Congenital heart disease

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Foreword

Future Cardiology

At the time the baby-boomers began their life's journey (babies born between 1946 and 1964), the majority of children born with serious congenital heart disease faced nearly uniform mortality in their first year of life [1]. In the ensuing two-thirds of a century, a global army of dedicated, and at times heroic pediatricians, cardiologists, cardiovascular surgeons, nurses and researchers worked tirelessly to change those statistics [2]. Today, circa 2012, there are now more adults with congenital heart disease than children, one of the greatest achievements in modern medicine [3]. In this special issue of *Future Cardiology*, we are provided with a 'glance of the skyline' that represents pediatric cardiovascular medicine, diagnosis, management, outcomes and the future landscape: from fetus to death.

To understand the strides achieved in outcomes, Matthias Greutmann (University Hospital Zurich, Zurich, Switzerland), examines the demographics of adult survivors with congenital heart defects, noting that with childhood mortality decreasing over the last decades, mortality has shifted almost entirely to the adult population. Patients with complex heart defects are not 'cured', and remain at risk for premature death. High-risk lesions include unoperated or surgically palliated cyanotic heart disease or Eisenmenger physiology, those with repaired tetralogy of Fallot, patients with a Fontan (atrial-dependent circulation) palliation for single-ventricle physiology and those patients with a subaortic (systemic) right ventricle. Caring for these patients will become a challenge for tertiary centers and will require planning for limited resource allocation [4]. The horizon for repair has changed dramatically with the development of interventional techniques in the pediatric population. Such catheter-based approaches are being developed for structural heart lesions and find themselves uniquely applicable in the adult population.

Harsimran Singh *et al.* provide us a view with their vision of future applications for percutaneous endovascular repairs [5].

“(In the fetus) education, training, imaging equipment and guidelines can improve detection rates.”

Gurleen Sharland from the Fetal Cardiac Unit at Evelina Children's Hospital (London, UK), examines the benefits, technical problems and resource utilization of a fetal screening program. Such programs can provide families with information about their child's cardiac condition, the available treatment(s), associated mortality and morbidity and the expected quality of life [6]. This fosters consideration of treatment options, including termination of pregnancy or active treatment or compassionate care after birth and to prepare for the eventual course of events to optimize care. Limitations still exist in detection rates, which vary considerably in different regions and countries. Education, training, imaging equipment and guidelines can improve detection rates.

Surgical repair has matured from the days of low diagnostic specificity to the potential for widespread fetal diagnosis allowing for planned early interventions, for a number of congenital defects, many in the first days of life. These improvements have resulted in a major decrease in mortality and an increased attention to morbidity and quality of life in survival, with recent focus directed towards the effects of neurological injury from strokes or seizures to learning disabilities and motor delay. The etiologies are multifactorial and include genetic, procedural (cardiopulmonary bypass) and social factors. Helen Holtby (The Hospital for Sick Children, University of Toronto, Toronto, Canada) presents an anesthesiologists perspective of a potentially modifiable risk, that administered anesthetic drugs may be a cause of CNS morbidity [7].

Highlighting these factors will stimulate further research to reduce exposure to this risk in such a vulnerable population.

A subaortic right ventricle is a risk factor for late mortality in the adult. Anita Szwast and Jack Rychik (The Children's Hospital of Philadelphia, PA, USA) outline advances in diagnosis and management for infants with hypoplastic left heart syndrome. A focus on understanding prenatal pathophysiology and the development of effective prenatal interventional strategies represent present challenges in fetal management of this lesion. Outcomes for prenatally diagnosed hypoplastic left heart syndrome continue to improve, with 5-year survival rates approaching 80–85% and stage I overall survival rates greater than 90% in the absence of risk factors. However, fetuses with an intact atrial septum continue to have a poor postnatal chance of survival and *in utero* surveillance of Doppler flow patterns can help in planning management options. Outlined are various pre- and post-natal interventions that may change or improve the morphological substrate for those high-risk subgroups and improve survival [8].

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Critical to improving outcomes are strategies to reduce interstage morbidity and mortality for infants with single ventricle following stage I of palliation. Russel Cross *et al.* (Children's National Medical Center, DC, USA) discuss various home care protocols used by pediatric units to monitor these at-risk children, including focused high-risk outpatient clinics and the use of home surveillance monitoring [9]. Such programs have been shown to reduce morbidity and improve nutrition and outcomes of the subsequent surgical stages, but standardized metrics to monitor them and their frequency need to be better defined. These efforts are sorely needed to identify children at a time when an intervention could avoid a catastrophic event.

Management options for babies with duct-dependent pulmonary blood flow are detailed by Mazeni Alwi (National Heart Institute in Kuala Lumpur, Malaysia). Maintaining ductal patency with the implantation of coronary stents has become an attractive alternative to systemic pulmonary shunt or neonatal repair. However, the technique is not applicable to all and this

review details the procedure, its associated pitfalls and complications [10]. An understanding of the diverse morphology of the duct, particularly the long tortuous duct, which often has a wide opening at the pulmonary end in addition to the duct with branch pulmonary artery stenosis at its site of insertion are critical before stenting is contemplated. Durability of such palliation is generally inferior to surgical shunts and acceleration of branch pulmonary artery stenosis in certain morphologies limits its widespread application.

At first glance, isolated arch coarctation is a simple obstructive lesion in the thoracic aorta. However, as outlined by Marc Gewillig *et al.* (University Leuven, Belgium), there is a wide array of anatomical and pathophysiological variations, which can result in important long-term morbidity and mortality [11]. As a management option, catheter-based therapies have proven to be hemodynamically effective, but not without some cost. Patient selection and interventional techniques are outlined in detail, to avoid complications, such as an excessive tear, dissection, aneurysm formation or rupture. The group emphasizes that the interventional technique be tailored by the patient age, size and growth potential, and by characteristics of the lesion, such as severity of obstruction, length and topology.

For the child with a single functional ventricle, ultimate palliation is the creation of a Fontan circulation: a total cavopulmonary circulation. Today this is one of the most common surgical procedures performed for the child with complex heart disease, and now Fontan patients represent a greater proportion of the adult population. Alessandro Giardini *et al.* (Great Ormond Street Hospital for Children, London, UK) note that such patients have decreased exercise capacity due to an inability to increase cardiac output during exercise and a clinical course often complicated by additional factors, which lead to considerable morbidity and mortality [12]. As the systemic and pulmonary circulations are in series without a subpulmonary ventricle, systemic venous pressure and the respiratory mechanics are the only forces that drive the pulmonary circulation. As such, pulmonary vascular resistance becomes an important factor affecting cardiac output. This review assesses the impact of treatments to decrease pulmonary resistance and improve cardiac output and exercise capacity. Whether long-term symptom improvement or a survival benefit attained is discussed.

Very rapid advances have been made in MRI over the last few years to the extent that there

is a reduced role for diagnostic cardiac catheterization, as anatomical information is better obtained by MRI. However, even more important is the potential for MR-guided interventions. The article by Israel Valverde *et al.* (King's College London, London, UK) highlights the huge potential and increasing role of MR imaging, transfer of images to the catheter laboratory, functional and hemodynamic assessment and for interventional procedures. The authors emphasize the more frequent use and value of techniques of functional assessment such as myocardial tagging and myocardial diffusion tensor imaging by MR [13]. Flow quantification provides valuable hemodynamic information and so 4D phase contrast flow MRI will have important clinical value in the future. The technology, in particular MR-guided intervention, still has some way to go, but it is not insurmountable and its clinical value will be enormous.

The future diagnostic and treatment paths for congenital heart disease will rely heavily on developments regarding our understanding of the genetic basis of the defects and the use of stem cells. Two articles in this issue update our understanding of these areas. The first, by Natalie Farra *et al.* (University of Toronto, Toronto, Canada) summarizes the proceedings from the International Symposium on Childhood Heart Disease: Personalized Medicine in the Genomics Era, held in October 2011. For many of us unable to attend this symposium, the summary provides an opportunity to keep up to date with developments in this area and the predicted huge expansion of genetic basis for complex congenital heart defects [14]. For progress to be made rapidly, large samples sizes are needed. The symposium brought together prominent experts from around the world to define and propose collaboration. Other areas including the application of genomics in order to improve the safety and efficacy of drugs, with an emphasis on children were discussed. The exciting role for future applications of human induced pluripotent stem cell therapy for safe transplantation was also discussed, with a focus on its use in patients with dilated cardiomyopathy, Rett's syndrome and Williams syndrome. The symposium emphasized the collaboration between genomics, bioinformatics, systems biologists and stem cell researchers to facilitate functional application of genomic discoveries towards the development of novel therapeutics. The second article by Emma Siân Pincott *et al.* (Great Ormond Street Hospital, London, UK) further discusses the role of stem cell therapy in

congenital heart disease. It is known that the heart is capable of turnover of a high number of cells, but may repair itself very slowly. The use of stem cells may accelerate the repair process. Stem cells can be implanted by direct intramyocardial or intracoronary injection but at present the outcome may depend on the selection, harvesting, process and storage of these stem cells. Nevertheless, stem cells have not been explored as much as they should have been in congenital heart disease. Even more exciting is the possible role of this therapy during fetal life. If this were to become a reality, then the outlook for babies with hypoplasia of either of the ventricles may improve considerably. Whether prenatal stem cell therapy is actually possible remains to be seen. Pincott *et al.* summarize the techniques, the current role and the future application of stem cell therapy and cardiac tissue engineering; however, they also discuss the important ethical and moral dilemmas of using embryonic stem cells [15].

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Evidence-based studies in congenital heart disease are rare and none more so than in adults with congenital heart disease. The article by Paul Khairy (Montreal Heart Institute, Montreal, Canada) addresses the future challenges of such studies being established in this heterogeneous population of patients, which is increasing rapidly as a result of major improvements in the treatment of congenital heart disease in neonates, infants and children [16]. Although the numbers of patients are increasing, in relative terms, this population base is still small and the number of end points is small for comparing outcomes. Clinical studies and trials to obtain the evidence base in adults with congenital heart disease is therefore of vital importance over the coming years.

Robotic techniques have been used in adults undergoing myocardial revascularization or mitral valve repair, but the use of robotics in conjunction with imaging in congenital heart surgery is the technology of the future. The technical limitations are the use of such technology in children less than 30 kg. The article by Nikolay Vasilyev *et al.* (Children's Hospital Boston, MA, USA) provides an appetizing

insight into this application. The major hurdles include tracking of rapidly moving tissues (in this case, a baby's heart) and how to combine imaging and surgery. The article summarizes the technology currently available and that which is currently practical, and the technology that will be used in the future. The needs of the technology include instruments that provide tactile feedback, limit interference with imaging tools, and provide steerability. In order to make this work, real-time, high-resolution imaging, which also provides tissue and instrument tracking, is required for safe navigation inside the heart. In their article Vasilyev *et al.* beautifully summarize the exciting developments regarding the future use of robotics in congenital heart disease [17].

The changing population of adults with congenital heart disease and their needs is emphasized succinctly by the article by Alan Stuart. Not only the absolute numbers, but also the complexity of the heart defects in the survivors is increasing. Improving survival means dealing with increasingly different types of long-term complications in these patients, who require further interventions, electrophysiological studies and surgery. Therefore there are major implications for the resources required to deal with this group of patients, as the workload is likely to continue to increase. An area hitherto not emphasized is the need of female patients and cardiac obstetric services. Therefore a multidisciplinary and holistic approach to the management of the adult congenital patient is required [3]. A related topic involves the management of complications in pregnant women with congenital heart disease, which is discussed very well by Rachael Hatton *et al.* Undoubtedly pregnancy imposes hemodynamic stress on the heart in these patients and may result in maternal, fetal and neonatal complications. This is therefore an important subgroup of patients, 'highlighting' the fact that their specific needs have to be catered for in any healthcare system. These needs include counseling, contraception, recurrence risks in the fetus, the use of different drugs during pregnancy and lactation, different physiological demands placed on the hemodynamics by the pregnancy, and issues related to labor and delivery of the baby. The article also discusses some specific issues, such as pregnancy and delivery in Fontan patients, or those with Eisenmenger's syndrome or after the arterial switch, systemic right ventricles, or mechanical heart valves, all of whom present with their own unique set of issues. This article by Hatton *et al.* is a must for those involved

in the care of pregnant women with congenital heart disease [18].

One problem that is fortunately uncommon at present, but may become more important with increasing numbers in the future, is heart transplantation in adults with congenital heart disease. The article by Luke Burchill (University of Toronto) and Heather Ross (Toronto General Hospital, Toronto, Canada) deals with this and emphasizes the need for collaboration between adult congenital and heart failure specialists. Similar to the earlier themes of developing services for the needs of adults with congenital heart defects, this group of patients is also likely to increase with increasing survival of congenital heart disease patients into adult life. Particular groups of patients include those with systemic right ventricles, long-term survivors of the Fontan operation and those with Eisenmenger's syndrome. Even after transplantation, the early mortality in these patients is higher than those without congenital heart disease. The reasons are multifactorial and include patients who require reconstruction of pulmonary arteries at the time of transplantation because of distortion due to previous systemic-to-pulmonary artery shunts, cavopulmonary anastomosis or pulmonary artery bands. Those who have previously undergone Mustard or Senning operations may require further atrial septal reconstruction. Any of these additional procedures result in longer operative times, as well as increased ischemic times. There may be postoperative bleeding due to adhesions or abnormalities of hemostasis, because of liver dysfunction or clotting abnormalities. Their article discusses the lack of universal guidelines and the need for their development for heart transplantation in patients with congenital heart disease. It provides excellent detailed guidance on how to evaluate, stratify and deal with this complex group of patients [19].

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