

Perspective on Congenital Heart Disease Research

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Congenital heart disease (CHD) is the most common birth defect and a leading cause of morbidity and mortality in patients with congenital malformations. The past 7 decades have witnessed dramatic advances in the medical, catheter, and surgical management of these patients. Clinical research has been a driving force to improve our understanding of the pathophysiology of disease and to refine therapy. Here, we identify some of the themes that have characterized the research process in the past and that have propelled the field to its present state. We discuss current research-related challenges and speculate about what trends may define the future of CHD research.

The historical canon of congenital heart disease (CHD) is replete with dramatic triumphs: the first open heart surgery, the first use of cardiopulmonary bypass, the first transcatheter interventional cardiac procedure, and many others. In the years since these seminal events, progress has been made in all aspects of the care for patients with CHD. Prompt diagnosis is routine, surgical management of the most complex lesions is achievable, and acute and chronic care of patients has been refined. Important challenges remain, including persistent mortality for particular complex defects and long-term problems such as neurodevelopmental abnormalities, arrhythmias, and heart failure. Nevertheless, there are many reasons to be proud, and clinical research has been a foundational feature that has helped drive much of this progress. We describe some trends in research that have propelled the field to its current state and speculate about what trends may define the future of CHD research.

Past and Present CHD Research

Individual to Group Science

A defining trend of the past 75 years of CHD research has been the change in focus from the individual to the group.

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Early CHD research was performed by individuals trying to solve problems, 1 child at a time. Innovative thinkers and doers—Gross, Lillehei, Rashkind, and Norwood—pushed the envelope, often in the face of opposition, to expand the realm of the possible. This early research is perhaps best exemplified by the first blue baby operation. Helen Taussig, a pediatric cardiologist at Johns Hopkins, systematically studied these babies and concluded that inadequate flow to the pulmonary artery was the cause of their hypoxemia. She convinced the surgeon, Alfred Blalock, and his collaborator, Vivien Thomas, to devise a surgical strategy to augment pulmonary blood flow. Working in the dog laboratory, Blalock and Thomas perfected the technique of anastomosing the subclavian artery to the pulmonary artery. Their systematic study led to one of the first translational research accomplishments in CHD, the first successful blue baby operation performed in 1944. No multicenter clinical trial was needed to confirm the enormous benefit of this operation, and the principle has proven remarkably durable for children with inadequate pulmonary blood flow.

This and other early, innovative approaches to management of CHD had tremendous effect sizes—infants and children, previously condemned to early demise, survived, and thrived. For example, Rashkind only needed 3 patients to demonstrate that his septostomy could prolong life in patients with transposition of the great arteries.¹ As these pioneering techniques improved and spread, more and more CHDs surrendered to treatment. Now, new therapies are incremental, with much smaller effect sizes. Therefore, to document advances of new ideas, larger sample sizes are needed, necessitating multicenter collaborative studies.

A recent example of this group science is the Single Ventricle Reconstruction Trial. Surgical palliation of hypoplastic left heart syndrome continues to have significant mortality, motivating the field to refine strategies.² The initial hypoplastic left heart syndrome palliation involves reconstructing the aorta using the main pulmonary artery and reestablishing another source of pulmonary blood flow. Classically, pulmonary blood flow has been supplied by a modified Blalock–Taussig shunt between the subclavian artery and the pulmonary artery. An alternative approach, placing a shunt between the right ventricle and pulmonary artery, was thought to yield potential advantages. To determine which approach resulted in improved outcome required a large number of investigators randomizing a large population (555 infants) to 2 surgical techniques. The multi-institutional National Heart, Lung, and Blood Institute–funded PHN (Pediatric Heart Network) accomplished this monumental challenge. We learned that the newer right ventricle to

Nonstandard Abbreviations and Acronyms

CHD	congenital heart disease
PCGC	Pediatric Cardiac Genomics Consortium
PHN	Pediatric Heart Network
STS	Society for Thoracic Surgeons

pulmonary artery shunt had superior transplant-free survival ≤ 12 months, but that this advantage diminished with longer follow-up. This landmark trial highlights the value of collaborative research and the feasibility of enrolling large numbers of patients with CHD in answering critical questions.²

Increasing Need for Multidisciplinary Approach

Another trend has been the increasingly multidisciplinary nature of CHD research. Early research was siloed within specific areas—surgical techniques, diagnostics, and interventional cardiology, but the many clinical improvements generated challenges in overlapping domains. With decreasing surgical mortality, it became imperative to improve postoperative care, necessitating collaboration among surgeons, cardiologists, anesthesiologists, critical care medicine physicians, and nurses. As children with CHD survived until school age years and began exhibiting neurodevelopmental abnormalities, research required the collaboration of cardiologists, surgeons, neurologists, neuropsychologists, developmental pediatricians, and neuroradiologists. In the current era, PHN study teams include a variety of experts such as cardiologists, surgeons, cardiac anesthesiologists, nurse researchers, statisticians, hematologists, neurodevelopmental experts, industrial engineers, and data scientists.

Small Studies to Big Data

Another trend in the evolution of CHD research has been the transition from small studies to big data. The single-center case series, long a hallmark of CHD research, has been valuable for describing disease and potential treatment strategies. However, detecting trends over time and across centers, comparing treatment approaches, and dissecting out the genetic cause of CHD require a different approach. Coincident with the need for increasing volume and diversity of data has been the emerging capacity to capture, store, and analyze that data. These independent developments have propelled us into the era of big data. The PCGC (Pediatric Cardiac Genomics Consortium) Data Hub currently stores 180 terabytes of sequence and phenotype data on over 10 000 subjects with CHD enabling investigators to discover novel genetic findings.³ The STS (Society for Thoracic Surgeons) Congenital Heart Surgery Database has detailed information on over 400 000 operations from 74 surgical centers in North America.⁴ The STS Database has been used to track mortality, identify practice variation, and determine associations between patient, operative, and center factors and outcome.

Future Trends in CHD Research

The current CHD research ecosystem is built on a foundation of collaborative, multidisciplinary research and more recent embracing of big data. What trends will emerge over the next 75 years of CHD research? Although we can only speculate, signs point to some intriguing possibilities.

Improving Research Efficiency

For the foreseeable future, research costs will continue to outpace increases in federal research budgets, with ripple effects likely to drive 2 important trends. First, improving research efficiency will be a motivating force behind many research innovations. One area where we are starting to see this effect is in data capture. Registries are being used as the data collection vehicle for research studies and trials. Trials within registries have minimal incremental costs per patient to collect end point data, and registry data have been shown to be complete and accurate for children undergoing surgery for CHD.^{5,6} The electronic health record will also become a more central tool for data capture in research. To facilitate this, the field will need to develop consensus common data elements for classification of CHD and adjudication of clinical outcomes.

Leveraging Resources and Partnerships

A second response to the constrained funding environment will be increased leveraging of funding resources and partnerships to fill the shortfall. One example can be found in the new reduced funding structure of the PHN. Investigator-initiated grants will be needed to conduct some PHN studies. Collaborations with industry are permitting the PHN to conduct additional trials. Industry will be able to leverage the expertise of the PHN in conducting trials, while PHN investigators will be able to advance science and bring new therapies to their patients.

Increasing Precision of Therapies

The prior 75 years of CHD research and clinical care has operated with diagnostic and therapeutic models based on structural anatomy and hemodynamic correction or palliation. We anticipate a paradigm shift over the next 75 years where an improved understanding of the genetic and cellular underpinnings of CHD will enable more precise definitions of disease and more targeted therapies. It is likely that diagnosis of a defect will rely not only on imaging findings but also on a molecular signature providing insight into causation, therapy, and future complications. PCGC investigators have recently identified a group of genes associated with both CHD and a high risk of neurodevelopmental abnormalities.³ It is possible to imagine in the foreseeable future a genetic test that will identify a subgroup of patients who should receive early, intensive therapies to mitigate anticipated neurodevelopmental issues. Also, we know that drugs beneficial for adult heart failure have not fully translated into the CHD setting. Teasing out the underlying molecular cause of heart failure in CHD will enable more targeted therapies for these survivors.⁷

Correcting Disease

Advances in manipulation and therapeutic alteration of genes and cells have paralleled improved understanding of the molecular cause of disease. These technologies will enable researchers to develop novel devices that more closely mimic physiology and possibly even therapies that can cure disease. Examples of these technologies include biological pacemakers to treat surgical heart block, tissue-engineered conduits that grow with the patient, and stem cell therapy to improve right ventricular function in patients with hypoplastic left heart syndrome.⁸ Although cure of CHD is a valiant goal with a distant horizon, it is one we should keep in our sights. Gene or gene product alteration, through genome editing, gene therapy, or

RNA interference, has shown promise for being able to significantly correct monogenic diseases in animal models.⁹ As we learn more about these approaches, the underlying genetic causes of CHD, and how to intervene at progressively earlier stages of development, novel corrective strategies may emerge.

Integrating Data

The big data revolution will continue to flourish in several ways within the CHD arena. First, data sources, like the registries (STS, IMPACT [Improving Pediatric and Adult Congenital Treatment Registry], PC4 [Pediatric Cardiac Critical Care Consortium Registry], etc.), are currently siloed and will need to be integrated at the patient level to understand the full scope of the patient experience.¹⁰ Current isolated efforts have been able to link 2 data sources for 1-time use. We think that this effort needs to be more comprehensive, continuous, and more accessible to the wider research community. Increased data sharing within and beyond the CHD research community and open platforms that will encourage collaboration between cardiologists and noncardiologists will be essential to advancing knowledge. Second, big data in medicine will incorporate nontraditional sources of information. These might include remote monitoring devices, social media, census and education records, environmental readings, and geographic information systems, to name just a few. And third, big data analytics and advancements in electronic health records will facilitate the fusing of research into patient care. The electronic health record will be a source of data and a vehicle for experimentation and recruitment. Quality improvement protocols and standardized management plans can be integrated into the electronic health record to identify practice variation and improve efficiency. Ideally, we would like to see all patients with CHD become participants in clinical research, much of which could be conducted in conjunction with their regular clinical care.

Engaging Patients

We are in a new era of research that respects the role of participants as active partners in the process. Patient-reported outcomes have become essential end points in clinical trials. Patient advocacy groups raise money and awareness about research and support recruitment into clinical trials. Patients are starting to partner with investigators to identify research priorities that are relevant to their experience.¹¹ In some cases, patients and their advocacy groups are establishing their own research initiatives, recruiting patients into registries, designating centers of excellence, and educating regulatory agencies about how best to support their community's needs.

Potential Concerns

As these trends emerge, new concerns will invariably arise. They include the following:

1. How will industry's involvement in sponsoring research affect the CHD research agenda and data access?
2. How do we promote data sharing while at the same time protecting patient privacy?
3. How do we ensure that research populations accurately reflect the diversity of the patient population?

In order for advancements to be made, a full accounting of these and other concerns will be needed.

Conclusions

The CHD research community has accomplished a tremendous amount in the past 75 years. We should continue to set for ourselves big, even audacious, goals. Can we envision a future where:

1. CHD diagnosis is based on a molecular signature rather than a description of anatomic structure?
2. Patients with heart failure are treated with a medication designed to address their specific pathophysiologic mechanism?
3. A right ventricle to pulmonary artery conduit surgically implanted in an infant with pulmonary atresia will grow with the patient and resist calcification?
4. Every infant with CHD detected by pulse oximetry screening will be enrolled into a longitudinal registry?

These are only a few of likely many, worthy goals. Clearly, much work remains to be done. However, our successful past predicts a hopeful future.

Disclosures

None.

References

1. Rashkind WJ, Miller WW. Creation of an atrial septal defect without thoracotomy. A palliative approach to complete transposition of the great arteries. *JAMA*. 1966;196:991–992.
2. Ohye RG, Sleeper LA, Mahony L, et al; Pediatric Heart Network Investigators. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med*. 2010;362:1980–1992. doi: 10.1056/NEJMoa0912461.
3. Homsy J, Zaidi S, Shen Y, et al. De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. *Science*. 2015;350:1262–1266. doi: 10.1126/science.aac9396.
4. Jacobs ML, Jacobs JP, Pasquali SK, Hill KD, Hornik C, O'Brien SM, Shahian DM, Habib RH, Edwards FH. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2016 update on research. *Ann Thorac Surg*. 2016;102:688–695. doi: 10.1016/j.athoracsur.2016.07.015.
5. Lauer MS, D'Agostino RB Sr. The randomized registry trial—the next disruptive technology in clinical research? *N Engl J Med*. 2013;369:1579–1581. doi: 10.1056/NEJMp1310102.
6. Nathan M, Jacobs ML, Gaynor JW, Newburger JW, Dunbar Masterson C, Lambert LM, et al; Pediatric Heart Network Investigators. Completeness and accuracy of local clinical registry data for children undergoing heart surgery. *Ann Thorac Surg*. 2016;103:629–636. doi: 10.1016/j.athoracsur.2016.06.111.
7. Burns KM, Byrne BJ, Gelb BD, Kühn B, Leinwand LA, Mital S, Pearson GD, Rodefeld M, Rossano JW, Stauffer BL, Taylor MD, Towbin JA, Redington AN. New mechanistic and therapeutic targets for pediatric heart failure: report from a National Heart, Lung, and Blood Institute working group. *Circulation*. 2014;130:79–86. doi: 10.1161/CIRCULATIONAHA.113.007980.
8. Ishigami S, Ohtsuki S, Tarui S, et al. Intracoronary autologous cardiac progenitor cell transfer in patients with hypoplastic left heart syndrome: the TICAP prospective phase I controlled trial. *Circ Res*. 2015;116:653–664. doi: 10.1161/CIRCRESAHA.116.304671.
9. Jiang J, Wakimoto H, Seidman JG, Seidman CE. Allele-specific silencing of mutant Myh6 transcripts in mice suppresses hypertrophic cardiomyopathy. *Science*. 2013;342:111–114. doi: 10.1126/science.1236921.
10. Pasquali SK, Jacobs JP, Farber GK, et al. Report of the National Heart, Lung, and Blood Institute working group: an integrated network for congenital heart disease research. *Circulation*. 2016;133:1410–1418.
11. Cotts T, Khairy P, Opatowsky AR, et al; Alliance for Adult Research in Congenital Cardiology (AARCC). Clinical research priorities in adult congenital heart disease. *Int J Cardiol*. 2014;171:351–360. doi: 10.1016/j.ijcard.2013.12.034.

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