Editorial

Pediatric Cardiology: Advances Over the Past 2 Years and Future Prospects

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During the past 2 years, worldwide considerable advances have been made in the field of pediatric cardiology, including the elucidation of the mechanisms responsible for cardiovascular diseases and the development of diagnostic techniques and treatment strategies. Meanwhile, we should be aware that the genetics, environmental factors and their interactions involved in the mechanisms for a variety of pediatric cardiovascular diseases have yet been unclear. The diagnostic techniques and treatment need to be further standardized and developed.

Advances Over the Past 2 Years

To understand the mechanisms for congenital heart disease (CHD), a recent study showed that *HIRA* (histone cell cycle regulator) gene expression was down-regulated at both the transcriptional and translational levels in tetralogy of Fallot (TOF) patients.[1] While we need to do further studies in the gene function in the development of TOF. For interventional therapy of pediatric CHD, considerable improvements have been made over the past 2 years. For instance, investigators retrospectively analyzed data from 1497 patients with patent ductus arteriosus (PDA) who underwent transcatheter PDA closure with a success rate of 99.6% (1492/1497).[2] Others[3] shared their preliminary experience with transcatheter closure of multiple perimembranous ventricular septal defects with giant aneurysms using double occluders in four patients. However, the long-term follow-up studies are urgently in need to better understand the effects of the intervention.

Arrhythmia is a common pediatric problem. A combination of an implantable cardioverter defibrillator and medical therapy is recommended for high-risk pediatric patients with inheritable channelopathies, cardiomyopathies, or CHD. However, further studies are needed to improve the treatment technology and guide clinical decision-making for arrhythmia in children.

Recently, the overall frequency of pediatric infective endocarditis (IE) has been increased, and the underlying conditions have changed from unoperated CHD and rheumatic heart disease to postoperative CHD. Successful treatment of IE relies on microbial eradication using antimicrobial drugs. In addition, urgent surgery is advised for IE complicated by cerebral embolism or transient ischemic events. However, the exact surgical indications for the treatment of IE and the operative mortality risk have not been well defined yet.

Children with myocarditis require early diagnosis and aggressive treatment. However, the diagnostic efficiencies of the current biomarkers are relatively low. Simpson *et al*.[4] reported that infants with clinical myocarditis had a higher rate of blood viral DNAemia detected by polymerase chain reaction (PCR) in blood samples than did healthy infant controls (80% vs. 3.5%, $P < 0.0001$), which suggested that blood viral PCR might be a useful diagnostic tool in infantile myocarditis. The application of intravenous immunoglobulins (IVIGs) and/or immunosuppression to stop the autoimmune response associated with myocarditis is a widely accepted targeted therapy for severe cases. However, more studies are needed to demonstrate the treatment efficacy on short- and long-term outcomes.

Based on the known mechanisms, 3 classes of drugs have been used to treat pediatric pulmonary hypertension (PH):

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prostanoids (e.g., epoprostenol and treprostinil), phosphodiesterase type 5 inhibitors (sildenafil and tadalafil), and endothelin receptor antagonists (bosentan and ambrisentan). A recent multicenter, blinded, placebo-controlled study reported that combined ambrisentan and tadalafil therapy achieved a significantly lower rate of treatment failure but a higher rate of side effects including nasal congestion, headache, and peripheral edema, than ambrisentan or tadalafil monotherapy among previously untreated PH patients.[5] Thus, in the future, we need to investigate targeted drugs according to the pathophysiology to improve the prognosis of pediatric PH.

Kawasaki disease (KD) is a childhood vasculitis and a common cause of pediatric acquired heart diseases globally. Clinical criteria are used to diagnose KD. Laboratory data including C-reactive protein, platelet count, and erythrocyte sedimentation rate and echocardiographic findings are helpful, especially in some incomplete or atypical cases. However, the absence of specific biomarkers is a big problem. Nonresponders to initial therapy remain a great challenge. IVIG retreatment, corticosteroids, infliximab, and other treatments have been discussed recently. Corticosteroid therapy is still controversial. Our team summarized that corticosteroids were more effective at controlling body temperature than IVIG retreatment in children with IVIG-resistant KD. However, corticosteroid therapy might be an independent risk factor for coronary artery aneurysms (CAAs) and giant CAAs. Thus, further studies are needed to investigate the treatment strategy for KD.

As a consequence of the above cardiac diseases, pediatric heart failure (PHF) represents an important cause of pediatric morbidity and mortality. Both pharmacological and nonpharmacological treatments are available for heart failure. The pharmacological therapies include diuretics, digoxin, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers, but these treatments lack powerful evidence and rely heavily on adult studies, limiting their application in PHF. The nonpharmacological therapies include mechanical circulatory support and heart transplantation (HTx). Li *et al*.[6] reviewed HTx at a single Chinese center, including 19 children, and showed satisfactory short-term results of pediatric HTx and acceptable complication rates at the institution. However, the implementation of pediatric HTx faces many problems, such as organ shortages and a high demand for transplant operations. Moreover, the long-term survival of patients who undergo HTx must be assessed.

Neurally mediated syncope (NMS) includes postural orthostatic tachycardia syndrome (POTS), vasovagal syncope (VVS), and orthostatic hypertension. The exact mechanism for VVS remains unclear. Yang *et al*.[7] reported that increased erythrocyte H_2S production might be responsible for the marked vasodilatation in patients with VVS by increasing flow-mediated dilatation. A recent study showed that elevated plasma C-type natriuretic peptide (CNP) production may also contribute to the pathogenesis of POTS in children. The reported therapeutic effects in children with NMS have varied. Therefore, some indicators for predicting the therapeutic response have been studied including baroreflex sensitivity,[8] the heart rate corrected QTd,[9] the body mass index, plasma CNP[10] and so on. These studies provide individualizing therapy for syncopal cases and need to be wildly applied in the clinics in the future.

Perspective

In the future, national wide or worldwide epidemiologic studies are needed to understand the current incidence of many cardiovascular diseases in children. Multicenter studies are encouraged to determine the exact mortality of pediatric cardiovascular diseases. Studies are also needed to elucidate the mechanisms underlying cardiovascular diseases at molecular and genetic levels. Furthermore, translational medicine studies should be performed to evaluate diagnostic and outcome predictive biomarkers for certain cardiovascular diseases, including cardiomyopathy, syncope, and KD. Additional multicenter-based randomized controlled trials are necessary to evaluate the long-term effects of therapies and therefore improve the prognosis of cardiovascular diseases. Furthermore, we really need more interdisciplinary studies to better understand the nature of cardiovascular diseases and the suitable management options for children with heart problems.

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