

Circulation Research Compendium on Congenital Heart Disease

Congenital Heart Disease: The Remarkable Journey From the “Post-Mortem Room” to Adult Clinics

Perspective on Congenital Heart Disease Research

Has the Congenitally Malformed Heart Changed Its Face? Journey From Understanding Morphology to Surgical Cure in Congenital Heart Disease

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Ali J. Marian, Editor

Congenital Heart Disease

The Remarkable Journey From the “Post-Mortem Room” to Adult Clinics

Ali J. Marian

The progress in congenital heart disease (CHD), since the first anatomic depiction of an anomalous pulmonary venous return by Leonardo da Vinci in 1513, has been unabated. The course has been decorated with occasional sparks stemming largely from the ingenuity of pioneering physicians and surgeons who departed from the prevailing notions and brought forth new brave ideas to diagnosis and management of patients with CHD (Table). The progress, however, was not without frequent disappointments. The extremely high mortality rate in the early days of open-heart surgery with the use of extracorporeal circulatory machine disappointed John Gibbons, the inventor of the first heart–lung machine, to the point that he called for a long-term moratorium on the use of his invention. Yet, the convictions of pioneering surgeons such as C. Walton Lillehei and John Kirklin led them to forge ahead with improved versions of the pump, ultimately changing the treatment of CHD. Advances in diagnostic methods

and surgical treatment during the past several decades have transformed CHD malformations from being “hopeless futilities” in neonates, infants, and children to treatable conditions with >90% of patients surviving into the adult years.

Of the ≈125 million children born every year (www.unicef.org), it is estimated that about 1 000 000 to 1 500 000 are born with a CHD. Because of the scientific and technological advances during the past several decades, the vast majority of these children survive to adulthood, and those with less complicated lesions expect a life expectancy similar to that of the general population. Consequently, it is estimated that worldwide ≈50 million adults live with CHD, including ≈1.5 million in the United States alone, more than the number of children with CHD. As a result of an excellent survival rate, the landscape of CHD has markedly changed, posing a new set of challenges in the care of these individuals, ranging from the management of heart failure to psychological stress. In the Compendium, Bouma and Mulder¹ provide a comprehensive and exceptional review of the large number of issues that patients with CHD and physicians face in the new landscape.

The relatively low incidence of CHD (≈8 in 1000 live births), along with its phenotypic diversity, necessitated coordinated efforts to promote advances in the field. A series of initiatives by the National Heart, Lung, and Blood Institute, discussed by Kaltman et al,² have transformed small single-center studies to coordinated multidisciplinary multicenter approaches in the diagnosis and management of patients with CHD. These initiatives have had a remarkable impact on the

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Table. Timeline of Some of the Scientific Discoveries and Developments in Congenital Heart Disease

| | |
|------|--|
| 1513 | Leonardo Da Vinci: anomalous pulmonary venous return |
| 1842 | Crawford W. Long: ether as anesthetic in surgery |
| 1852 | London Hospital for Sick Children |
| 1870 | Adolph Fick and Arthur Grollman: Cardiac output |
| 1895 | Wilhelm Konrad Roentgen: x-ray |
| 1929 | Werner Forssman: right heart catheterization |
| 1933 | John H. Gibbons: heart–lung machine |
| 1937 | A. Castellanos, R. Pereiras, and A. Garcia: right heart angiography |
| 1938 | R.E. Gross and J.P. Hubbard: surgical ligation of PDA |
| 1944 | Alfred Blalock: Blalock–Taussig shunt |
| 1944 | Crafoord and Nylin: resection of coarctation |
| 1946 | F. Bloch and E. Purcell: the NMR phenomenon |
| 1952 | W.H. Muller and J.F. Dammann: Pulmonary artery banding |
| 1953 | I.G. Edler and C.H. Hertz: echocardiography |
| 1953 | John H. Gibbons: ASD closure using heart–lung machine |
| 1953 | Wilfred G. Bigelow: hypothermia for open-heart surgery |
| 1955 | C.W. Lillehei: cross circulation |
| 1955 | John W. Kirklin: heart–lung machine |
| 1956 | R.A. DeWall: pump-oxygenator system |
| 1960 | R.R. Lower and N.E. Shumway: orthotopic cardiac transplantation |
| 1966 | Christian Bernard: cardiac transplantation |
| 1966 | W.J. Rashkind and W.W. Miller: balloon atrial septostomy for complete transposition of the great arteries |
| 1967 | W. Portsmann, L. Wierny, H. Warnke: interventional closure of PDA |
| 1976 | Terry King: catheter closure of ASD |
| 1981 | A. de la Chapelle et al: genetics of DiGeorge syndrome |
| 1982 | Robert Jarvik: first implantation of permanent artificial heart |
| 1983 | Aldo Castaneda: arterial switch operation |
| 1988 | O.H. Frazier: first human use of Hemopump |
| 1988 | W.F. Bernhard: long-term implantation of left ventricular assist device |
| 1997 | C.E. Seidman et al: TBX5 as the causal gene for ASD |
| 1998 | C.E. Seidman et al: NKX2-5 as the causal gene for CHD |
| 2010 | Pediatric Heart Network Investigators: 1st randomized trial in hypoplastic left heart syndrome |
| 2014 | S. Ishigami et al: stem-cell therapy in congenital heart disease (TICAP trial) |
| 2015 | Pediatric Heart Network Investigators: shared genetic cause of congenital heart disease and neurodevelopmental abnormalities |

elucidation of the genetic basis of CHD and have made it possible to conduct randomized clinical trials.

A genetic predisposition to CHD has long been recognized. Helen Taussig described CHD as developmental error or genetic variant, a concept that is not dissimilar from our current understanding of CHD, which one might define

as developmental abnormalities caused by mutations in genes and pathways involved in spatiotemporal differentiation and proliferation of cardiovascular cells. Nevertheless, elucidation of the genetic basis of CHD had to await the development of modern molecular genetic tools, such as cytogenetics, genetic linkage mapping, DNA microarrays, and large-scale DNA-sequencing platforms. Basson et al³ and Schott et al⁴ identifies *TBX5* and *NKX2-5* as the first 2 causal genes for familial CHD. A rapid pace of discoveries ensued shortly thereafter, along with the enormous impact of the Pediatric Cardiac Genomics Consortium, collectively leading to partial elucidation of genetic basis of CHD, as elegantly discussed by Zaidi and Brueckner.⁵

The initial genetic discoveries pointed to the role of transcription factors, such as *NKX2-5*, *GATA4*, *TBX5*, and *NOTCH1*, which regulate cardiogenesis, in the pathogenesis of CHD. Accordingly, CHD might be considered a phenotypic consequence of developmental abnormalities of the heart. The group led by Galdos et al⁶ offers a sophisticated discussion of how the limited regenerative capacity of the adult heart restricts the therapeutic options in repairing the damaged heart in patients with CHD. The authors suggest that a better understanding of the regulation of cell cycle reentry and cardiac myocyte proliferation might enable new approaches to the treatment of patients with CHD. Similarly, progress in enhancing maturation of cardiac myocytes derived from pluripotent stem cells, more effective techniques of cell transplantation, and improved efficiency of transdifferentiation of cardiac fibroblasts to myocytes could offer valuable therapeutic options.

Despite the remarkable progress in the survival and coming of age of children with CHD, the threat posed by the underlying genetic mutation and developmental abnormalities has remained unabated. The hemodynamic burden, even in those with surgically corrected anatomy, along with the underlying developmental abnormalities involving the myocardium and the cardiac conduction system, increases the risk of heart failure and arrhythmias during adulthood. Indeed, heart failure has emerged as the main cause of death in adults with CHD, followed by sudden cardiac death. Likewise, CHD is the most common cause of heart failure in children. Hinton and Ware⁷ provide an elaborate discussion of the causal basis, diagnosis, and treatment of heart failure in children and adults with CHD.

Abnormalities that predispose the heart to failure and arrhythmias in patients with CHD, including the underpinning genetic defects, hemodynamic stress, and hypoxia, also impart a considerable risk of lifelong neurodevelopmental abnormalities, such as cognitive impairment, impaired social interaction, and compromised communication skills. In a sense, CHD is not an exclusive disease of the heart; it also encompasses a variety of phenotypes involving other organs, such as neurodevelopmental abnormalities. The higher prevalence of neurodevelopmental abnormalities in patients with CHD, which was clinically suspected for years, has been further substantiated with advanced neuroimaging discoveries, which have clearly documented functional and structural derangements. Furthermore, recent genetic discoveries have offered a shared genetic basis as a mechanism for the higher

prevalence of neurodevelopmental abnormalities in patients with CHD. Specifically, it is now appreciated that a subset of CHD is caused by mutations in genes involved in the epigenetic regulation of chromatin, which impact the development not only of the heart but also of other organs, including the brain. Jonas et al⁸ provide a comprehensive and informative review of the various aspects of neurodevelopmental abnormalities in patients with CHD.

Advances in cardiovascular imaging, from the first image of cardiac catheterization by Werner Forssman in 1929, have been instrumental for the success of surgical correction of CHD and even more so for catheter-based interventions. The predominantly x-ray-based imaging techniques in the early days have evolved into advanced multimodality imaging approaches, including 3-dimensional echocardiography, computed tomographic angiography, cardiac magnetic resonance imaging, and 3-dimensional printing, which play instrumental roles in the precise delineation of the anatomy and characterization of the functional defects, including myocardial abnormalities and intracardiac shunts. The applications of multimodality cardiovascular imaging, meticulously discussed by Burchill et al,⁹ have enabled physicians and surgeons alike to provide better care to patients with CHD.

The history of CHD is marked by the pioneering actions of visionary surgeons and physicians who transformed this syndrome from being a matter for the postmortem room to a treatable disease of predominantly adult populations. Advances in the surgical correction of CHD, along with multidisciplinary approaches to the anatomic and functional characterization of CHD, have revolutionized the outcome by reducing the postoperative mortality rate of $\approx 95\%$ for simple CHD in the early days of Gibbons heart–lung machine to $<5\%$ for most complex CHD in the modern era. Dearani et al¹⁰ provide the state of the art of surgical correction of CHD.

The invention of cardiac catheterization by Forssman in 1929 ushered in the era of invasive approaches to the diagnosis and management of patients with CHD. The complexity of the lesions required continued refinement and development of the new procedures and devices by creative physicians, such as Charles Mullins at Texas Children's Hospital. These advances transformed cardiac catheterization from a diagnostic to a therapeutic procedure in CHD. Kenny and Hijazi,¹¹ pioneers of the field, outline the current state of the art in the applications of interventional transcatheter approaches to the treatment of patients with CHD.

The stunning successes of physicians and surgeon caring for neonates, infants, children, and adults with CHD during the past several decades have profoundly transformed the hopeless

futilities to manageable medical conditions. In the coming years, unabated progress is expected to usher in new diagnostic and therapeutic approaches, based on molecular genetics and biology, to the care of patients with CHD. To quote Sir Winston Churchill, “this is not the end. It is not even the beginning of the end. But it is perhaps the end of the beginning.”

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Disclosures

None.

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