Congenital heart disease in the 21st century

David Winlaw

ABSTRACT

Paediatric cardiac surgery is now a mature specialty, yielding good results for those born with congenital heart disease (CHD). The current status of this surgery is considered, highlighting progress in genetic studies, improvements in intensive care management, and contemporary management of the low cardiac output syndrome. Emerging issues include the neurodevelopmental status of patients undergoing cardiac surgery, and known issues with the Fontan circulation. A framework for considering adults with CHD is described, including a review of common procedures and expected outcomes. Similarities and differences between routine adult cardiac intensive care and care of adults with CHD are also discussed.

Some patients classed as the "successes" of paediatric cardiac programs, as well as those with known persisting problems, need close follow-up in adult facilities. There is every indication that significant numbers of patients with complex disease are now entering a phase of life when late complications may present. Some overlap in experience between paediatric and adult care settings is invaluable in providing optimal care.

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Paediatric cardiac surgery is now a mature specialty, yielding good results for those born with congenital heart disease (CHD). Incremental changes over the past decade have consolidated the leaps made in the 1980s and 1990s. Established international bench marks for mortality and major morbidity are < 5% and < 10%, respectively, for most conditions. These figures are the result of an integrated approach involving cardiology, neonatology, anaesthesia, surgery and intensive care.

A result of these advances is an increasing pool of adults with treated CHD, most of whom will require additional medical management as they age. Ideally, these patients will be followed up in an "adult congenital" clinic, by cardiologists with a special interest in this population. Like other patients with chronic disease, those with adult CHD may not be conscious of the severity of their physical limitation, and some may be helped by further interventions.

Epidemiology and genetic basis

CHD affects nearly 1 in 100 newborn infants[1-3] and is the leading non-infectious cause of death in this age group. More specifically, the incidence of moderate and severe forms of CHD is 6 per 1000 live births. With the inclusion of bicuspid aortic valve, this rises to 19 per 1000 (about 1 in 50 individuals). Overall, a third of those affected need surgical or catheter-based intervention in the first year of life. In 2002, CHD accounted for 224 deaths of Australian children.[3] In the United States, there are more than 35 000 new CHD cases each year, and over 1 million survivors of CHD in the community.[4] This represents a significant economic and social burden, and an impetus for research into causation and risk assessment.

Diagnosis and treatment of CHD has improved dramatically over the past 15 years. Fetal echocardiography has broadened the window of diagnosis and revealed how the severity of a defect may compound during development in response to flow abnormalities.[5] Detection of syndromes and chromosomal anomalies associated with CHD, especially velocardiofacial syndrome (VCFS or 22q11 deletion syndrome), has greatly improved over the past decade with routine screening of newborns with abnormalities of the cardiac outflow tracts.

CHD associated with a syndrome (such as Down syndrome or VCFS) and rare dominantly inherited forms constitute only 30% of all cases (for review see Gruber and Epstein[6]). The remaining 70% comprise the so-called sporadic or isolated form, where the proportion of first-degree relatives affected is low (5%). Population studies demonstrate that the risk of occurrence in siblings and transmission to further offspring is 3%–5%, but 10%–15% for certain lesions (for review see Burn and Goodship[7]). The risk to offspring is greater for affected females than for affected males.[8] Common CHD is likely to be the result of multiple gene defects and/or an interaction between defective genes and the fetal environment. Life expectancy is below normal, and risks of transmission become important as children reach reproductive age.[9]

Surgical procedures for congenital heart disease

Surgery for CHD in the paediatric age group can be broadly divided into four groups.

Isolated septal defects. Secundum atrial septal defects are usually closed by device or surgery at preschool age. Important perimembranous ventricular septal defects are usually closed in infancy.

Two-ventricle repairs with "normal" physiology recreated. An example is transposition of the great arteries; although a major operation is required during the neonatal period, the outlook is generally good, with a low rate of subsequent reintervention and excellent functional result.

Two-ventricle repairs with "abnormal" physiology remaining. An example is tetralogy of Fallot, where pulmonary valvectomy and outflow augmentation is often required, leaving free pulmonary incompetence and a substrate for right ventricular enlargement, arrhythmias and diminished exercise capacity.

Single-ventricle operations for functional single ventricles. The common pathway is a staged series of operations, culminating in the Fontan circulation (complete cavopulmonary connection), where systemic venous return is directly connected to the pulmonary arteries. There is considerable variation in complexity of underlying morphology, from tricuspid atresia to hypoplastic left heart syndrome. The fundamental difference is the complexity of the first operation; thereafter, the pathway to Fontan is very similar.

Patients in the third and fourth groups are the most likely to require treatment later in life, with problems including conduit failure, pulmonary insufficiency, arrhythmias, impaired ventricular function and endocarditis.

Outcomes of surgery

The principal cause of morbidity and mortality after paediatric cardiac surgery remains impaired cardiac function. After most large operations involving cardiopulmonary bypass and myocardial ischaemia, there is a predictable decline in cardiac performance over the first 6–18 hours.[10] This is temporally associated with an increase in body water. The principal causes are haemodilution at surgery, the systemic inflammatory response to cardiopulmonary bypass, and accumulation of fluid and protein in the interstitium as a result of capillary leak. These changes affect the heart and lungs as well as other tissues.[11] Additional risk factors include the need for ventriculotomy, complicated intracardiac surgery and pre-existing morbidity, such as severe ventricular hypertrophy. In general terms, achieving an adequate systolic pressure is not difficult, but gaining satisfactory cardiac output is problematic, highlighting the role of diastolic dysfunction (failure of the ventricle to actively relax and fill) in the pathophysiology of this condition (for review see Egan et al[11]).

In most cases, this period of low cardiac performance can be managed with usual measures to optimise cardiac performance and reduce end-organ oxygen requirements. These include optimising preload, reducing afterload, cooling to 35.5–36°C, and increasing myocardial contractility. Over recent years, significant gains have been made in neonatal surgery through recognition of the importance of reducing afterload, beginning before weaning from cardiopulmonary bypass, and continuing through the first postoperative days.[12] This is associated with better outcomes than simply driving the heart harder with catecholamine-based inotropes. The role of the inodilator milrinone has been increasing even for "routine" surgery.[13]

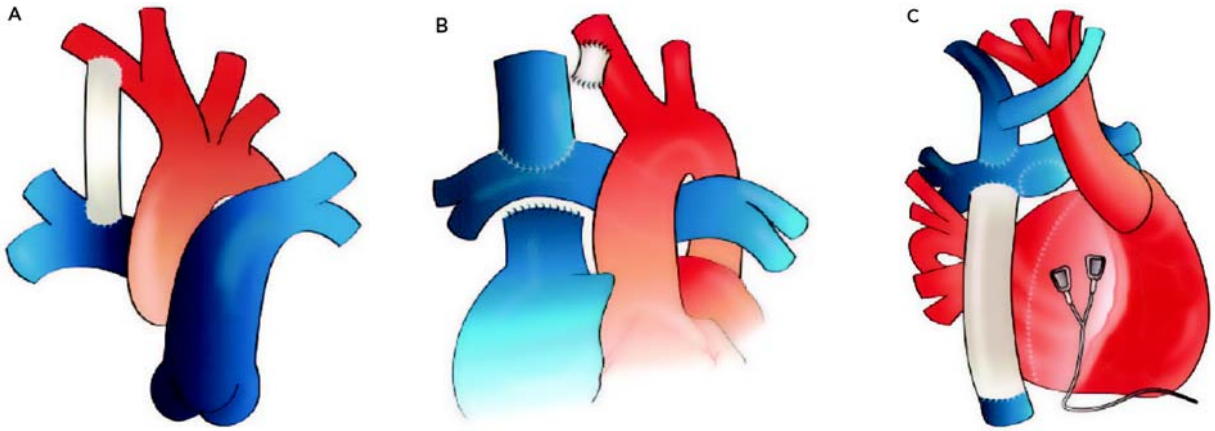
Where standard measures are insufficient to maintain satisfactory tissue oxygenation, particularly for the brain and kidneys, mechanical support is increasingly used. This is mostly achieved with central cannulation and a circuit comprising a pump, an oxygenator and a haemofilter (extracorporeal membrane oxygenation [ECMO]). Improvements in oxygenator longevity have improved outcomes for supported children. While the potential for neurological injury through embolic complications of mechanical support remain, this may be less than the risk of global brain hypoperfusion seen in a critical low cardiac output state. Near infrared spectroscopy monitoring of both brain and somatic regions assists in decision-making.

As mortality declines, the focus is increasingly on quality of outcome. Measures to improve cardiac performance postoperatively are paramount. We are increasingly aware that some survivors of neonatal and infant surgery suffer a form of neurological injury that may manifest only when they are toddlers or begin school.[14] This may affect 15%–30% of neonates undergoing major surgery, and a significant proportion have evidence of structural or functional abnormalities before surgery. Behavioural issues, including attention deficit hyperactivity disorder, impairment of fine motor skills and poor handwriting, are characteristic. So-called "executive functions" appear to be compromised. Prematurity and the presence of associated syndromes heighten the risk.[15]

For children who require surgery in the first 30 days of life — the highest risk period — there are rarely alternative approaches that allow it to be postponed. Our focus then is on reducing the impact of surgery on the brain, through minimising circulatory interruption, ensuring adequacy of flow during all phases of the operation, and maintaining good cardiac performance postoperatively. Deep hypothermic circulatory arrest may in part explain some of the adverse neurological outcomes of previous decades and is now rarely used. Understanding and minimising neurological injury is an international focus of research and clinical practice. Cardiac units in Melbourne, Auckland and Sydney are undertaking significant prospective research in this area.

Surgery for hypoplastic left heart syndrome (HLHS) deserves mention because of the attention paid to this condition by parent groups, health administrators and the media. It is not the only condition that may be associated

Figure 1. Example of a pathway to a Fontan circulation for tricuspid atresia*



A. *Systemic-to-pulmonary shunt (neonatal procedure).*

B. *Creation of a superior cavopulmonary connection (Glenn shunt), takedown of systemic-to-pulmonary shunt, atrial septectomy (not shown).*

C. *Completion of the Fontan circulation with an extracardiac conduit. Permanent pacemaker leads have been placed.*

Reproduced with permission from Khairy P, Poirier N, Mercier LA. Univentricular heart. *Circulation* 2007; 115: 800-812.[17] A depiction of the various types of Fontan connection and further details on functional single ventricles are found in that article and in Gatzoulis et al.[18]

with bad outcomes. For example, early mortality of up to 30% and significant early morbidity is also seen in subsets of patients with less controversial conditions, such as pulmonary atresia with intact ventricular septum. The notoriety of HLHS is largely a result of the easy identification of the patient group, the need for an exacting procedure as a neonate (a Norwood operation), the resource-intensive nature of the surgery and after care, as well as concerns regarding intellectual and cardiac performance of survivors. In fact, results for Norwood surgery are steadily improving, and, in some specialist centres, hospital survival is in excess of 90%.[16] The expertise and team approach required to achieve these results has had a positive impact on quality of care for many other complex cases.

Box 1. Late complications of the Fontan circulation[18]

Right atriomegaly and hepatic dysfunction
Obstructed pulmonary venous return in the Fontan pathways
Myocardial dysfunction and failure
Thromboembolic events (those at high risk receive anticoagulation therapy)
Pulmonary arteriovenous malformations (reducing systemic SpO_2)
Systemic venous collateralisation (reducing systemic SpO_2)
Sinus node dysfunction
Atrial re-entry tachycardia
Protein-losing enteropathy (often end stage, related to above)

The complete cavopulmonary connection, or Fontan circulation, is the final common pathway for patients with functional single ventricles. An overview of common stages toward a complete cavopulmonary circulation is shown in Figure 1. The effective function of this circulation depends on passive flow of venous return into the pulmonary arteries, taking advantage of the momentum of the blood, acceleration provided by muscle pumps of the lower limbs, and the negative intrathoracic pressure generated during inspiration.

The failings of the Fontan circulation are acknowledged, but this approach does provide a good quality of life for most children into and beyond the third decade. Late complications after Fontan are common presentations, and are listed in Box 1 (adapted from Freedom et al[18]). They should be considered in Fontan patients undergoing non-cardiac surgery, as well as those presenting for further cardiac procedures.

The so-called "failing Fontan" combines a number of these late complications. An acute decompensation may be related to onset of atrial arrhythmias on a background of worsening ventricular function. Hypotension and desaturation are common. Unlike other patients with heart failure, patients with a failing Fontan may not respond well to conventional positive pressure ventilation, as this diminishes blood flow through the lungs. In fact, they may respond well to fluid, depending on the degree of ventricular dysfunction, as this augments cardiac output and hence pulmonary blood flow. Rhythm control, pacing as required,

afterload reduction and inotropes are useful in the acute phases.

"Graduates" of paediatric programs: adult CHD

It is estimated that more than 80% of children with CHD survive into adulthood. Extrapolating findings from the United Kingdom and the US, we would expect the addition of 1000 patients with moderate to severe congenital lesions in Australia each year. A group approach, starting in an established adult CHD cardiology service, and including all elements of the acute care team, is required to achieve good results in patients with complex conditions. Practitioners with paediatric and adult experience are required in each specialty. For example, in surgery, the combined skill set offers benefits to both groups, and surgery for CHD is seen as an emerging hybrid specialty.

As Price et al reported from the experience of more than 300 patients at Brompton Hospital, London, between 1997 and 2002,[19] many routine aspects of adult cardiac care apply to patients with adult CHD. Specialist experience in some aspects of relevant cardiopulmonary physiology is needed, particularly in relation to fluid administration, systemic oxygen delivery and management of poor ventricular function. The mortality in their series was low at 4.4% (surgical mortality, 3.2%). They concluded that standard severity of illness scores overestimated mortality in most, but underestimated mortality for complex cases.

This finding was recently mirrored by that of Jacquet et al in a small specialist practice,[20] where adult CHD comprised 6% of the workload. They divided their presentations for surgery into four groups, on which the following classification is loosely based.

Aortic valve and aortic procedures. These are frequently pulmonary autograft procedures or replacements, often in the context of bicuspid aortic valve disease. Concomitant aortic dilatation may necessitate replacement. These are often long and technically demanding procedures, but expected postoperative function is good.

Patients with operated tetralogy of Fallot and similar physiologies. The most common presentation is right ventricular dilatation due to free pulmonary incompetence. These patients undergo pulmonary valve replacement, sometimes more than twice in their adult life, and may have associated issues with atrial and ventricular dysrhythmias. These may themselves require treatment with arrhythmia surgery (Maze equivalents with radiofrequency or cryotherapy ablation).

Also in this group are patients with right ventricle-to-pulmonary artery conduits, having undergone surgery for pulmonary atresia, or truncus arteriosus in the past. Third- and fourth-time sternotomy is not unusual in this group.

Box 2. Items to consider in an adult patient with congenital heart disease

To better understand a patient during an acute presentation or before surgery, the following could be considered:

- **Where does the blood flow now, and how will it be different after surgery?**
  This has implications regarding expected oxygen saturations and loading conditions of the ventricles.
- **Is the patient cyanosed?**
  This has implications for bleeding and ventricular dysfunction, and the level at which to maintain the haematocrit.
- **How difficult will it be to access the heart and establish cardiopulmonary bypass? Is there potential for massive bleeding from collateral vessels?**
  This has implications for volume replacement during the start and finish of the operation, especially in cyanosed patients with systemic-to-pulmonary shunts.
- **Are there pulmonary resistance issues?**
  This has implications for patients with a previous shunt who are undergoing biventricular repairs, for those with cavopulmonary connections and for transplantation.

There are also a number of "balanced" individuals for whom the potential for excessive pulmonary blood flow is restricted by concomitant pulmonary stenosis. These individuals may not have had surgery in the past, but eventually require attention because of ventricular dysfunction (massive right ventricle hypertrophy) and mild to moderate cyanosis.

Simple congenital defects not identified in childhood. These include atrial septal defects and partial anomalous pulmonary venous drainage. Individuals may present as their diastolic function worsens with age, increasing the left-to-right shunt. A good outcome is generally expected.

Complex conditions with previous palliation. This group includes individuals with cavopulmonary connections (Fontan circulation) and failing cardiac function related to atrioventricular valve regurgitation and haemodynamically inefficient pathways between vena cavae and the pulmonary arteries. Many have had old-style Fontan operations (atriopulmonary connection, Bjork variant Fontan and lateral tunnel Fontan) and may require conversion to an extracardiac conduit, valve repair and rhythm procedures. This is a particularly challenging group, as the combination of cyanosis and poor ventricular function, sometimes coexisting with protein-losing enteropathy, is difficult to manage. Bleeding is often significant.

Similarly, those who have undergone palliation with systemic-to-pulmonary shunts may present specific surgical challenges. Examples include adult patients with tetralogy of Fallot palliated with a Pott's shunt (descending aorta to left pulmonary artery). Control of the shunt is required as cardiopulmonary bypass is commenced, otherwise run off into the lungs prevents adequate systemic perfusion.

An exhaustive list of abnormalities and potential problems is beyond the scope of this review, and most patients with adult CHD require individualised surgical and intensive care. To better understand a patient during an acute presentation or before surgery, a short list of items for consideration is shown in Box 2.

Emerging catheter-based approaches may add to our repertoire of interventions (see Inglessis and Landzberg[21] for overview). Septal occluders and approaches to closing collateral vessels are well established. Stenting of pulmonary arterial and aortic narrowing provides useful options which may be utilised instead of, or in addition to, surgery. The next frontier is catheter-based delivery of valves for treating pulmonary incompetence. These are largely glutaraldehyde-treated bovine jugular venous valves mounted within expandable stents.[22] As the technology improves, it may be possible to deliver adult-sized devices, which would be of great benefit to patients with free pulmonary incompetence after surgery for tetralogy of Fallot. Regrettably, these devices will themselves have a limited life and require replacement due to structural valve deterioration. There is an ongoing effort to identify a better right ventricle-to-pulmonary artery device, possibly involving scaffolds populated with patient-derived cells before implantation.

Conclusions

In summary, many individuals undergoing surgery for adult CHD require long and complex operations. Postoperative care may be time- and resource-intensive. If significant haemodynamic improvements can be achieved through surgery, then improvements in ventricular function and level of activity can be expected.

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