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Cardiovascular Disease in the Young Council's Science and Clinical Education Lifelong Learning Committee: Year in Review

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The American Heart Association (AHA) established the Science and Clinical Education Lifelong Learning committee to oversee the various channels of the AHA/American Stroke Association's robust learning enterprise, which includes scientific meetings, professional education online learning, spotlight series, journals, and journal webinars. As a part of this learning enterprise, the Science and Clinical Education Lifelong Learning committee of the Council on Cardiovascular Diseases of the Young embarked on writing "The Year in Review" compilation highlighting the scientific progress made in the pediatric cardiology and cardiac surgery community between May 2016 and May 2018. The purpose of this article is to highlight 1 to 2 original research or guideline publications that have been the most impactful and innovative in the various areas of pediatric and adult congenital cardiovascular research that have the potential to dramatically change pediatric and adult congenital cardiovascular care and outcomes.

Experts in the field were invited from the Council on Cardiovascular Diseases of the Young committees to focus on the following categories: congenital cardiac defects including imaging, electrophysiology, cardiac intensive care, interventional cardiology, heart failure/transplantation, and pulmonary hypertension, congenital cardiothoracic surgery, rheumatic fever/endocarditis/Kawasaki's disease, adult congenital heart disease (CHD), basic science research, preventative cardiology, and early career and mentoring. Among the many worthy recent publications across pediatric cardiology, the authors summarized the following papers.

Advances in Cardiac Imaging

Fetal echocardiography is an invaluable tool for the identification of CHD, and is critical to the preparation of the medical team and family for postnatal care. While considerable ongoing efforts target diagnostic rates, Bensemlali and colleagues[1] identified significant issues in diagnostic accuracy. Among the 1258 patients reviewed, there was a 29.3% discordance of pre- and postnatal diagnosis leading to a major change in the planned neonatal treatment in 10.6% of cases. These discordances also led to changes in planned care beyond the neonatal period in 4.9% of cases: more complex CHD that was deemed unsuitable for biventricular repair, need for additional surgeries, increase in the complexity level of the Aristotle score, and unplanned compassionate care. Continued efforts to improve the accuracy of prenatal diagnosis of CHD are needed.

Three-dimensional echocardiography is now integrated into most clinical laboratories. Simpson and colleagues[2] provided an expert consensus document about the use of 3-dimensional echocardiography in the setting of CHD with a focus on technical considerations, image orientation, procedural guidance, and functional assessment. This report serves as an important reference for the field as the technology matures to the point of routine use.

Cardiac magnetic resonance imaging continues to provide new insights on cardiovascular disease through tissue characterization. Axelsson and colleagues[3] used late gadolinium

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enhancement to identify myocardial replacement fibrosis in children with hypertrophic cardiomyopathy. Late gadolinium enhancement was noted in almost half of subjects with overt hypertrophy. In those with serial measurements over 2.5 years, late gadolinium enhancement, left ventricular mass, and left atrial size increased, thereby providing insight in understanding disease course.

Challenging Existing Knowledge of Wolf-Parkinson-White and Brugada Syndrome

This year, 3 articles advanced our understanding of Wolf-Parkinson-White and Brugada syndromes, challenging existing knowledge and provoking new thoughts about current paradigms for treatment and management of these diseases.

Practice guidelines for management of Wolf-Parkinson-White in children have largely been based on the assumption that risk of sudden death is both predictable and ascertainable. A large retrospective multicenter international study of 912 children with Wolf-Parkinson-White provided evidence to suggest that, while risk of sudden death in children remains low, the ability to identify those at highest risk remains difficult.[4] These findings raise questions about future management recommendations and will likely affect the manner by which physicians counsel patients in the future.

Brugada syndrome has classically been considered a primary ion channel disorder. Although small case studies had previously suggested ablation as a curative therapy, multiple studies this year provide further evidence that epicardial ablation may successfully treat ventricular arrhythmias associated with Brugada syndrome in symptomatic adults.[5] While long-term follow-up following ablation is lacking and studies in children have not been performed, these preliminary results provide new insights into this disease. Regardless of whether ablation is found to be a treatment option for children with symptomatic Brugada syndrome, the manner in which we approach this disease and counsel patients regarding long-term prognosis is likely to change.[6]

Intensive Care Medicine: Temperature Control After Cardiac Arrest and Management of Hyperglycemia

Management strategies in cardiovascular intensive care have historically relied on evidence from adult studies or, at times, from expert opinion. Recent large multicenter randomized trials in pediatric patients highlight the importance of evidence-based trials in our patients and the need to challenge existing care paradigms.

Early clinical trials in comatose adults with out-of-house ventricular fibrillation–related cardiac arrest supported the use of mild hypothermia to improve neurologic outcome. The recommendation for therapeutic hypothermia was frequently extrapolated to pediatric patients who had experienced out-of-hospital and in-hospital cardiac arrest. In the multicenter THAPCA trial (Therapeutic Hypothermia After In-Hospital Pediatric Cardiac Arrest), children at 37 centers who experienced in-hospital cardiac arrest were randomized to normothermia or mild hypothermia for 48 hours.[7] The primary

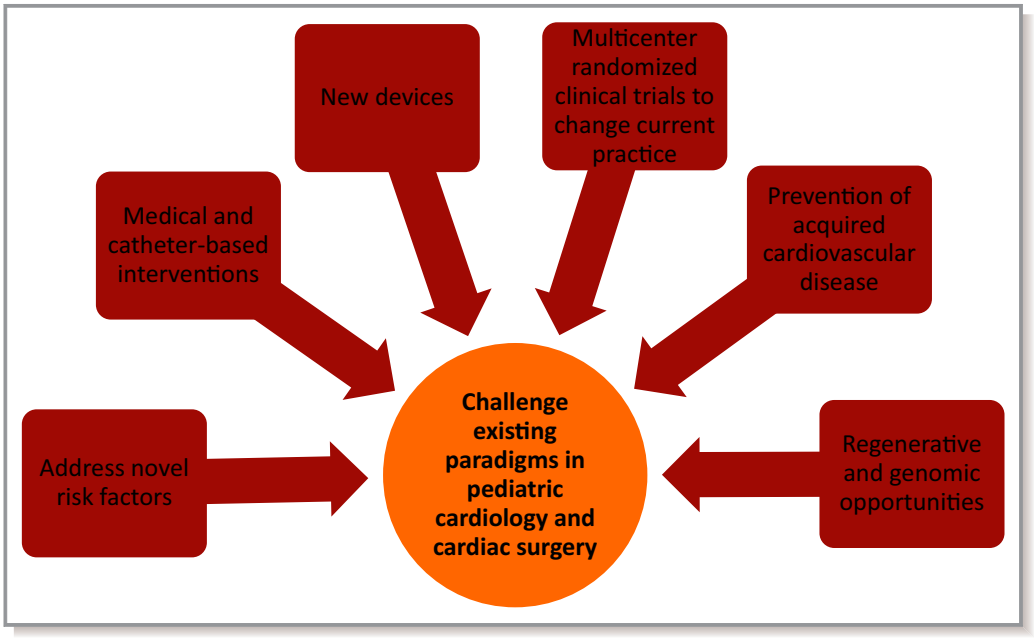

Figure. Summary of advances in pediatric cardiology and cardiac surgery to challenge existing paradigms in care.

outcome was survival to 12 months. The trial was terminated because of futility after 329 patients had been randomized, with no difference in neurologic outcomes between groups. There was also no difference in secondary outcomes including the use of blood products, serious adverse events, or mortality at 28 days and 1 year. Based on these findings, newer recommendations are to maintain normothermia in pediatric patients following in-hospital cardiac arrest.

In the PALISI-sponsored HALF-PINT (Heart And Lung Failure - Pediatric INsulin Titration) trial from 35 institutions, critically ill pediatric patients with hyperglycemia (excluding cardiac surgery) were randomized to tight glucose control (80–100 mg/dL) or a more liberal strategy (150–180 mg/dL). The primary outcome was number of intensive care unit (ICU)–free days to day 28. The study found no benefit to tight glycemic control and the study was stopped early because of futility and possible harm. No significant differences were seen in the primary outcome or in secondary outcomes of mortality, ventilator-free days, or severity of organ dysfunction.[8] Interestingly, patients in the tight control group had a higher incidence of infections. These findings support a more liberal glucose goal in critically ill pediatric patients.

Novel Interventional Catheter-Based Techniques and Technologies

A tenet in the field of pediatric interventional cardiology is the exploration of new techniques and technologies to offer alternatives to surgical therapies.

To date, transcatheter pulmonary valve technologies have been designed for patients with a circumferential right ventricle to pulmonary artery conduit, leaving the majority of patients with dilated right ventricular outflow tracts without a device specifically designed for their heterogeneous anatomies. The new Harmony transcatheter pulmonary valve (Medtronic, Minneapolis, MN) is a self-expandable device, designed to accommodate the dilated right ventricular outflow tract.[9] In a US Food and Drug Administration–approved early feasibility study, 20 Harmony valves were implanted in patients at a median age of 25 years; nearly all of these patients had tetralogy of Fallot with severe pulmonary regurgitation. The procedural success rate was 95% with good valve function by echocardiography at 6 months follow-up. Long-term outcome assessment is required, as is the introduction of a wider variety of device types and sizes.

Infants with ductal-dependent pulmonary blood flow have traditionally been palliated with a Blalock-Taussig shunt. Recently, stenting of the patent ductus arteriosus has become more commonly used. However, a balanced comparison of Blalock-Taussig shunt and patent ductus arteriosus stent as treatment options was lacking. Multicenter studies from the National Congenital Heart Disease Audit in the United Kingdom[10] and from the Congenital Catheterization Research Collaborative[11] reported no difference in death or unplanned reintervention between Blalock-Taussig shunt and patent ductus arteriosus stent. However, the patent ductus arteriosus stent group had lower adjusted length of intensive care unit stay, less diuretic use, and fewer procedural complications.

A high level of scrutiny and rigor should continue to be applied to all interventional therapies emerging from the cardiac catheterization laboratory.

Innovations in Heart Failure and Heart Transplantation Medicine

Recent innovations in pediatric heart failure are highlighted by the ever-growing and highly adaptive use of mechanical circulatory support. The Second Pedimacs Registry report provides the most comprehensive, contemporaneous data on ventricular assist device (VAD) indications for children with heart failure.[12] While these devices are still primarily used as a bridge to transplant, outcomes by patient age/size and device-type vary significantly. Adolescents and children 6 to 10 years of age, in whom implantable continuous devices predominate, experienced lower morbidity and mortality compared with infants and children <6 years old, in whom paracorporeal devices (both pulsatile and continuous) predominate. Other key findings included the increasing use of VADs to support children with CHD, including many with single-ventricle anatomy (62% of CHD), and an inferior 6-month survival (48%–60% versus 80% for cardiomyopathy). Overall these data highlight a clear need for better strategies/devices for small patients and those with CHD. “Temporary” VADs (eg, CentiMag/PediMag, Rotaflow) may also be successfully used for support from weeks to months in children with CHD, cardiomyopathy, or retransplant, including many who are small (<5 kg). Temporary VADs provided longer survival than extracorporeal membrane oxygenation for children awaiting heart transplantation.[13]

Finally, in an innovative multicenter analysis of racial disparities in pediatric heart transplantation outcomes (530 recipients, 6 US centers), Green et al analyzed clinical data and data on allelic variations across 20 genes involved in allograft immune responses.[14] After adjusting for clinical and genetic differences associated with rejection, graft loss, and death, black race remained a significant predictor of adverse outcomes, with large hazard ratios (1.58–3.13), suggesting that societal implications of race also influence pediatric heart transplantation outcomes.

Congenital Cardiothoracic Surgery

With the high prevalence of neurodevelopmental delays and the impact on quality of life, the surgical focus has shifted to collaborative research on long-term morbidity.

The International Cardiac Collaborative on Neurodevelopment assessed factors associated with neurodevelopmental outcome in children undergoing cardiac surgery.[15] Patient and preoperative factors impacted 30% of the variability in Psychomotor Development Index and Mental Development Index of the Bayley Scales of Infant Development. Longer cardiopulmonary bypass duration in infants undergoing cardiac surgery was associated with lower Psychomotor Development Index and Mental Development Index, while deep hypothermic circulatory arrest and regional cerebral perfusion were not predictive. In the postoperative period, significant predictors of lower Mental Development Index included extracorporeal circulation membrane oxygenation/VAD use and longer length of stay. After adjusting for patient and perioperative factors, intraoperative and postoperative factors accounted for only 5% of the variance in scores. The current study re-emphasizes the importance of patient and preoperative factors (30% versus 5%) to neurodevelopmental outcomes. The study did not identify any factors that could be modified during the intraoperative or postoperative period.

The landmark Single Ventricle Reconstruction Trial was the first and only randomized controlled trial in congenital heart surgery evaluating the impact of shunt type on transplant-free survival for single ventricle patients.[16] The study was notable for a survival advantage with the right ventricle to pulmonary artery shunt at 1 year. However, by 6 years, the early survival advantage of the right ventricle to pulmonary artery shunt did not persist. This trial has demonstrated through repeated interim analyses and long-term follow-up that the conclusions from this cohort are dynamic. Thus, the perpetuation of long-term data on congenital heart surgery patients is essential to our understanding of these surgical strategies. The current update sadly shows that despite the most recent innovations, only 60% of patients with single right ventricle heart lesions are alive and free of transplant at 6 years.

Rheumatic Fever, Endocarditis, and Kawasaki Disease

Global Burden of Disease estimates in August 2017 revealed that 33.4 million persons have rheumatic heart disease (RHD).[17] Despite this, RHD research has remained largely neglected.

Echocardiography can detect RHD before symptoms develop (latent RHD). In 2012, echocardiographic screening for latent RHD was named among the AHA's "Top 10 Advances in Cardiovascular Disease and Stroke." However, deployment of echocardiographic screening has stalled as the impact of early case detection remains unclear. In a longitudinal outcomes study (median 2.3 years) in 227 Ugandan children with latent RHD,[18] those children with moderate-to-severe latent RHD had poor outcomes; 47.6% progressed and 2 died. Children with mild latent RHD had more heterogeneous outcomes, but were at risk of progression (10%–25%). Importantly, these data were insufficient to determine whether penicillin prophylaxis (penicillin G) improved outcomes, providing the critical stimulus for the GOAL (Gwoko Adunu pa Lutino) trial, currently in progress to determine the impact of penicillin in latent RHD.

Adult CHD

With the dramatic improvement in survival for children and adolescents with CHD, there are now more adults living with CHD than children. Despite this shift in demographics, there are limited studies on long-term outcomes in adults with CHD. Utilizing long-term regional/national databases and establishing multicenter research networks have allowed investigators to generate meaningful long-term outcomes data.

Patients with CHD may undergo a significant number of imaging procedures (eg, cardiac catheterizations, chest radiographs, and computed tomography) utilizing ionizing radiation over their lifetime. While low-dose ionizing radiation theoretically conveys a low risk of developing cancer, it is difficult to determine the cumulative effects of multiple exposures. Utilizing the Quebec CHD database, Cohen et al demonstrated that CHD patients with a higher ionizing radiation exposure had a cancer incidence of 8.5% versus 3.3% in CHD patients with lower exposure with an odds ratio of 1.10 (95% confidence interval, 1.05–1.15) per 10 mSv.[19] After controlling for age, sex, CHD severity, comorbidities, surgical history, and competing risk of death, patients with high exposure were found to be at a 2.4-fold greater risk of developing cancer than the low-exposure group. The study sets the stage for further prospective studies that will ultimately guide radiation policy recommendations and regulations in CHD patients.

Most quality-of-life studies performed in the CHD population do not account for cultural or geographical determinants. APPROACH-IS (Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart Disease—International Study) is a cross-sectional study that evaluated quality of life in 4028 adults with CHD, from 15 countries across 5 continents utilizing a uniform research methodology.[20] Quality of life among adults with CHD was generally good, and varied more with patient characteristics than country-specific factors. Based on these results, the authors proposed that uniform criteria could identify CHD patients with poorer quality of life regardless of geographical location.

Stem Cell Therapy and Genome Editing

The emergence of novel technologies using human induced pluripotent stem cells and genome editing are unique

opportunities for studying cardiovascular disease related to development, mechanism of disease, drug toxicity, and therapies to enhance the regenerative capacity of the heart.

There are limited stem cell–based clinical trials in patients with CHD, and these primarily focus on hypoplastic left heart syndrome. The PERSEUS randomized phase 2 controlled trial used cardiac progenitor cell infusions to treat univentricular heart disease. Intracoronary cell infusions were performed followed superior cavopulmonary connection and modified Fontan procedures and demonstrated the safety of this approach.[21] While cardiovascular regenerative medicine has yet to transform our practice, the future holds great promise.

Genome editing is targeted, genetic modification in the human genome and can be done using transcription activator-like effector nucleases. Karakikes et al designed transcription activator-like effector nucleases constructs to knock out human genes associated with cardiomyopathies and CHDs.[22] As proof of concept, a pathogenic mutation causing dilated cardiomyopathy (TNNT2 p.R173W) was selectively knocked out using transcription activator-like effector nucleases in patient-specific inducible pleuripotent stem cell-derived cardiac myocytes, rescuing the dilated cardiomyopathy phenotype in vitro. In addition, Holt-Oram syndrome was modeled in inducible pleuripotent stem cell-cardiac myocytes in vitro and uncovered novel pathways regulated by TBX5 in human cardiac myocyte development.

Prevention: Ideal Health Behaviors and Factors

The AHA Strategic Impact Goal Through 2020 and Beyond initiative recommends adoption of 4 ideal health behaviors and 3 ideal health factors that when implemented can prevent heart disease in 80% of cases. The 4 health behaviors include the following: abstinence from smoking, maintenance of a body mass index <85th percentile, participation in 60+ minutes of physical activity daily, and adherence to a heart-healthy diet. The 3 ideal health factors include maintenance of a normal cholesterol, hemoglobin A1c, and blood pressure. Unfortunately, adoption of these recommendations by American youth has been abysmally poor. While >80% of youth do not smoke, <1% have an ideal diet. The prevalence of pre/diabetes mellitus type 2 has increased from 9% to 23% and 11% of youth have abnormal blood pressure.[23] The diagnosis of hypertension is not made in 77% of youth. The 2017 Clinical Practice Guideline for the Diagnosis and Management of High Blood Pressure in Children and Adolescents updates definitions and management strategies and proposes methods for improved recognition of hypertension.[24]

The National Institutes of Health funded i3C Outcomes Study is the first longitudinal cohort study to assess the impact of childhood cardiovascular risk factors on adult cardiovascular end points.[25] Results from this study will further our knowledge of the relationship between childhood factors and adult heart disease.

Early Career and Mentorship

Employment opportunities in pediatric cardiology have been diversifying. The United States Pediatric Cardiology 2015 workforce assessment survey showed that nearly 60% of all third-year graduates pursued additional subspecialty training and nearly 90% of them accepted academic positions. Greater difficulty in securing positions was seen in subspecialty areas including cardiac catheterization and electrophysiology.[26]

There are numerous obstacles to becoming a successful physician-scientist. The Early Career Committee of the Cardiopulmonary, Critical Care and Resuscitation Council of the AHA recommends that mentoring be sought early during training and initial faculty appointments. Career success requires meaningful mentorship relationships that in addition to obtaining grant funding can lead to the development of adaptive skills to the meet demands of academic careers and improve the integration of our professional and personal lives. A physician-scientist's long-term academic success needs to combine long-term higher-risk projects with short-term low-risk projects.[27]

Conclusions

Our scientific knowledge and clinical capabilities in the field of pediatric cardiology and cardiac surgery continue to expand. Notable reports in the last 2 years challenge existing paradigms in pediatric cardiology and cardiac surgery (Figure) and encourage us to identify and address novel risk factors, medical and catheter-based interventions, new devices, multicenter randomized clinical trials to change our current practice, and increase focus and attention on prevention of acquired cardiovascular disease and regenerative and genomic opportunities. These articles also highlight the need for collaborative science across the T1 to T4 research paradigm.

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