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Ventricular dysfunction clinical research in infants, children and adolescents

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Abstract

These two issues of *Progress in Pediatric Cardiology* comprehensively illustrate the wealth of currently available information on the pathophysiology of heart failure, age-related myocardial responsiveness, energy metabolism, cardiopulmonary interactions, the pressure-volume relationship, the systemic inflammatory response, the management of heart failure, pediatric pharmacology, the use of heart failure therapies including digoxin, ACE inhibitors, beta-adrenergic blockers, inotropic agents, diuretics, vasodilators, calcium sensitizers, angiotensin and aldosterone receptor blockers, growth hormone, and future gene therapy. The etiology and course of ventricular dysfunction in children is poorly characterized. Furthermore, many changing developmental properties of the pediatric myocardium and differences in the etiologies of ventricular dysfunction in children compared with adults are illustrated in these articles, invalidating the concept that children can safely be considered small adults for the purpose of understanding heart failure pathophysiology and treatment. However, these articles reveal that strikingly little research in children with ventricular dysfunction exists in terms of well-designed large-scale studies of the epidemiology or multicenter controlled clinical therapeutic trials. A future research agenda is proposed to improve understanding etiologies, course and treatment of ventricular dysfunction in children that is based on organized and funded cooperative groups since no one pediatric cardiac center treats enough children with a particular etiology of ventricular dysfunction. In conclusion, significant understanding of basic mechanisms of pediatric ventricular dysfunction and effective therapies for adults with ventricular dysfunction exist. A multicenter pediatric cardiac ventricular dysfunction network would allow improved understanding of diseases and treatments, and result in evidence-based medicine for pediatric patients with ventricular dysfunction.

Keywords: Congestive heart failure; Pediatrics; Ventricular function; Cardiomyopathy; Clinical trials

1. Introduction

The pathophysiology and pharmacologic treatment of ventricular dysfunction in infants, children, and adolescents have been reviewed in these two issues of *Progress in Pediatric Cardiology*. The large amount of work by contributors to highlight pediatric issues demonstrates many unique and potentially important aspects of ventricular dysfunction related to children. These articles, however, also illustrate how little has been done thus far to understand the pathophysiology and pharmacotherapy of ventricular dysfunction in this population. This summary of where the field of pediatric ventricular dysfunction stands will review unique aspects of pediatric research, challenges in the study of children with ventricular dysfunction, and principles of pediatric ventricular dysfunction. Tremendous opportunities exist to advance our understanding in this area at an unprecedented pace. However, many obstacles need to be overcome, including ourselves. I was recently approached by a respected colleague who explained at great length why he could not participate in an active double-blinded, placebo-

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controlled clinical trial of therapy for asymptomatic LV dysfunction in children because he just knew, without the benefit of a controlled clinical trial, that this was an effective therapy for his patients. Other pediatric cardiologists have lectured at national meetings stating it is sufficient to study, for example, pharmacologic agents for ventricular dysfunction in adults and, if benefit is found, use the drugs in children with the same illness without clinical trials in this age group. Some of the problems with this approach are that the disease processes resulting in ventricular dysfunction are often different in children than adults. Many pediatric conditions have no close analogies in the adult. Secondly, the effects of the intervention may be unlike those seen in adults. The pharmacokinetics of many drugs vary with age and their beneficial or adverse effects are different in children and adults. Thirdly, children differ from adults. Some therapies may not be tolerated by young children because they are unpalatable or difficult to administer. A final point is that, because the antecedents of many adult diseases are thought to have their origins in early life, studies in very young children, and even antenatally, may identify strategies for preventing diseases which have important public health consequences [1].

Tremendous advances in pediatric cardiology with catheter, surgical, and diagnostic procedures have occurred during the past four decades [2]. Unfortunately, the fields of prevention, therapeutics, and decision analysis based on very limited or biased data for all pediatric ventricular dysfunction have not kept pace. A network of cardiologists willing to participate and adequate funding for an infrastructural network would facilitate research in this area.

2. The current status of clinical research in pediatric ventricular dysfunction

2.1. Reliance on data from studies in adults

In many areas of pediatric practice, therapies have been studied only in adults, and pediatricians must consider whether it is appropriate to generalize from adult to child. Although some pediatric cardiologists have advocated that treatments proved effective for adults with myocardial dysfunction be used in pediatric patients based on data from adults this may not be prudent without further testing.

There appears to be real differences in incidence, implications, expectations, causes, treatment styles, and prevention between children and adults with ventricular dysfunction suggesting that for ventricular dysfunction, children should not be considered 'small adults'. Known ventricular dysfunction occurs frequently in adults and is extremely rare in childhood. Yet, for children there are greater productive years saved by preventing symptomatic ventricular dysfunction. There may be a higher potential for cure from ventricular dysfunction in children than in adults. As a result, the potential goal of pediatric therapy for ventricular dysfunction is more likely to be curative in intent, in contrast to the palliative intent of most adult therapies. Ventricular dysfunction in children is more likely to be due to genetic factors while in adults exogenous exposures predominate. At this time adult causes of ventricular dysfunction may be more amenable to prevention than pediatric causes.

2.2. Reliance on anecdotal experience

The art of learning medicine as a series of clinical anecdotes is important but an over reliance on anecdotal experience, to the exclusion of clinical research, has pitfalls as well [3].

2.3. A lack of appreciation for the need to consider the length of subsequent survival to understand disease process and therapeutic response

The longer a patient remains with LV dysfunction the worse the LV dysfunction becomes. Snapshot studies examining a high-risk population for LV dysfunction at a single point in time are inadequate to state that the population is normal or non-progressive. Natural history studies of LV dysfunction are particularly important in children where we have found that the long length of subsequent survival coupled with the need of the pediatric myocardium to grow in response to increasing somatic growth may result in accelerated progressive LV dysfunction. A small amount of LV dysfunction early in childhood may be particularly problematic later in life [4–40].

2.4. Paucity of data

The risk factors for (e.g. age, sex, ethnic origin and geographic differences) and course of myocardial dysfunction in infants, children, and adolescents have also been studied in a very limited fashion. Consequently, the results of studies to examine the effectiveness of therapies for the prevention, treatment, or beneficial alteration of the subsequent course of pediatric myocardial dysfunction are scarce. This is especially relevant for pediatric congestive heart failure where essentially no prospective multicenter controlled clinical trials have occurred. Yet, the consequences of mild left ventricular dysfunction may be more significant than in adults and due to growth and length of future survival. Heart disease remains the leading cause of death in the United States with

deaths from congestive heart failure on a steadily upward course.

2.5. Lack of evidence-based medicine

The emerging discipline of research synthesis (evidence-based healthcare) has led to greater awareness of the need to evaluate critically what is already known before either making recommendations for clinical practice or embarking on further research [41]. Evidence-based medicine is defined as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. By highlighting the strengths and weaknesses of clinical research in different specialities, this process of critical appraisal has shown that, by comparison with situations in adults, research questions relevant to the health of children may have been addressed not at all or only by small, poorly designed studies [42]. Reviews of randomized trials published during a 15-year period in one specialist pediatric journal showed that sample sizes were generally small (less than 20 in approx. one-half of the studies), only a small proportion were multicenter, and reporting of key quality indices was inadequate. When subspecialty areas have been reviewed, the conclusions have been similar. For example, one review characterized recent advances in pediatric cardiology that have led to improved outcomes for surgical repair of complex cardiac malformations to clinical trial-and-error and the common sense and accumulated wisdom of astute clinicians, rather than to basic science or epidemiology [42]. Clinical trial-and-error can occasionally lead to serious errors.

The four steps involved in translating research into practice include: (1) creating evidence through basic science research, phenotype–genotype correlations since different etiologies may lead to different phenotypic outcomes and a heterogeneous population is of limited value, randomized controlled trials, and observational studies; (2) summarizing evidence by published meta-analyses; (3) disseminating evidence by clinical practice guidelines; and (4) implementing evidence by clinical pathways [41].

The clinical effectiveness of therapy comes from randomized controlled trials [43–45]. Observational studies have several advantages over randomized, controlled trials, including lower cost, greater timeliness, and a broader range of patients. Although nonrandomized or observational studies have in the past been criticized for bias related to overestimating the true efficacy of a given therapy or leading to erroneous conclusions, recent comparisons to randomized, controlled trials suggest little evidence that estimates of treatment effects in well-designed observational studies (with either a cohort or a case–control design) are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials [43–45]. These prior concerns led observational studies to be limited in their use to the identification of risk factors and prognostic indicators and to situations in which randomized, controlled trials would be impossible or unethical.

The clinical data for non-therapeutic questions can be derived from observational studies with long follow-up periods to assess prognosis and from large cross-sectional or cohort studies to evaluate the validity and importance of diagnostic tests [41]. The validity of a diagnostic test frequently relies on surrogate endpoints rather than actual patient outcomes and its utility is its ability to meaningfully effect patient outcomes. Diagnostic tests are rarely evaluated in this manner.

Problems encountered in translating research into pediatric practice include a paucity of pediatric clinical trials, underfunding of pediatric research, lack of trained pediatric clinical investigators, frequency of small underpowered studies, heterogeneity of studies, inconsistency between meta-analyses and large randomized, controlled trials, lack of awareness of existing efforts, access to evidence, information overload, format not helpful, labor-intensive, expensive, and waning effectiveness [41].

A schism exists between laboratory-based medical scientists (who attempt to understand the biologic and molecular processes underlying health and disease) and epidemiologists (who try to assess health and disease states [outcomes] in groups of human subjects, exposure to factors that may increase or reduce the likelihood of health or disease, and the causal relationship between these outcomes and exposures), as well as between classical (population-based) and clinical (patient- and clinical intervention-based) epidemiologists [42].

Most pediatric subspecialists, including cardiologists, have not acquired the methodologic skills in research design and statistical analysis required to conduct fundable, hypothesis-driven research. Good science requires focus, depth, and a good question. Rigorous methods should be coupled to substantive expertise to ensure that the hypothesis tested is a useful one. Good epidemiologic science is time-consuming and often quite expensive, especially when it requires long-term follow-up. There are currently 1470 US board-certified pediatric cardiologists with approximately 38 new members each year that trained in the 46 certified US centers [46]. Most centers graduate 1–2 physicians each year and over the past decade the percentage of all pediatric cardiology graduates choosing careers in full-time academic medicine has fallen from nearly 65 to 40%, making it more

concerning whether research in pediatric cardiology will expand in the coming years without an organized research infrastructure [47]. An annual account of research grants funded by the NIH in 1998 showed that the number awarded on topics related to pediatric cardiology to be 117 [48]. Yet, only nine of them involved a pediatric cardiologist as the project's principal investigator [48]. This is occurring at a time when laboratory-based discoveries of new preventive or therapeutic interventions will continue to require demonstration of efficacy and safety in randomized trials. Although more and better epidemiologic studies are needed, so too are laboratory investigations that can confirm or undermine the associations observed in human populations, and explain the biochemical and cellular processes underlying them. Kramer points out that the future of pediatric research will depend on the collaboration of basic scientists and epidemiologists [42]. He cites as an example the use of molecular and other biologic markers that cannot only provide more valid and precise measurements of potentially causal exposures and disease outcomes but can also be used to assess causal mechanisms and pathways [42].

The 1990 US Department of Health and Human Services report entitled 'Healthy People 2000' noted that heart disease was among the five most common causes of death in childhood at any age [49]. An official policy report approved by the Board of Directors of the American Heart Association and written by the Task Force on Children and Youth of the American Heart Association noted that cardiovascular disease occurs more often in children than is generally appreciated [50,51]. More than 600 000 children in the United States have an abnormality of the cardiovascular system, including at least 40 000 whose life expectancy is shortened by an acquired disease such as cardiomyopathy. The annual cost of pediatric cardiovascular disease is $> \$8$ billion in medical expenses and lost contributions to the gross national product. Cardiomyopathy accounts for an increasing number of the pediatric cardiac transplants. Genetic abnormalities in contractile proteins or energy-producing enzymes, among others, cause cardiomyopathy that becomes manifest in adulthood. Recent advances in genetics allow molecular diagnoses in fetal life. This report acknowledges that cardiomyopathy in children is increasing, and while the prevalence is unknown, 'Eventually more precise classification based on genetic advances will allow detection of people at risk and provide information about the basis of the disease.... With improved understanding of precise etiology, more effective and specific treatment can be developed' [50,51].

Children represent one-third of the United States population, yet they are virtually unrepresented in cardiovascular research. A paucity of funding for such research, including cardiomyopathy, is related in part to the small number of pediatric cardiovascular scientists. According to the Manpower Advisory and Pediatric Cardiology Committees of the American College of Cardiology, there were < 1000 certified specialists in pediatric cardiology in the United States in 1994, almost all of whom were centered on patient care and diagnostic or interventional techniques [52]. Only a limited number of them devoted a substantial effort to either clinical or basic biomedical research; furthermore, such research was largely retrospective, descriptive, and not controlled. Only 3% of responding certified pediatric cardiologists had completed ≥ 22 months of research training, suggesting that the growth of basic and clinical sciences within the field is limited. This was similar to a prior manpower study of pediatric cardiology that demonstrated that 20 years earlier only 6% of professional activities were devoted to research [53].

Cooperative groups in pediatric cardiology have been helpful at achieving research goals. The Pediatric Cardiomyopathy Registry, for example, has increased the likelihood of collaboration and research, since it allows prospective capture of cases and, in this era of molecular biology, permits new techniques to be applied to the study of pediatric cardiomyopathy [54]. It is hoped that many advances in the prevention, diagnosis, and treatment of cardiomyopathy in the young will be realized by the Registry. The field of pediatric cardiology has always worked well together on multicenter studies and registries. As evidenced by their publications, many of the most important clinical advances in pediatric cardiology have been done in the setting of multicenter studies, such as the New England Regional Infant Cardiac Program, the United States Multicenter Kawasaki Study Group, the Pediatric Cardiac Surgical Registry, the Northern Great Plains Regional Cardiac Program, the Baltimore–Washington Infant Study, the Electrophysiology Study Group, the Valvuloplasty and Angioplasty of Congenital Anomalies Registry, and the Pediatric Heart Transplantation Study Group.

Decoding the human genome will trigger developments that will change our daily lives [55–57]. The finding of genes responsible for diseases will require phenotypically well characterized populations of affected patients to determine patients whose genotypes reveal homogenous defects at high risk of disease and then to test etiology-specific therapies on these populations. Indeed, even at this time single-nucleotide polymorphisms of different genes can be studied by CHIP technology and determine, for example, whether a patient with ventricular dysfunction is likely to decline rapidly on standard drugs for the condition, and hence might need more aggressive treatment

Dr Francis Collins, director of the Human Genome Research Institute, recently said at the 2000 AAP meeting that understanding the human genome will result in routinely predicting and preventing diseases, and treating patients with highly potent designer drugs tailored to their own genes. Collins said 'It's going to have a profound impact on the practice of medicine and probably nowhere more so than in pediatrics. Virtually all diseases have a genetic component and having the genome will accelerate finding genes for varied diseases.' Collins predicted that by 2010 there will be predictive genetic tests available for at least 10 disorders and treatments to lower risks for several conditions. By 2020 he predicted gene-based designer drugs targeted to the molecular fingerprint of the patient's problem will be available and doctors will be ordering genotype tests on patients before writing prescriptions. By 2030 Collins stated that individualized preventive medicine keyed to a person's genetic profile will be routine, infants will be tested at birth, and gene therapy and gene-based drug therapy will be available.

2.6. Lack of well-designed pharmaceutical industry sponsored studies

Pharmaceutical company placebo-controlled trials have been inadequately performed in children in the past. Prescriptions (25%) in pediatric wards were for drug courses that were either unlicensed or for off-label uses. In neonates, only 35% of prescription episodes were licensed [1]. Industry objectives are frequently more short-term in duration or low cost (e.g. survey data assembly if possible) to meet FDA requirements. However, a large increase in industry-sponsored pediatric drug trials is currently underway due to a new federal law and new FDA regulations that 2 years ago began requiring the pharmaceutical industry to test the effects of many adult products on children (pediatric drug-study proposals filed with FDA, 1999–2000: 184, expected number completed: 150). In December 2000 the FDA will require pediatric study of any adult disease-fighting drug that could be prescribed for children with the same disease. This is expected to increase the number of US children in clinical drug trials from < 1000 in 1990 to 18 000 by 2002. Prior to this legislation there were very few pediatric drug-study proposals filed with the FDA (1991–1997: 70, number completed: 11) [58–62].

3. The necessary clinical research agenda in pediatric ventricular dysfunction

3.1. Understanding heterogeneous etiologies in children

When trying to understand the proper therapy for children with ventricular dysfunction it is usually important not to view the child as a small adult and extrapolate the effects of ventricular dysfunction therapy for adult ischemia or post-infarction patients to the child where a multitude of non-ischemic, non-post-infarction etiologies exist. For example, in the article on angiotensin-converting enzyme inhibitors in this issue we reviewed the effects of this therapy based on the pathophysiology of the condition and found different reported effects of this therapy [63]. A goal is to have effective individualized, etiology-specific therapeutics. An individualized therapeutic approach, based on the etiology of ventricular dysfunction and possibly other factors, such as drug levels or the levels of neurohormones, could result in major progress in treating these patients. We have examined the effect of growth hormone replacement therapy in pediatric LV dysfunction following anthracycline therapy over a 10-year period and found that, unlike adults with LV dysfunction from other etiologies, there was not an improvement in LV dysfunction on growth hormone therapy compared to controls [64]. This suggests that the etiology is extremely important in determining whether the therapy will work. Similar to etiology-specific therapies for children with ventricular dysfunction we have utilized a similar etiology-specific preventive approach for pediatric

Table 1
Detection of doxorubicin cardiotoxicity during therapy by cause and comparison to late cardiotoxicity

Cause of cardiotoxicity	During therapy echocardiogram	During therapy serum cTnT[a]	Late echocardiogram
Depressed energetic (mitochondrial)	−2	0	±
Cytokine myocardial depressant	−2	0	–
Apoptosis	±	±	−1
Free radical injury	−1	≥ +1	≥ −1
Myocarditis	−2	+2	≥ −1

[a] cTnT, cardiac troponin T.

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