume load on the circulation, and typically develop signs of congestive heart failure with cardiomegaly, pulmonary plethora, and hepatomegaly with increasing tachypnoea. This situation might progress into respiratory distress, increasing acidosis, and circulatory collapse.

At the other end of the spectrum, patients with a restrictive patent foramen ovale or even intact atrial septum have pulmonary venous congestion and are cyanosed and tachypnoeic from birth. Survival depends on the severity of the obstruction and whether or not there is a patent mitral and aortic valve to allow at least some egress of blood from the left heart. Severe cases are profoundly cyanosed, rapidly decompensate, and are incompatible with life.

Within this spectrum, cases might have a moderate-sized duct and a degree of coarctation of the aorta exposed so that femoral pulses are weak or absent, and evidence of congestive heart failure exists because of the combination of high pulmonary blood flow and high systemic afterload. These changes might only become apparent as the ductus begins to close, and so might only manifest a few days after birth. The degree of cyanosis is variable and, although there is mixing of the circulation, the high pulmonary blood flow could mask this, maintaining arterial saturations in the 90s.

Clinical presentation might resemble that of neonates with other left-sided obstructive lesions, in whom systemic circulation depends on ductal flow. These conditions include critical aortic stenosis, coarctation of the aorta, and interrupted aortic arch. Other non-structural cardiac diseases with clinical presentation in a shock-like state, such as neonatal myocarditis and neonatal sepsis, should also be taken into account in the differential diagnosis.

Plain chest x-ray might reveal cardiomegaly with pulmonary plethora and oedema, but is not diagnostic. An electrocardiogram (ECG) is generally non-specific but could show signs of right ventricular hypertrophy with tall R-waves in the anterior leads. The heart rhythm is usually normal. The mainstay of diagnosis is by echocardiography, which can show all aspects of the condition and confirm the diagnosis. Further imaging is rarely indicated and cardiac catheterisation normally has no role.

Many cases present after collapse and death at home. A study[18] from 1985–90 indicated that 15% of registered cases of hypoplastic left heart syndrome were only diagnosed at necropsy. A large epidemiological population-based study[19] showed that 78% of cases with hypoplastic left heart syndrome were discharged from hospital before diagnosis. Such numbers are hopefully being reduced through the introduction of routine neonatal postductal pulse oximetry, perhaps together with screening echocardiography.[20]

Prenatal diagnosis and management

Prenatal diagnosis allows detection of hypoplastic left heart syndrome with the visualisation of an abnormal four-chamber view on fetal echocardiography, most commonly between 18 and 24 weeks.[10,21] However, some variants of hypoplastic left heart syndrome are not easily recognisable at this gestational age and only become apparent at follow-up ultrasound examination in the third trimester or on postnatal assessment.[22] Currently in the UK, only 23·4% of all congenital heart diseases are detected prenatally.[4] However, because hypoplastic left heart syndrome is one of the most straightforward lesions to identify, about two-thirds of cases are diagnosed prenatally with ultrasound, a much higher detection rate than any other cardiac malformation. The highest detection rates have been achieved in regions of the UK where structured prenatal diagnosis and training in fetal echocardiography have been emphasised. The Royal College of Obstetricians and Gynaecologists guidelines have since been published for the ultrasound examination of the fetal heart at 18–24 gestational-week scan to increase detection rates.[23,24]

Fetal screening for congenital heart disease, including hypoplastic left heart syndrome with prenatal ultrasound, occurs in two common periods: (i) first-trimester screening: nuchal translucency measurement of more than 95th centile for crown–rump length is predictive of congenital heart disease (both dependent and independent of karyotypic anomalies),[25] and up to 46% of the cardiac anomalies identified at this gestational period with such nuchal translucency screening have been either left inflow or outflow obstructions that comprised the hypoplastic left heart syndrome spectrum.[26] Furthermore, detailed fetal echocardiography at 14 weeks is feasible and might confirm or refute the screening risk.[27] Although it is not routinely available in the UK, first-trimester screening for hypoplastic left heart syndrome, along with other congenital heart disease, can be offered. However, this examination should be repeated (even if normal) between 20 and 24 weeks, because an additional 20% of congenital heart defects become evident later.[28] (ii) Second-trimester screening. The mainstay of fetal cardiac screening is fetal echo-

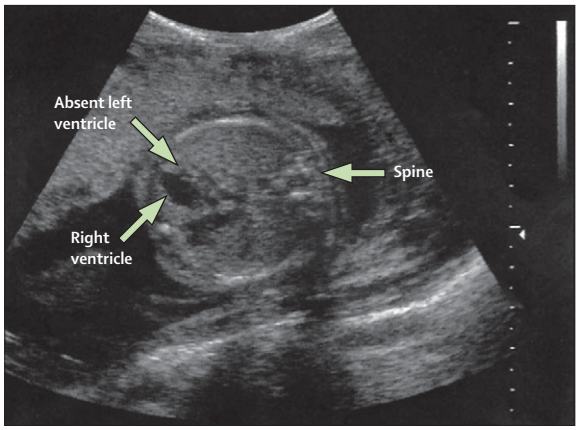

Figure 2: **Fetal echocardiogram showing a small hypoplastic left ventricle**
The echocardiogram shows a transverse, cross-sectional view of the fetal thorax.

cardiography between 18 and 24 weeks, which is part of the recommended national screening programme for the detailed anomaly scan of the fetus at 20 weeks,[23] including visualisation of a four-chamber view and identification of the outflow tracts of the great vessels. Such screening of low-risk and high-risk populations should detect up to 70% of cardiac malformations.[29] In typical hypoplastic left heart syndrome, a classical four-chamber view of the fetal heart shows a normally sited right ventricle with a hypoplastic left ventricle (figure 2), often associated with hypoplasia of the ascending aorta. However, the four-chamber view might seem normal at 20 weeks, and it is only at subsequent prenatal echocardiography (often in the third trimester) that subnormal left ventricular growth is identified.[22] Improved education, training, and ultrasound technology are likely to continue to increase detection. If hypoplastic left heart syndrome is detected, a detailed scan to exclude extracardiac anomalies should be done, and parents should be offered rapid fetal karyotyping.

Prenatal diagnosis has two important functions. First, it enables parents to be counselled in a timely and rational manner, and to present prognosis and possible outcomes, including the option of elective termination of pregnancy. In a cohort study of prenatally diagnosed fetuses with hypoplastic left heart syndrome in our centre in 1994–2000,[28] 44% (38 of 87) of parents opted for termination of pregnancy, which decreased to 25% (20 of 79) in the subsequent group in 2000–04 (p=0·01). This result might be due to various factors but certainly indicates that counselling has changed as surgical outcomes have improved. In a study just at the establishment of Norwood programmes in the UK, the termination rate was 71%.[4]

Second, prenatal diagnosis enables planning of postnatal management—ie, for the birth to be near or at a specialist cardiac surgical centre and to arrange for all preoperative intensive care facilities to be more ready and available. However, only one small study[30] has shown an increase in survival, although evidence exists that prenatal diagnosis improves preoperative condition of patients and reduces comorbidity.[31]

Other prospective studies have suggested a worse prognosis for antenatally diagnosed hypoplastic left heart syndrome, with survival of only 38% in our study,[32] improving to 64·5% in a later cohort.[16] The reasons for worse prognosis are not clear and might indicate that the more severe spectrum of the disease is detected antenatally and that babies that would not otherwise have survived transfer to a specialist unit are already fast-tracked into the system.

Fetal intervention has been proposed in hypoplastic left heart syndrome for critical aortic stenosis. The aim is to do balloon dilatation of the aortic valve in utero to improve forward flow through the fetal left ventricle and encourage growth. The technique remains experimental with only a small number of cases having been treated worldwide. Results have been mixed with fetal loss of 20% associated with the procedure and only 15% of cases surviving with an adequate sized left ventricle.[33] When placed alongside current outcomes with conventional surgical therapies, serious ethical and clinical considerations remain when considering fetal intervention.[34] Other fetal interventions include atrial septoplasty to alleviate restrictive or intact atrial septum at an early stage, but these also have only been attempted in few patients.[35]

Postnatal management

The main aim of initial management is to stabilise the infant's condition so that a diagnosis can be confirmed and a treatment plan can be made. Initial management is to secure ductal patency with prostaglandin E2 infusion. This is standard procedure and can be done even before a definitive diagnosis has been made. Congestive cardiac failure is treated with diuretics but, if there is worsening tachypnoea and acidosis with peripheral constriction, inotropic support (typically dobutamine 5–10 µg/kg/min) might be needed for the volume loaded right ventricle. Intubation and ventilation might be necessary to remove the work of breathing and allow for haemodynamic stabilisation. Positive-pressure ventilation alleviates pulmonary oedema, and permissive hypercapnia can be used to allow the pulmonary vascular resistance to rise and so to reduce pulmonary overcirculation, although this is rarely necessary. Similarly, the addition of nitrogen to the ventilator circuit to reduce the fraction of inspired oxygen (F_iO_2), and so further increase pulmonary vascular resistance, is nowadays rarely done.[36] These measures stabilise most patients, enabling surgery to be planned over the following days. Frequently, patients present when the duct is closing and, after reopening with prostaglandin E2, the condition usually improves. Patients who have been antenatally diagnosed are started on a prostaglandin infusion from birth, but are otherwise managed in the same way.

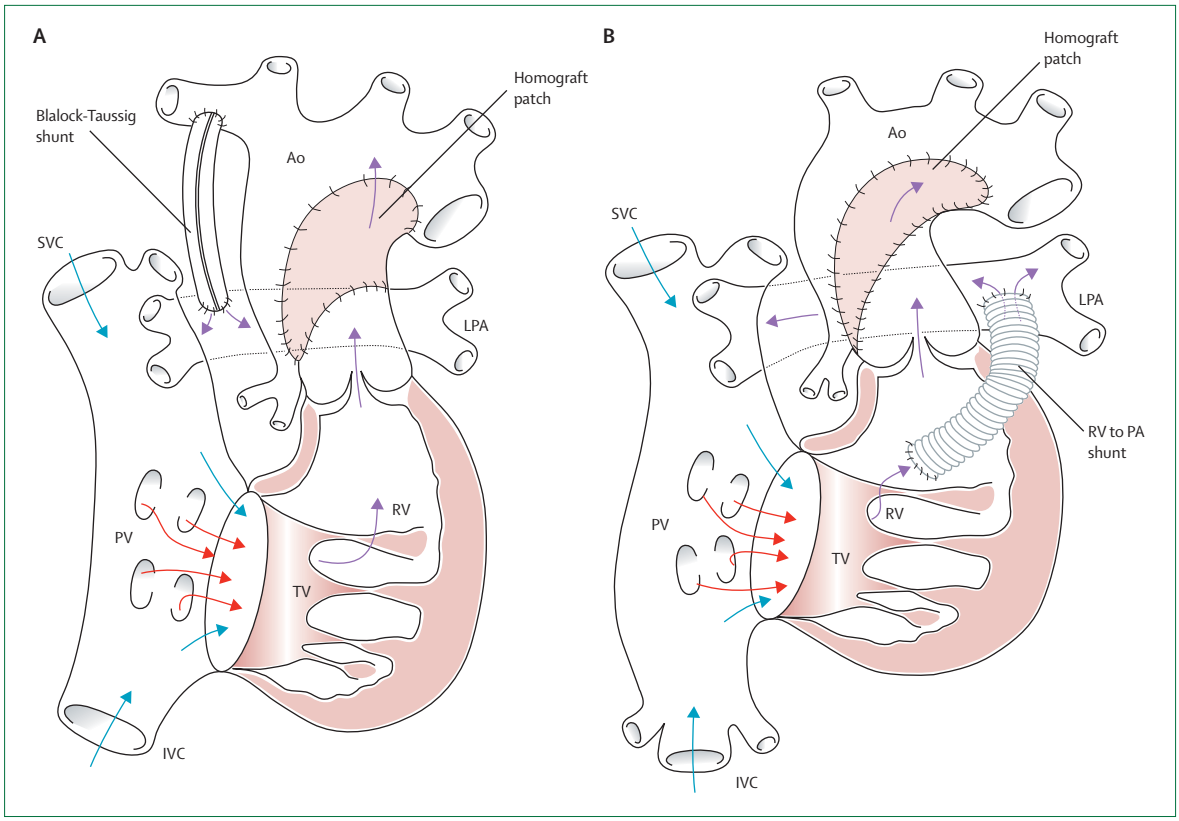

Figure 3: **The Norwood procedure for hypoplastic left heart syndrome**
The figure shows the two variants in surgical technique according to the way in which pulmonary blood flow is established. (A) The classical procedure with a systemic pulmonary artery shunt (Blalock-Taussig). (B) Modification with a right ventricle–pulmonary artery conduit. Ao=aorta. IVC=inferior vena cava. LPA=left pulmonary artery. PV=pulmonary valve. PA=pulmonary artery. RPA=right pulmonary artery. RV=right ventricle. SVC=superior vena cava. TV=tricuspid valve.

Patients with restrictive or even intact atrial septum pose a more urgent situation, depending on the severity of the obstruction and subsequent lung injury. The most severe cases are not compatible with life, but those who remain profoundly cyanosed despite ventilatory support need urgent decompression of the left atrium with either balloon atrial septostomy in the catheter lab or early surgery.

Once the diagnosis has been confirmed, treatment options need to be clearly explained to the families to allow them to make an informed decision. The option of no intervention (comfort care) should also be discussed, although this has inevitably become a less common choice as the results and enthusiasm for surgical Norwood programmes have improved.[37] Most centres would agree that comfort care is a valid option and this has become an area of sensitive ethical debate. The issues are not dissimilar from those surrounding extreme prematurity, and parents should be given balanced and clear advice that focuses on what is ethically acceptable rather than on what is strictly preferable.

The Norwood procedure

The aims of surgery are to secure the right ventricle in an unobstructed systemic circulation while providing a secure but balanced flow to the pulmonary circulation. The first is achieved by removing the atrial septum (atrial septectomy), reconstructing the aortic arch to remove any hypoplasia or coarctation, and to connect the main pulmonary artery into this reconstructed arch so that the right ventricle ejects directly into the systemic circulation. The latter is achieved through the placement of a small Gore-Tex shunt between systemic and pulmonary circulations, which is either in the form of a Blalock-Taussig shunt (the classical procedure) or, recently, with a right ventricle–pulmonary artery conduit (figure 3).

This complex procedure is called the Norwood procedure (panel 1), named after the surgeon who first described it, Bill Norwood, at Children's Hospital of Philadelphia in 1980.[38] The result is a functionally univentricular circulation based on the right ventricle with a balanced pulmonary blood flow, aiming to achieve a pulmonary-to-systemic (Qp:Qs) blood flow ratio of 1 to 1, which is the optimum balance of adequate oxygen delivery without undue volume overloading the circulation. The product of the Norwood procedure is referred to as a palliative circulation because it does not restore a normal biventricular circulation. The term should be used with care because of its widespread connotations in the management of terminal disease and

Panel 1: The Norwood procedure

Provide a pump for systemic circulation
The right ventricle is used to support the systemic circulation

Ensure pulmonary venous return can bypass the left ventricle
The atrial septum is excised

Produce an unobstructed systemic outflow tract
The aorta is reconstructed with homograft patch and the main pulmonary artery is plumbed into this reconstruction to create a neo-aorta

Provide a controlled pulmonary blood supply
A small Gore-Tex shunt is created between the systemic and pulmonary circulation

Panel 2: Risk factors for the Norwood procedure[1–3,43–46]

Strong factors

Weight
As continuous variable (<3 kg) and any weight lower than 2·5 kg

Intact or restrictive atrial septum
Can result in severe pulmonary congestion. Severely affects preoperative state

Ascending aortic size
As continuous variable and any diameter of 2 mm or less

Associated genetic anomalies
Strongly influence both early and long-term outcome

Weak factors

Ventricular function
Difficult to separate on multivariate analysis because of many competing factors

Preoperative ventilation

Tricuspid regurgitation
If moderate or severe tricuspid regurgitation

Prematurity
Any gestation before 36–40 weeks. On multivariate analysis is a separate factor to weight alone

Age at surgery
Especially if present late

Cardiopulmonary bypass time and deep hypothermic circulatory arrest time
Reflect ischaemic and inflammatory insult. Might be surrogate marker of difficult anatomy to repair

Anatomic subtype
Aortic or mitral atresia groups do less well than aortic or mitral stenosis

should not undermine the fact that the Norwood procedure is the definitive procedure for the condition.

Success of the procedure needs precise anaesthetic and cardiopulmonary bypass management, and has become one of the most challenging of neonatal operations. Initially, only a few centres could reproduce the outcomes in a handful of North American centres, but the procedure has gradually been adopted worldwide with steadily improving results. Early mortality was about 30–35% in series in the early to middle 1990s but has improved to the extent that many large centres are now reporting early survival (ie, 30 days) of 85–90%.[1,39–41] Nationally collected statistics within the UK from the Central Cardiac Audit Database (CCAD) show an early survival of 82% for all cases across the UK between 2001 and 2006, a total of 514 cases.[42]

There has been extensive analysis of the risk factors associated with the Norwood procedure (panel 2); the most frequently cited are the small size of the ascending aorta (both as a constant variable and as <2 mm)[1–3,47] low birthweight, tricuspid regurgitation (moderate or severe), intact or restrictive atrial septum and pre-existing impaired ventricular function (table).[48] The presence of syndromic or other genetic defects is also strongly associated with poor outcome.[43,49,50] We have published an algorithm predicting outcome based on the most important factors of aortic size and patient weight.[51] Experience with the technique is important, and units need to have regular exposure to the management of complex cases not only to develop surgical expertise but also for all other aspects of care. Abundant data suggest that centres dealing with high numbers of cases are achieving better outcomes than centres dealing with less than five cases per year. The argument is a strong one to concentrate the expertise for these types of procedures into a small number of specialised institutions, where mortality is less than 50% than that in small-volume centres.[52,53]

Various improvements and refinements of the techniques have been made over the years, including the use of smaller aorto-pulmonary shunts[54] and methods to reduce the period of deep hypothermic circulatory arrest. The most important of these has been the institution of antegrade cerebral perfusion during arch reconstruction, which might improve clinical outcomes.[55–57] Some investigators have recommended the use of postoperative circulatory support (extracorporeal life support) to enable myocardial recovery and improve oxygen delivery in the early postoperative phase, which might in turn improve neurological outcomes.[58]

The Norwood procedure is the best balance that can be achieved given the substrate, but it remains one of the highest risk procedures in paediatric cardiac surgery. An indication of the risk is given in the Risk Adjustment for Congenital Heart Surgery (RACHS) scoring system, which allocates a risk assessment to all cardiac procedures and groups the operations according to the perceived risk. The Norwood procedure sits alone in the highest risk category (group 6).[59]

Postoperative management brings together the most challenging areas of neonatal cardiac intensive care with the aim of balancing systemic and pulmonary

circulations. Postoperative management is focused around the importance of achieving balance with systemic saturations of about 80%.[60] The risk of high F_iO_2 or of allowing the partial pressure of carbon dioxide (p_aCO_2) to fall is that these might lower pulmonary vascular resistance, volume loading the circulation, and lead to cardiac failure. Recent focus has been given to lowering systemic vascular resistance to secure better systemic perfusion, using vasodilators such as phenoxybenzamine and the phosphodiesterase inhibitor milrinone.[61,62] Mixed venous saturations are also closely monitored to optimise oxygen delivery, and some investigators have advocated the use of continuous in-line measurement of mixed venous saturations.[63] The chest is usually left open after these procedures to avoid the compressive effect of the closed chest on right-ventricular compliance, and is generally closed after 24–48 h in the intensive care unit, when heamodynamic stability has been maintained and any tissue and myocardial oedema have resolved. Anti-coagulation with heparin is started in the intensive care unit to reduce the risk of shunt thrombosis and is substituted for low-dose aspirin (5–15 mg/kg) once oral feeding is established.

The right ventricle–pulmonary artery conduit

One of the concerns over the classical procedure using a Blalock-Taussig shunt is that flow occurs throughout the cardiac cycle, creating diastolic run-off away from the aorta, which can result in retrograde diastolic flow in the aorta and risk of coronary steal phenomenon. Patients tend to have low diastolic pressures and incidences of sudden death, in which no clear cause can be ascertained even at post-mortem examination, have been attributed to this low diastolic pressure.

One of the most important and still controversial surgical modifications has been the use of a right ventricle–pulmonary artery conduit (in the form of a large simple Gore-Tex tube of 5–6 mm) in place of the Blalock-Taussig shunt as the source of pulmonary blood flow.[64] Most flow takes place in systole and, because there is no run-off during diastole, the diastolic blood pressure in maintained. The technique became popular with the work by Sano and colleagues[64] and has become increasingly widely adopted. Several studies have indicated improvement of survival with the use of this technique,[40,41,51] and evidence shows that an increase of diastolic pressure is achieved.[65–67] Furthermore, right ventricle–pulmonary artery shunts might result in decreased tricuspid-valve regurgitation, reduced inter-stage mortality,[68] and might stimulate improved and more symmetrical growth of native pulmonary arteries.[69] Nevertheless, the technique needs a small ventriculotomy, which might impair ventricular function in the short or long term, although at present little evidence exists to support this.[70,71] Some occurrences of late obstruction of the right ventricle–pulmonary artery conduits might need re-intervention earlier than planned. A multicentre randomised prospective trial[72] is currently underway to assess the two techniques but, until results are published, there is no consensus and proponents of both techniques continue to debate (panel 3).

	Procedure	Sat_aO_2	Survival
Neonate	Norwood procedure: complex bypass surgery; 1 week in intensive care unit; 3 weeks inpatient stay	75–80%	80–85%
5–6 months	Stage II procedure (cavopulmonary shunt): bypass surgery; 1–2 days in intensive care unit; 10 days inpatient stay	80–85%	95–98%
4–5 years	Stage III procedure: bypass surgery; 1–2 days in intensive care unit; inpatient stay might be prolonged because of persistent pleural drainage (the consequence of high systemic venous pressure)	90–95%	95–98%
Lifelong	Regular surveillance. Anticoagulation recommended by most. Likely to develop heart failure in adult life. Slow attrition rate, yet more than 80% patients currently remain well after stage III	..	..

Sat_aO_2=typical arterial oxygen saturation after the procedure.

Table: **Timescale of staged surgical treatment**

Panel 3: Controversies

Transplantation versus Norwood surgery
- Neonatal transplantation not available in the UK
- Concern over mortality while waiting on transplant list
- Results of Norwood strategy currently better than those of transplantation
- Quality of life might be better for transplant survivors

Norwood surgery: source of pulmonary blood flow
- Blalock-Taussig shunt or right ventricle–pulmonary artery conduit
- The right ventricle–pulmonary artery conduit is becoming increasingly popular
- Improved survival in some series
- Randomised trial currently in progress

Postoperative management
- Shift towards systemic vasodilatation rather then manipulating pulmonary vascular resistance
- Use of smaller shunts
- Monitoring mixed venous S_vO_2

Hybrid procedure
- Innovative combination of interventional cardiologists and cardiac surgeons to mimic Norwood physiology with bilateral pulmonary artery bands and ductal stenting
- Avoids cardiopulmonary bypass but outcomes still unclear
- Currently only used in high-risk groups where bypass carries increased risk

Antenatal diagnosis
- Allows for timely counselling and for planning of delivery
- Conflicting evidence in terms of effect on outcome
- First-trimester screening could be soon available

S_vO_2=mixed venous oxygen saturation.

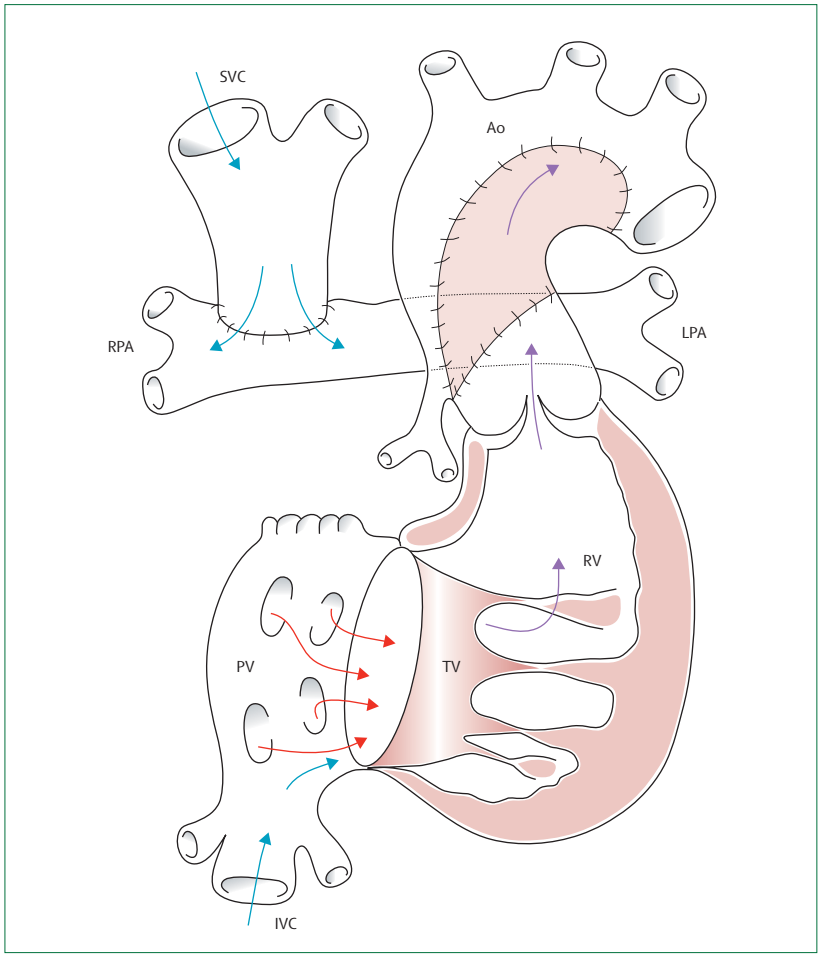

Figure 4: **The stage II procedure: the cavopulmonary shunt**
Ao=aorta. IVC=inferior vena cava. LPA=left pulmonary artery. PV=pulmonary valve. RPA=right pulmonary artery. RV=right ventricle. SVC=superior vena cava. TV=tricuspid valve.

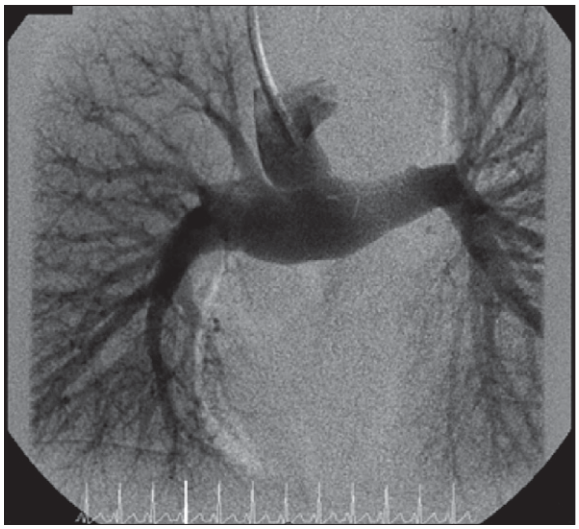

Figure 5: **Angiogram after a stage II procedure (cavopulmonary shunt)**
The angiogram shows the superior vena cava connected directly into the right pulmonary artery.

Post-stage I progress

Recovery from the critical early postoperative period marks the transition to a period of surveillance. Vigilant postoperative care and monitoring are crucial elements for any successful treatment strategy for hypoplastic left heart syndrome. Most patients are discharged with oral diuretics, although caution must be taken to avoid inducing vascular volume depletion with subsequent reduction in cardiac output or hyperviscosity with increased risk for shunt thrombosis. Afterload reduction with an angiotensin-converting enzyme inhibitor is given only to patients with increased ratio of pulmonary over systemic blood flow, those who have congestive heart failure, moderate or severe atrio-ventricular valve insufficiency, or as part of a North American trial using captopril as an afterload-reducing agent.

Interim mortality is high and remains one of the most challenging areas to improve outcomes, with figures of 4–15% of hospital survivors dying after discharge before stage II operation. Some patients who are thought to be clinically well at hospital discharge die unexpectedly. Residual aortic-arch obstruction, restrictive atrial septal defects, imbalance of pulmonary and systemic blood flow, diastolic run-off with coronary ischaemia, shunt stenosis or thrombosis, and chronic volume overload of the single ventricle have all been implicated as possible causes for interstage mortality.[73] However, the only identifiable preoperative findings predictive of interstage death are restrictive atrial septum and late initial presentation.[74]

The most successful interventions have been the use of home monitoring of pulse oximetry, education of parents to seek advice if oxygen saturations fall below 70%, which might help to pick up early signs of respiratory illnesses or the insidious development of shunt stenosis or thrombus. This simple measure reduces interim mortality, and in one study[75] it eliminated it completely.

Various interim interventions might be needed to address residual lesions or complications, most of which can be done by interventional catheterisation. The most common problems are residual coarctation, tricuspid regurgitation, and left pulmonary artery stenosis or hypoplasia. Residual coarctation occurs in 5–10% of patients after the Norwood procedure, usually related to residual ductal tissue in the distal aortic arch, and can be successfully treated by balloon arterioplasty in 90% of cases. Tricuspid regurgitation is a secondary phenomenon related to right ventricular dilatation, which is usually managed conservatively and often decreases after stage II. Occasionally, surgical repair is warranted as a separate procedure or as a concomitant component during subsequent stages.[76] The evolving image quality of cardiac MRI and CT has made them important tools in assessing anatomy after stage I, and can help to guide treatment and re-intervention.

Stage II: the cavopulmonary shunt

The second stage procedure is done at 4–6 months of age, by which time children have often doubled their birthweight and are beginning to outgrow the original shunt. By this age, pulmonary vascular resistance has fallen (almost to adult levels), which means that they no longer need a high-pressure source of blood supply to the lungs. The exact timing depends on clinical state, but most centres would formally assess circulation with cardiac catheter or MRI at 3–4 months, and plan stage II surgery after this, guided by saturation levels that tend to fall as the child grows.[77] At stage II, the original shunt is removed and the superior vena cava is disconnected from the heart and joined directly into the pulmonary arteries.

Thus, all the venous return from the superior vena cava is directed into the lungs—the so-called cavopulmonary shunt or bidirectional Glenn shunt (figures 4 and 5). This is still a major procedure needing cardiopulmonary bypass, but it takes all volume load off the circulation and so unloads the heart, substantially improving the mechanical efficiency of the ventricle. The azygous vein is ligated as part of the procedure to prevent venous run-off to the lower body and ensuring that all superior vena cava flow is directed into the pulmonary circulation. Combined with the age of the patient, this is a far less risky procedure than stage I, and generally has a 96–99% survival.

Completion of stage II is a landmark and patients are generally far more robust after this surgery than they were before. The anastomosis grows with the patient and saturations are maintained around 80% with the superior vena cava return flowing passively through the pulmonary circulation. There is little mortality between stages II and III, and the timing of the third (and final) stage procedure partly depends on institutional preference. Most children are well for several years with this circulation. It is only when the child becomes more active and progresses from crawling to walking to running that the degree of desaturation becomes gradually more severe, especially during exercise. Although some centres follow a policy of routinely progressing to stage III surgery at a fixed age (sometimes as young as 18 months), most are guided by deteriorating patient symptoms and degree of desaturation. This is most commonly around the age of 4 years.

Stage III: the total cavopulmonary connection

The third and final stage of the palliative approach to hypoplastic left heart syndrome is to redirect the inferior vena cava return through the pulmonary vasculature so that all the systemic venous blood runs passively into the lungs, effectively bypassing the right ventricle. In achieving this, systemic and pulmonary circulations are separated from each other and, for the first time, the child is no longer cyanosed. However, in contrast to normal circulation in which pulmonary and systemic circulations are separated by a pumping chamber, here they are two circulations in direct series and a single ventricle must provide enough energy to the circulating blood to drive it through two capillary beds before it returns to the heart. This innovative circulation in series was originally conceived by Francis Fontan over 30 years ago as a palliative procedure for other less complex forms of functionally univentricular circulation such as tricuspid atresia.[78] This so-called Fontan circulation has undergone various technical modifications over the years and is now referred to as the total cavopulmonary connection but, essentially, is the final common pathway for a whole range of congenital heart defects characterised by a functionally single ventricle circulation.

The procedure is done on cardiopulmonary bypass during which the inferior vena cava is tunnelled through to the underside of the right pulmonary artery (figure 6). This can be achieved either with a baffle sewn within the right atrium to direct the inferior vena cava blood along a lateral tunnel within the atrium, or by disconnecting the inferior vena cava from the right atrium and connecting a large-bore Gore-Tex tube graft from the inferior vena

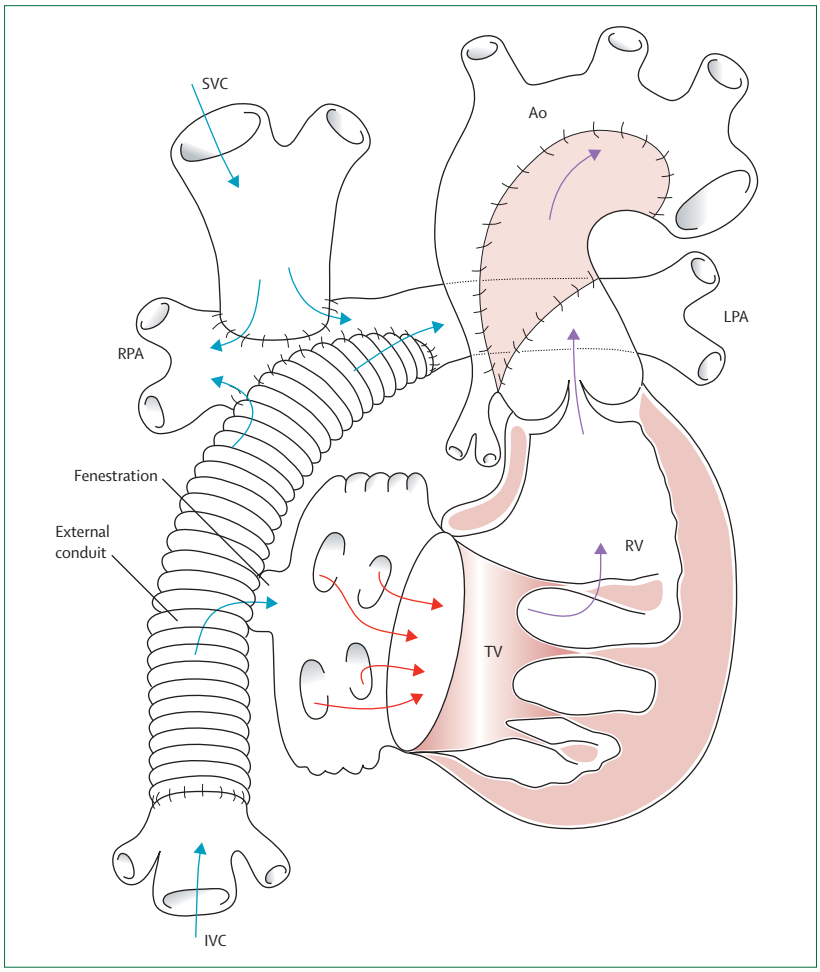

Figure 6: **The stage III procedure: the total cavopulmonary connection**
The technique uses an extracardiac conduit to direct the inferior vena cava flow into the pulmonary arteries. Ao=aorta. IVC=inferior vena cava. LPA=left pulmonary artery. RPA=right pulmonary artery. RV=right ventricle. SVC=superior vena cava. TV=tricuspid valve.

cava up to the underside of the pulmonary arteries. The latter is the extracardiac total cavopulmonary connection and can be done without arresting the heart. In-hospital mortality is similar to that of stage II, generally around 3–4%.[79] Outcomes have been improved with a small fenestration in the Fontan circulation that allows some blood to bypass the lungs and return directly to the systemic circulation; this improves systemic blood flow at the expense of a small degree of desaturation and is used by most centres (figure 6).

As patients with hypoplastic left heart syndrome have a morphological right ventricle and already have two surgical procedures, they are expected not to have the same functional capacity or long-term prognosis as other Fontan patients who have a morphological left ventricle. However, the evidence to date does not support this assumption. Patients with hypoplastic left heart syndrome are no worse (or better) than other groups of patients undergoing the Fontan-type procedures both in terms of early and mid-term survival. Outcome of the Fontan procedure highly depends on factors that are independent of morphology—ie, preoperative pulmonary artery pressures and ventricular function. Although some weak endpoints, such as long postoperative pleural effusions and long in-hospital stay, have been associated with patients with hypoplastic left heart syndrome, no evidence exists to establish that the early or intermediate outcome is any different from other groups, so long as ventricular function is good.[80,81] Long-term performance of these Fontan circulations in patients with hypoplastic left heart syndrome remains unknown and detailed follow-up of this cohort is essential to establish whether this will be maintained in later years. The expectation is that these ventricles are likely to decline, on the basis of observations of other situations in which the right ventricle functions in the systemic circulations, such as congenitally corrected transposition (ccTGA).

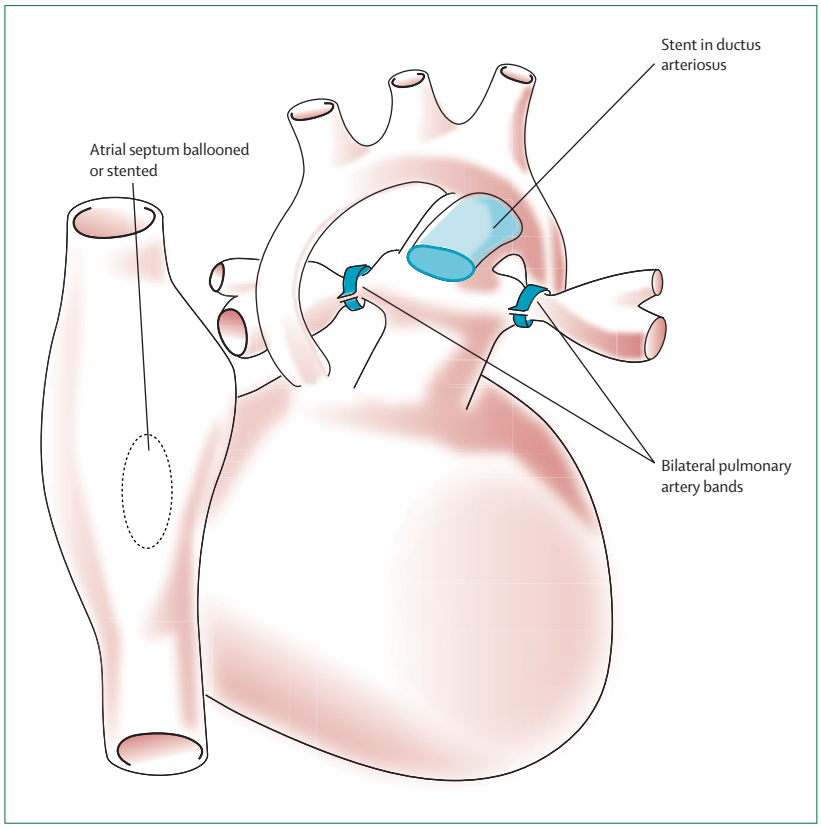

Figure 7: **The hybrid procedure: an alternative approach to the Norwood procedure**
The hybrid procedure uses bilateral pulmonary artery bands to limit pulmonary blood flow and places a stent in the ductus arteriosus to hold it open. A balloon atrial septostomy is also done.

Neonatal transplantation

The concept of transplantation as a treatment for hypoplastic left heart syndrome developed together with the palliative approach of the Norwood procedure. The principles of surgery are very much the same as for heart transplantation at any age and share the same limiting factor of donor availability that hinders all heart transplant programmes worldwide. However, the issue of donor availability is even more extreme for neonatal heart transplantation. The scarcity is such that neonatal heart transplantation has never been pursued as a treatment option in the UK. Only a handful of centres worldwide have embarked on such a programme and the numbers remain very small. Loma Linda in North America has the largest reported numbers, with a total of 176 patients and 14% early (30 days) mortality, and a further 20% of patients who died waiting for a transplant.[82] Other multicentre studies average 25% mortality awaiting transplant.[83] Furthermore, individuals with hypoplastic left heart syndrome tend to have a higher operative mortality than other groups of infant transplant.[84] The vast imbalance between demand and organ availability has led to transplantation remaining an option in only selected centres. Many critics would feel that mortality on the waiting list alone is not acceptable because of continued improvements in results of the Norwood procedure.

However, the benefit of a biventricular physiology produces better quality of life in children who receive a successful transplant compared with age-matched palliative-staged patients, but this benefit has to be balanced against the side-effects and morbidities of immunosuppressant therapies, the constant threat of rejection and late malignancy, and the difficult ethical considerations of considering second and third transplants later in life.

Nevertheless, results of infant transplantation have improved over the past two decades, and the donor pool has benefited from the realisation that ABO incompatibility is possible in neonatal transplantation because the immune response is not mature.[85] Newborn infants do not produce isohaemagglutinins, serum anti-A or anti-B antibody titres are low until 12–14 months of age, and the complement system remains functionally incomplete. Thus, the main factors that would initiate

hyperacute rejection are absent during early infancy[86] (the maximum age at which this protocol can be applied is still not known).

Overall, transplantation is reserved for patients who have embarked on the palliative staged programme but are in incipient cardiac failure and no longer responding to conventional therapy. In these cases, children are generally at an age in which there is a wider donor pool and transplantation can be a planned procedure. However, this is not without its issues and patients might not always be good candidates for transplantation because of other organ system failure, indolent pulmonary hypertension, and the presence of multiple reactive antibodies due to recurrent exposure to blood transfusions and homograft tissue.[87]

The hybrid procedure

Over the past 5 years, an innovative alternative to the stage I Norwood procedure has emerged. The approach has developed from the need to try to keep the insult of cardiopulmonary bypass to a minimum in these fragile neonates, together with the emergence of a new idea of combining interventional cardiac catheterisation techniques with surgery—the so-called hybrid technology.

The procedure aims to replicate the physiological state of the Norwood procedure by placing bilateral pulmonary artery bands to limit flow to the lungs whilst placing a stent (a bare metal transcatheter stent similar to those used in coronary artery disease) in the arterial duct to hold it open. The final component is to ensure atrial mixing with a balloon septostomy with or without a stent in the atrial septum to hold it wide open (figure 7). The procedure is an ingenious application, combining the skills of surgeon and interventional cardiologist working together in the operating theatre using image intensification system to deploy the stent(s). It is done through a standard sternotomy but does not require cardiopulmonary bypass. Also, it can be undertaken sequentially in the operating theatre and then in the angiography suite, but a new generation of hybrid angiography suites, where surgery and intervention can be done simultaneously, are becoming of increasing interest. Alternatively, patients can be managed with the placement of pulmonary artery bands and prolonged use of prostaglandin E2 to avoid ductal stenting completely.

Preliminary results have been encouraging with early mortality certainly comparable with that of standard protocols (about 15–20%).[88,89] Direct comparison has been difficult because the procedure has been reserved for patients generally regarded as high risk for bypass surgery (low birthweight, unstable haemodynamics, and poor ventricular function). Interstage mortality is high (15–20%)[90] and case-matched studies have shown no benefit over conventional surgery.[89] The difficulty is that results of conventional surgery in the low-risk groups are now so good that many centres have been reluctant to undertake a new procedure.

Other concerns exist regarding the hybrid principle: the technique of placing bilateral pulmonary artery bands is difficult because branch pulmonary arteries are small in a neonate. Another concern is that the duct-stent position is crucial and, if patients have a diminutive ascending and transverse aorta, then the procedure does not address this obstruction to coronary flow. If the transverse aorta is small, a risk exists that the stent itself might distort or interfere with retrograde flow into the arch, and for this reason most centres do not recommend the hybrid approach in the setting of a small transverse arch. Nevertheless, the procedure has a role in the types of treatments for hypoplastic left heart syndrome and, with continued encouraging results,[91] it will most likely find a niche among high-risk patients. It might also have a role in stabilising patients in transplant centres awaiting donor-organ availability, therefore improving survival while awaiting transplantation.[92]

There have been interstage issues with stent migration and occlusion, with up to 50% of patients needing catheter re-inteventions;[90] furthermore, the stage II procedure becomes much more extensive than the conventional stage II because the aortic arch needs to be reconstructed (excising the ductal stent), the bands removed, and the pulmonary arteries repaired with a patch in addition to creating the the cavopulmonary connection. Consequently, the stage II after the hybrid procedure carries substantial operative mortality (10–15%) and this needs to be taken into account when comparing it with conventional techniques.[90,91]

No consensus exists on the future of the hybrid approach. It is innovative and offers potential benefits that still need to be proven.

Future challenges

The story of the Norwood procedure and parallel advances in intensive care and other surgical approaches are an extraordinary chapter in neonatal cardiac surgery, and have transformed what was previously a fatal condition. Innovations have characterised the progress that has been made in neonatal cardiac surgery and have had widespread positive repercussions on the development of the specialty on the whole. The role of transplantation and of hybrid procedures remains to be established. Assessment of different strategies is difficult because techniques are evolving rapidly and individual centres tend to focus on single management strategies with variable reporting of selection and exclusion criteria (panel 3). Consequently, multi-institutional databases might be the only way in which this comparative knowledge can be generated within a clinically relevant timeframe. The current National Institutes of Health trial[72] that is comparing the aorto-pulmonary with the right ventricle–pulmonary artery shunt is an excellent example of a collaborative approach to address an important operative decision.

The philosophical and ethical debate over the role of such an investment in a series of complex procedures to produce what is a palliative circulation is not yet resolved. Extensive studies have attempted to assess the quality of life for these children,[93,94] and most markers show that they underperform compared with healthy controls, although they remain in the normal range. Nevertheless, most children (>80%) who reach schoolage have normal intelligence quotient.[95] While proponents celebrate what has been achieved in these children, the question of whether the investment of the health systems is appropriate for a still unknown long-term outcome is debated. The burden on the families of repeated admissions and chronic health problems must not be overlooked, and the financial implications on health-service resources are substantial. Indeed, the future for these children, the oldest of whom in the UK are in their early teenage years, remains unknown and offers a new set of challenges for adult congenital heart services.

Most cases are still not diagnosed before birth and have no associated syndrome or dysmorphism. Parents can be faced with an impossibly difficult decision with what can be a completely healthy-looking baby. It is helpful to bear this scenario in mind when casting moral viewpoints and to consider that perseverance with the technique has reduced early mortality from 30–40% only 15 years ago to 10–15% in the modern era. There is no doubt that lessons learnt both in the operating room and the intensive care unit have profoundly contributed to the development and progress of neonatal cardiac surgery.

Contributors

All authors contributed to the main text. MDK supervised the section on prenatal diagnosis, whereas BD supervised the search strategy.

Conflicts of interest

We declare that we have no conflicts of interest.

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