Review Article

Advances in pediatric cardiology in 2019: a narrative review

Quming Zhao[1], Fang Liu[1,2], Guoying Huang[1,2]

[1]Pediatric Heart Center, Children's Hospital of Fudan University, Shanghai 201102, China; [2]Shanghai Key Laboratory of Birth Defects, Shanghai 201102, China

Contributions: (I) Conception and design: G Hunag; (II) Administrative support: all authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Guoying Huang. Pediatric Heart Center, Children's Hospital of Fudan University, 399 Wan Yuan Road, Minhang District, Shanghai 201102, China. Email: gyhuang@shmu.edu.cn.

Background and Objective: This article reviews the research progress made in 2019 for the diagnosis and treatment of cardiovascular diseases focusing on congenital heart disease, Kawasaki disease, and its associated arterial lesions, arrhythmias, myocarditis, cardiomyopathy, heart failure, functional cardiovascular disease, pulmonary hypertension, and fetal cardiac disease in the pediatric populations.

Methods: A keyword search of PubMed and the Chinese database SinoMed were searched for peered-reviewed articles published between January 2018 and December 2019. The findings of the thirty relevant studies included were synthesized thematically.

Key Content and Findings: Considerable advances worldwide have been made in the field of pediatric cardiology in the past year, and the issuance of expert consensuses in different subspecialties, along with the publication of several clinical studies, have shown to be invaluable in improving the diagnosis and treatment of cardiovascular disease in children.

Conclusions: This review provides insights into the current and future challenges associated with optimal diagnosis and treatment of pediatric cardiology.

Keywords: Congenital heart disease (CHD); Kawasaki disease (KD); arrhythmias; cardiomyopathy; pulmonary hypertension (PH)

Received: 05 February 2020; Accepted: 24 February 2020; Published: 20 May 2020.
doi: 10.21037/pm.2020.02.01
View this article at: http://dx.doi.org/10.21037/pm.2020.02.01

The year 2019 has seen substantial contributions being made on an international scale in the discipline of pediatric cardiology, with progress in the diagnosis and treatment cardiovascular disease in children coming in the form of consensus-building in a variety of subfields and a number of published clinical studies. Pediatric cardiologists in China have also made significant breakthroughs including those involving radiofrequency ablation and device implantation for pediatric arrhythmias, and fetal cardiac intervention (FCI). A large number of clinical cases in China have been translated into clinical research results. This article reviews the progress on congenital heart disease (CHD), Kawasaki disease (KD) and its associated arterial lesions, arrhythmias, myocarditis, cardiomyopathy, heart failure, functional cardiovascular disease, pulmonary hypertension (PH), and fetal cardiac disease in 2019.

Method

Studies were identified by comprehensive searches of PubMed and the Chinese bio-medical literature and retrieval system SinoMed for relevant studies published from January 2018 to December 2019, using text terms with appropriate truncation and relevant indexing terms without language restriction. The search term was in the following form: ("*cardiovascular disease*") *AND* ("*diagnosis*" or "*therapy*" or "*treatment*") and ("*child*" or "*pediatrics*") (see *Table 1* for search strategies in PubMed). Additionally, the reference

Table 1 Search strategies in PubMed for original articles reporting the diagnosis and treatment of cardiovascular diseases in the pediatric population from January 2018 to December 2019

Query	Results	Time
Search: ((cardiovascular disease*[Title/Abstract]) AND (diagnosis[Title/Abstract] OR therapy[Title/Abstract] OR treatment[Title/Abstract]) AND ((2018/1/1:2019/12/31[pdat]) AND (allchild[Filter]))) OR (("Cardiovascular Diseases/diagnosis"[Majr:NoExp] OR "Cardiovascular Diseases/therapy"[Majr:NoExp]) AND ((2018/1/1:2019/12/31[pdat]) AND (allchild[Filter]))) Filters: Child: birth-18 years, from 2018/1/1-2019/12/31 Sort by: Publication Date	681	02 January 2020

lists of the original studies and review articles identified from the searches were cross-checked to include potentially relevant articles that may not have been identified in the initial literature search. In all searches, when the relevant information was not reported, or there was doubt about duplicate publications, we contracted authors for clarification.

The results for the searches were combined, and duplicates were removed. Two independent reviews (Q Zhao and F Liu) screened articles for inclusion on the basis of titles and abstracts, with a minimum of 10% duplication to ensure consistency in agreement. Articles that clearly did not meet the inclusion criteria were excluded. Full-text articles, however, were obtained if deemed potentially suitable for inclusion and as a precaution for any article for which suitability was unclear from screening. The full text of all articles collected was independently screened. Original articles reporting the diagnosis and treatment of cardiovascular diseases focusing on congenital heart disease, Kawasaki disease, and its associated arterial lesions, arrhythmias, myocarditis, cardiomyopathy, heart failure, functional cardiovascular disease, pulmonary hypertension, and fetal cardiac disease in the pediatric populations were included in this narrative review.

CHD

The interventional technology of common CHD has been mature for quite some time, and thus the spectrum of CHD suitable for interventional therapy is difficult to expand upon; the exploration of new interventional procedures and device innovation has nonetheless become a focal point of research interest. At present, China ranks first in the world in the number of CHD interventional treatments and is at the global forefront of simple echocardiography-guided percutaneous interventions for CHD, the clinical application of fully biodegradable occluders, and the development of pulmonary artery stents (1-3). For instance, the team at West China Second University Hospital was first to reveal the overall incidence, risk factors, and follow-up outcomes of complete left bundle branch block after device closure of a perimembranous ventricular septal defect (pVSD) (4), which was invaluable in the management of the population with pVSD device closure. Nonetheless, developed countries still have advantages in the field of clinical application of percutaneous pulmonary valve implantation (PPVI) in pediatric patients. The medium-term follow-up of a German study showed excellent results of the mechanical valve function, although advanced manipulations of the patched or native right ventricular outflow tract might be associated with significant ventricular arrhythmias (5).

KD and its associated arterial lesions

In terms of the etiopathogenesis of KD, a systematic review by Peking University First Hospital identified 16 gene polymorphisms correlated with KD susceptibility and 10 gene polymorphisms associated with coronary artery lesions (CALs) (6). A European population analysis revealed that the FCGR2C-ORF haplotype (rs759550223 and rs76277413) is strongly associated with KD susceptibility; however, this FCGR2C-ORF variant is virtually nonexistent in Asian populations (7). The Children's Hospital of Fudan University was first to propose that systemic artery aneurysms (SAAs) are not rare in KD (8). The proportion of patients with SAAs was estimated to be 2% of all patients with KD. Patients with SAAs had a younger median age (5 months) at onset and a longer duration of fever (12 days). All patients with SAAs had CAAs, with z scores >8. Of patients with giant CAAs, 38.6% had SAAs. With regards to first-line treatments, a meta-analysis by West China Second University Hospital reported no difference between low (3–5 mg/kg/day) and high (>30 mg/kg/day) doses of aspirin in terms of incidence of CALs, intravenous immunoglobulin (IVIG) resistance, duration of fever and hospitalization,

and the occurrence of adverse events (9). A Japanese study published in *The Lancet* found that combined primary therapy with IVIG and ciclosporin was safe and effective for favorable coronary artery outcomes in KD patients who were predicted to be unresponsive to IVIG (10). Similarly, studies in the United States demonstrated that corticosteroids or infliximab in addition to IVIG could significantly improve the prognosis for KD patients with CAA on baseline echocardiography (11). Another study found that the tumor necrosis factor α receptor antagonist etanercept helped reduce IVIG resistance in patients >1 year of age, and that this treatment appeared to ameliorate coronary artery dilation (12).

Arrhythmias

There is still a long way to go in the diagnosis, treatment, and basic research of pediatric arrhythmia in China as compared with developed countries. Nevertheless, in recent years, Chinese researchers have made significant progress in the clinical application of the three-dimensional mapping system, cryoablation, zero-fluoroscopy catheter ablation, and inherited cardiac arrhythmia. One study conducted by Beijing Anzhen Hospital and published in *EP Europace* was able to use a large sample of pediatric cases to demonstrate that overt right-sided accessory pathways in the septum or free wall might impair ventricular wall motion and left ventricular function, resulting in decreased left ventricular ejection fraction and increased left ventricular end-diastolic diameter. The prognosis of accessory pathway-induced abnormal ventricular wall motion and left ventricular dysfunction after ablation was excellent (13). Through a retrospective analysis of 30 pediatric cases, research by the Guangdong Provincial Cardiovascular Institute revealed that the mortality rate was high in pediatric inherited cardiac arrhythmia and syncope. The therapeutic effect of drugs was not satisfactory, and, as of now, implantable cardioverter-defibrillator (ICD) implantation is the most effective treatment to prevent sudden cardiac death, but the frequent postoperative discharge should be brought to the forefront and handled in a timely manner (14). In a non-Chinese study, Dutch researchers found that pediatric patients with CHD undergoing catheter ablation exhibited a broad spectrum of arrhythmias. Complete or partial procedural success was achieved in the majority of cases (84%), although arrhythmia recurred in 49% of patients. Despite recurrence and emergence of novel mechanisms after a successful procedure, ablation can be performed safely and successfully resulting in decreased arrhythmia burden (15).

Myocarditis, cardiomyopathy, and heart failure

In 2019, an expert consensus on diagnosis of pediatric myocarditis and hypertrophic cardiomyopathy was developed in China, which provided an essential reference for Chinese clinicians (16,17). The American Heart Association has also issued a scientific statement on the classification and diagnosis of pediatric cardiomyopathy (18), which assigns dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy, restrictive cardiomyopathy, noncompaction, and arrhythmogenic cardiomyopathy into the highest subcategory in the hierarchy. The incidence of pediatric cardiomyopathy is about 1 per 100,000 children, and cardiomyopathy remains the leading cause of transplantation for children older than 1 year of age. Nearly 40% of children who present with symptomatic cardiomyopathy undergo heart transplantation or die within the first 2 years after diagnosis. Current evidence has shown that causes are established in very few children with cardiomyopathy, and genetic causes are likely to be present in most cases. Although the pharmacotherapy of heart failure in children has not made much progress, a few medical institutions in China have some accumulated experience in cardiac resynchronization therapy to improve pediatric heart failure (19). Some investigators have proposed cell-based treatment in pediatric patients with end-stage heart failure, and pulmonary arterial banding to improve cardiac function in young children with DCM. Still, these approaches need more evidence to support them (20).

Functional cardiovascular disease

Researchers from Peking University First Hospital have published several papers in international journals in the field of functional cardiovascular disease. They found that the daytime ultra-low frequency of heart rate variability (HRV) may be a useful measure for the differential diagnosis between vasovagal syncope (VVS) and postural tachycardia syndrome (POT) in adolescents (21). Subsequent studies on the baseline HRV indicators showed that combined triangular index ≤33.7 and standard deviation of all normal-to-normal intervals index ≤79.0 ms were useful preliminary measures to predict therapeutic response to metoprolol in pediatric postural orthostatic tachycardia syndrome (POTS) patients (22), and the acceleration index may help predict the efficacy of orthostatic training on pediatric VVS (23).

Finally, one review showed that female pubertal hormone was involved in modulating cardiovascular homeostasis and therefore may play a role in predisposing females to VVS and POTS during puberty (24).

PH

A multicenter study in North America between 2014 and 2018 demonstrated significant racial variability in the prevalence of PH subtypes and survival outcomes among children with PH. Pulmonary arterial hypertension (PAH) was more prevalent among Asians, lung disease-associated PH Blacks, idiopathic PAH Whites, and pulmonary veno-occlusive disease Hispanics (25). In September 2019, the European Pediatric Pulmonary Vascular Disease Network updated the consensus statement on the diagnosis and treatment of pediatric PH, and a set of specific recommendations on the management of PH in middle- and low-income regions were developed for the first time (26). In terms of progress in the treatment of pediatric PH in China, bosentan dispersible tablets were approved by the National Medical Products Administration in 2019, becoming the first approved targeted drug for children with PH in China. Qingdao Women and Children's Hospital is the first in China to explore the feasibility of percutaneous pulmonary artery denervation in pediatric idiopathic PAH and has achieved good clinical results. However, the effectiveness of this approach still needs to be confirmed by multicenter studies with a larger sample size and an extended follow-up (27).

Fetal cardiac disease

In recent years, significant progress has been made in FCI in China, and the spectrum of diseases that can be treated has risen to an international level (28). In this context, an expert consensus on FCI was developed in 2019, which provides a basis for the gradual promotion of this technology in China (29). A recent review by US experts showed that only approximately 5% of fetuses with major CHD are likely to benefit from an intrauterine intervention at present. More recent attempts have focused on feasibility studies for the implantation of intrauterine pacemakers to treat complete atrioventricular conduction block and thus help prevent in utero demise. Another possible innovation is the use of chronic maternal hyperoxygenation for improving the growth of left-sided cardiac structures. However, these methods are still far from routine clinical practice (30).

In summary, considerable advances worldwide have been made in the field of pediatric cardiology in the past year, and the issuance of expert consensuses, along with the publication of several clinical studies, have shown to be invaluable in improving the diagnosis and treatment of cardiovascular disease in children, including CHD, KD and its associated arterial lesions, arrhythmias, myocarditis, cardiomyopathy, heart failure, functional cardiovascular disease, PH, and fetal cardiac disease.

Acknowledgments

Funding: This work was supported by the National Key Research and Development Program (No. 2016YFC1000506), the Natural Science Foundation of China (No. 81273168), and the Innovation Unit of Chinese Academy of Medical Science (No. 2018RU002).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm.2020.02.01/coif). GYH serves as an editor-in-chief of *Pediatric Medicine*. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pm.2020.02.01
Cite this article as: Zhao Q, Liu F, Huang G. Advances in pediatric cardiology in 2019: a narrative review. Pediatr Med 2020;3:5.