Published in final edited form as:

Pediatr Cardiol. 2017 June ; 38(5): 974–980. doi:10.1007/s00246-017-1605-x.

Trends in National Institutes of Health-Funded Congenital Heart Disease Research from 2005 to 2015

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Abstract

In an era of ongoing need for research to enable evidence-based care for the expanding population with congenital heart disease (CHD), economic fluctuations have impacted research funding. We characterize trends in NIH-funded CHD research from 2005 to 2015. We searched the NIH RePORTER database from 2005 to 2015 using the terms “congenital heart” and “cardiac morphogenesis”. Projects were characterized by year, institute, mechanism, costs, type and topic, and funding trends were analyzed. From 2005 to 2015, NIH funded 633 CHD research projects with total costs of \$991 million. The National Heart, Lung, and Blood Institute funded 83% of CHD projects (528, \$857 million). The R01 mechanism was used for 45% of projects (288, \$421 million). Projects were 70% basic/early translational research, 27% clinical research, and 3% both. Cardiac developmental biology was the most common topic (52%), followed by technology/therapy development (15%), and diagnosis/management (12%). The total number of CHD projects ranged from 153 to 221 per year (30–58 new projects/year), and costs per year ranged from \$58 to \$116 million. The number of projects and total costs increased until 2012, but decreased again thereafter. CHD research did not experience as much erosion as overall NIH purchasing power; in constant dollars, CHD research funding levels in 2015 were \$12 million higher than those in 2005. The NIH supported a diverse portfolio of CHD projects from 2005 to 2015. Support of CHD research projects trended upward until 2012, but declined thereafter due to fiscal austerity measures.

Keywords

Congenital heart defect; Pediatrics; Trials; Research; Funding

Introduction

Congenital heart disease (CHD) is the leading cause of infant deaths in the United States [1] and accounts for more than half of all deaths from congenital anomalies worldwide [2]. CHD represents a heterogeneous group of structural defects that arise during heart development. It is the most common type of birth defect, affecting about 8 per 1000 live

Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest or relationships with industry to disclose. The views expressed are those of the authors and do not necessarily reflect official National Heart, Lung, and Blood Institute positions.

births in the United States [3, 4], approximately 25% of whom will require invasive treatment within the first year of life [5]. Bicuspid aortic valve, which is present at birth but often not detected until much later in life, affects an additional estimated 1.4% of the population [4]. Although innovations in diagnostic and management tools have led to improved detection and survival as well as an increase in the population of adults living with CHD, long-term complications such as arrhythmias and heart failure remain a challenge, particularly for complex lesions. CHD-related hospital discharge mortality is the highest among neonates (10%) [5] but is also substantial among adults with CHD (2–5%) [5, 6]. Resource utilization is high for individuals with CHD [7–10], particularly among those requiring cardiovascular surgery.

Descriptions of CHD and endeavors to understand cardiac development began hundreds of years ago, but the first classification scheme for CHD was proposed in 1858 by Thomas Peacock. Maude Abbott's 1908 chapter on "congenital cardiac disease" echoed Peacock's sentiment that CHD is likely caused by arrested cardiac development. The surgical era of CHD began in 1939 with Robert Gross' first patent ductus arteriosus ligation, followed in 1944 by the blue baby operation for tetralogy of Fallot championed by Helen Taussig, Alfred Blalock, and Vivien Thomas [11]. The National Institutes of Health (NIH) has a long track record of support for research in CHD; in fact, Blalock received NIH funding in 1949 for his pioneering work on CHD. Since then, researchers have uncovered vital insights into disease mechanisms and have developed many novel treatment strategies. The results of NIH investments in CHD research are apparent through improving outcomes and a multitude of publications from prolific scientists, yet much remains to be done. The persistent burden of disease, the growing population of survivors with CHD, and the rising costs of their healthcare underscore the importance of research in understanding the mechanisms of abnormal cardiac development and translating those findings into evidence-based preventative, diagnostic, and therapeutic strategies to guide care.

Over the last decade, funding levels for NIH research have been relatively flat, and starting in 2013, automatic spending cuts resulted in a 5.5% decrease in the NIH budget. Such budget cuts combined with the effects of inflation resulted in an erosion of purchasing power by almost 25% for biomedical research at NIH over the past decade [12]. It is unclear how this erosion has impacted research in CHD because descriptions of the NIH's financial allocations to CHD funding have not been published previously. The purpose of this study was to analyze the NIH research portfolio to characterize trends in investments in CHD research over the past decade.

Methods

The NIH Research Portfolio Online Reporting Tools (RePORT) system is a publicly available searchable website that provides access to reports, data, and analyses of research funded by NIH. The system contains information on NIH-funded intramural and extramural research projects since 1989 [13]. The database is organized by research, condition, and disease categorization codes. In 2015, a specific code for CHD was created, but prior to 2015, CHD projects were classified under cardiovascular disease.

In the absence of a code for CHD prior to 2015, we searched one of the modules within RePORT, the Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER) database of NIH-funded projects for active grants and contracts between 2005 and 2015 using the search terms “congenital heart” and “cardiac morphogenesis”. The search terms needed to be present in the title, abstract, specific aims, or public health relevance section of the application. We excluded projects on cardiomyopathy, arrhythmia, and pulmonary hypertension, unless the research focused on these entities in the setting of CHD. We also excluded projects on genetic syndromes if the research was not focused on the cardiac manifestations, as well as research on generalized organogenesis that was not specific to the heart. We cross-checked our internal portfolio to identify projects that may have been missed by our search terms.

After manually filtering out non-CHD related projects, each project was characterized by year, awarding institute, funding mechanism, funding announcement, and total costs per year. We categorized each project by type: clinical research, basic/early translational research, or both (e.g., training grants often include both clinical and basic/early translational research exposure). Among clinical research projects, we identified the clinical trials. We then classified each project by the following topic areas: cardiac developmental biology, diagnosis/management, epidemiology, human genetics, physiology, therapy/technology development or multiple topics. Discrepancies were adjudicated among the authors.

NIH definitions were used to describe grants; contracts; basic, early translational, and clinical research; and clinical trials [14]. NIH funding mechanisms were grouped into the following categories: research project grants, career development/training grants, small business projects (SBIR/STTR), intramural research performed on the NIH campus, contracts, and other less-common research support mechanisms (e.g., conference, resource, and challenge grants, high-impact research grants and biomedical research support shared instrumentation grants). The research project grant category included investigator-initiated research projects (R01), program project grants involving multiple research projects (P), exploratory research grants (R21), small research grants (R03), academic research enhancement awards (AREA-R15), research transition awards (R00), planning grants (R34), method to extend research in time grants (MERIT-R37), bridge awards (R56), linked research project grants (RL1), and cooperative agreements (U) requiring significant NIH staff involvement. The career development/training category included career development awards (K), fellowship grants (F), early independence grants (DP5), and institutional training grants (T).

Descriptive statistics were used to characterize the number of projects and awards, amount of funding, institute, mechanism, category, topic, and trends over time. The Consumer Price Index calculator was used to calculate constant 2005 dollars from current dollars [15]. Data analysis was performed using Microsoft Excel 2016.

Results

The RePORTER search identified 1074 projects, of which 441 were excluded as described above or for lack of relevance. (Fig. 1) Thus, 633 CHD research projects were funded by NIH from 2005 to 2015 at a total cost of \$991 million. The National Heart, Lung, and Blood Institute (NHLBI) supported the majority of CHD projects (83%, 528 projects, \$857 million), followed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (8%, 48 projects, \$86 million).

Funding mechanisms focused on fostering the next generation of scientists, including career development, fellowship, early independence, and institutional training grants, made up a total of 23% of all CHD projects (144 projects, \$60 million). Research project grants made up 66% of projects (419 projects, \$776 million). (Fig. 2a) The most common funding mechanism was the investigator-initiated R01 research project grant (288 projects, \$421 million), while cooperative agreement (U) mechanisms made up 49 projects (\$235 million). Most of these cooperative agreements represent institute initiatives designed to stimulate multicenter, collaborative research, such as the NHLBI Bench to Bassinet Program, comprised of the Pediatric Heart Network (PHN), the Pediatric Cardiac Genomics Consortium, and the Cardiovascular Development Consortium. Others represent large clinical trials that required significant NHLBI staff involvement.

Early-stage investigators and new investigators led 65 projects (30% of the eligible R01 and DP2 grants). Investigator-initiated projects made up 80% of CHD research (505 projects, \$555 million), whereas 20% of CHD projects (128 projects, \$437 million) were funded in response to NIH initiatives or as intramural projects carried out on the NIH campus.

From 2005 to 2015, NIH funded 441 basic/early translational research projects (70%, \$595 million), 172 clinical research projects (27%, \$372 million), and 20 projects involving both basic/early translational and clinical research (3%, \$24 million). (Fig. 2b) Among clinical research projects, ten investigator-initiated CHD clinical trials were funded from 2005 to 2015 outside of NIH networks. Within NIH networks, 37 grants (\$101 M) were awarded to conduct CHD research. Cardiac developmental biology was the most prevalent area of CHD research (52%, 328 projects, \$401 million), followed by technology/therapy development (15%, 96 projects, \$165 million) and diagnosis/management (12%, 78 projects, \$187 million) (Fig. 2c).

The total number of CHD research projects funded by NIH from 2005 to 2015 ranged from 153 to 221, of which 30–58 per year were new projects. The American Recovery and Reinvestment Act (ARRA) of 2009 provided funding for an additional 39 grants (and 26 supplements, \$23 million) during 2009 and 2010. (Fig. 3a) The number of funded CHD research projects trended upward after 2005, with a transient additional increase due to ARRA funding, but subsequently decreased after federal automatic budget cuts (called sequestration) started in 2013. The number of new projects was the lowest in 2013, but there was an increasing trend in the number of new projects funded in 2014 and 2015.

Trends in funding over time are shown in Fig. 3b for NIH overall, NHLBI, research project grants, career development/training projects, and investigator-initiated new projects. Costs

per year for NIH-funded CHD projects ranged from \$58 to \$116 million. Total costs for research project grants followed similar trends as the number of projects over time, increasing after 2005, with an additional increase in 2009 and 2010 in the context of the ARRA economic stimulus package, and decreasing after 2013 after the start of the automatic budget cuts. Funding for career development/training projects on CHD remained constant over time. Funding for investigator-initiated projects peaked in 2009 and decreased from 2010 to 2013, but showed a more recent increasing trend.

Figure 3c demonstrates NIH funding for CHD research in current dollars and in 2005 constant dollars. Funding for CHD research trended upward over time and then decreased after 2010. Despite decreases after 2013, in constant dollars, CHD research funding levels in 2015 were \$12 million higher than they were a decade ago.

Discussion

Our analysis provides an important snapshot of NIH investments in CHD research over the past decade, and our results will facilitate future comparisons with projects categorized under the NIH Research, Condition, and Disease Categorization code for CHD that was created in 2015. We demonstrate a significant investment in CHD research by NIH from 2005 to 2015 through a robust portfolio of research projects. The high proportion of basic/early translational CHD projects provides a rich knowledge base that is ripe for translation to clinical trials. Funding for CHD research increased over time until 2012, but decreased thereafter in the setting of fiscal austerity measures. Yet CHD research did not experience as much erosion as overall NIH funding over the past decade.

Consistent with research in other diseases [16, 17], investigator-initiated R01 grants are the mainstay of NIH support for CHD research. Creative ideas from innovative scientists will continue to provide a breadth and depth to CHD research necessary to advance a field known for its heterogeneous lesions, ages, and outcomes. Our data also demonstrate the NIH's consistent commitment to training the next generation of scientists through its distribution of nearly one quarter of CHD projects towards career development, fellowship, and training mechanisms.

We noted a higher number of basic/early translational projects than clinical research projects in CHD. Similar trends have been seen in an analysis of NIH-funded research on hypertension [18]. In the mid-1980s, Constance Weinstein, a program official at the NHLBI, acknowledged the importance of basic research in cardiac development to inform the biological basis of CHD by initiating a series of requests for applications to stimulate science in that area. A vibrant research community has grown out of those efforts. Many of the findings from this basic science research have relevance not only to CHD, but to cardiovascular disease more broadly. For example, research on cardiomyocyte development and proliferation has informed research on stem cell therapy for ventricular dysfunction after myocardial infarction.

To maximize health impact and the return on investments made in CHD research, it is essential to also support clinical trials that help translate fundamental discoveries and

insights from basic/early translational research to clinical and public health practice. Bourgeois examined several high disease burden conditions among children in high-, middle-, and low-income countries and found that 60% of disease burden was attributable to children, but only 12% of studies in ClinicalTrials.gov were pediatric trials [19]. Hill's analysis of the portfolio on ClinicalTrials.gov [20] revealed a low number (116) of pediatric cardiovascular clinical trials relative to 2561 adult cardiovascular trials. Of the pediatric cardiovascular trials identified, approximately one-third were focused on diseases that may be amenable to testing a new drug, such as hypertension and dyslipidemia, rather than CHD. Hill also found that the number of pediatric cardiovascular trials was low compared to that of other pediatric conditions, including cancer.

To address the historical lack of infrastructure for multicenter clinical research in CHD, NHLBI created the PHN in 2001. During the time of our analysis (from 2005 to 2015), the PHN conducted 18 clinical research studies in CHD and pediatric cardiovascular disease, including four Phase III and two Phase I/II clinical trials. In addition to the PHN clinical trials, our data demonstrate ten investigator-initiated clinical trials for CHD funded by the NIH from 2005 to 2015. While this small total number of CHD-related clinical trials may reflect the relative youth of the field of CHD research, it may also suggest barriers in translating fundamental discoveries to inform clinical practice through rigorously conducted clinical trials and clinical research. Although regulatory efforts such as the Best Pharmaceuticals for Children Act and the Orphan Drug Act have attempted to increase the number of pediatric therapeutic clinical trials, the gap persists in CHD research. To address the potential barriers to translation, NHLBI created the Bench to Bassinet Program in 2009 to foster translation of findings from basic science research to clinical studies in CHD.

Trends in the number of projects and total costs for NIH-funded CHD research increased from 2005 to 2012, with an additional boost in funding provided by the ARRA economic stimulus package. But the trend took a concerning downturn in 2013, coincident with the implementation of automatic federal spending cuts called sequestration. In the face of fiscal limitations, NHLBI has prioritized increasing its funding pay line for investigator-initiated applications. Our analysis reveals increasing trends in funding new investigator-initiated CHD applications in 2014 and 2015, reflecting this focus. Reassuringly, funding for CHD research has not experienced as much of a decline over the last decade compared overall NIH funding.

In this time of fiscal austerity, NHLBI staff members have used a myriad of approaches to ensure ongoing support of the science, including conducting portfolio analyses such as this and undertaking a recent strategic visioning process. These exercises provide an opportunity to identify and prioritize high impact research areas in CHD that lend themselves to rapid translation from the bench to the bedside.

Our study should be interpreted in light of its limitations. The authors' assignment of categories was subjective, but discrepancies were adjudicated among multiple authors. In addition, using isolated search terms "congenital heart" and "cardiac morphogenesis" may not have captured all projects that are related to CHD research and may have underestimated studies of cardiac developmental biology. Initial attempts at using the search term "cardiac

development” resulted in far too many false positive results, so we opted for the narrower term of “cardiac morphogenesis”. We recognize that no search strategy would return results with 100% sensitivity and specificity; therefore, we attempted to balance comprehensiveness with a search strategy that was simple, consistent, and could be replicated. Although the creation of an NIH Research, Condition, and Disease Categorization code for CHD in 2015 will help to more comprehensively identify CHD research projects in the future, investigators should also consider standardization of keyword terminology for CHD research to improve reporting.

Conclusions

The NIH demonstrates an ongoing and significant commitment to CHD research through substantial support for basic/early translational and clinical projects via a variety of mechanisms. Although previous increases in CHD research funding levels have been hampered by recent fiscal austerity measures, CHD research funding has been maintained despite economic fluctuations. Future efforts should focus on funding science with high potential for translation of findings from the bench to the bedside.

Acknowledgments

The authors wish to thank Drs. George Mensah and Bruce Gelb for providing valuable guidance that improved this manuscript.

Funding No external funding sources were used for this study.

Abbreviations

CHD	Congenital heart disease
NIH	National Institutes of Health
RePORT	Research Portfolio Online Reporting Tools
RePORTER	Research Portfolio Online Reporting Tools Expenditures and Results
SBIR/STTR	Small business projects
NHLBI	National Heart, Lung, and Blood Institute
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
PHN	Pediatric Heart Network
ARRA	American Recovery and Reinvestment Act
RPG	Research project grants

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Fig. 1.

Search results. This figure demonstrates the results of the NIH RePORTER database search using the terms "congenital heart" or "cardiac morphogenesis". CHD research projects were categorized by mechanism, type, and topic, and were characterized by number of projects and total costs. *CHD* congenital heart disease, *NIH* National Institutes of Health, *RePORTER* Research Portfolio Online Reporting Tools Expenditures and Results

Fig. 2.

a Research Mechanisms for CHD Projects. Illustration of the **a** various categories of funding mechanisms for CHD research. The most popular category of mechanism was the research project grant, followed by career development/training mechanisms focused on training the next generation of scientists. **b** Types of CHD Research. Demonstration of the various types of CHD research projects. The majority of CHD projects from 2005 to 2015 were basic/early translational projects. **c** CHD Research Topics. Illustration of the proportion of CHD projects by topic. The most popular topic was cardiac developmental biology, followed by technology and therapy development, and diagnosis/management. *CHD* congenital heart disease

Fig. 3.

a Number of CHD Projects Over Time. Illustrates the number of CHD research projects funded by NIH from 2005 to 2015, divided into new and ongoing projects. A transient increase in funded projects is reflective of supplemental funding of 19 new grants during 2009 and 20 grants during 2010 via the American Recovery and Reinvestment Act (ARRA) of 2009. **b** Funding for CHD Projects Over Time. Illustrates the amount of NIH funding for CHD research projects over time for NIH, NHLBI, research project grants, career development/training projects, and investigator-initiated new projects. **c** Funding for CHD Projects Over Time in Constant Versus Current Dollars. Illustrates the amount of NIH funding for CHD research projects over time in 2005 constant dollars compared with current dollars. In constant dollars, funding for CHD research in 2015 was \$12 million higher than

in 2005. *ARRA* American Recovery and Reinvestment Act, *CHD* congenital heart disease, *NIH* National Institutes of Health, *NHLBI* National Heart, Lung, and Blood Institute, *RPG* research project grants

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