Pediatric heart failure (HF) is the inability of the heart of an infant, child, or adolescent to meet the body’s metabolic demands. It involves circulatory, neurohumoral, and molecular abnormalities that manifest as edema, respiratory distress, growth failure, and exercise intolerance. The myriad causes include inherited and acquired myocardial anomalies (cardiomyopathy [CM]), volume overload (intracardiac shunts, valvular regurgitation), and the unique hemodynamics predicated by a functional single ventricle (palliated complex congenital heart disease [CHD]).

Although the societal and financial costs of adult HF are well known, the burden of pediatric HF is less familiar, but no less onerous. New-onset HF requiring hospital admission occurs in 0.87 per 100,000 children, yet that does not include the growing population with CHD-related HF. In 2006, there were nearly 14,000 pediatric hospitalizations for HF from all causes in the United States. The rate of HF-related admissions was nearly 18 per 100,000 children, which is comparable to severe sepsis.

The mortality for pediatric HF hospitalizations is significant. The 7% overall hospital mortality rate exceeds the 4% mortality of adult HF admissions and represents a 20-fold increase over children without HF. With comorbidities like renal failure, sepsis, or stroke, hospital mortality in pediatric HF can exceed 20%; yet the risk does not end with discharge. After an initial HF hospitalization, only 21% of children in a study avoided readmission, death, or transplantation.

Pediatric HF treatment is resource intensive. Although the total healthcare costs for pediatric HF are lower than for adults, per-patient costs are higher. The estimated hospital charge per pediatric HF admission in 2006 was >$135,000, with aggregate charges exceeding $1.8 billion. Certain subpopulations of pediatric HF incurred disproportionally higher costs. For example, single-ventricle CHD averaged >$200,000 per hospitalization, whereas adult HF admissions averaged <$25,000. These data do not account for the full burden of pediatric HF. There are no national cost estimates for outpatient pediatric HF management, and, because long-term survival rates are higher in children, the lifetime costs of HF in children are likely to be much higher than in adults.

Few HF therapies are developed specifically for children, and drugs that benefit adults have not clearly demonstrated clinical effectiveness in pediatric HF. In fact, pediatric HF therapy has not improved survival significantly over the past 30 years. Consequently, we need to understand the mechanisms unique to pediatric HF to inform the development of appropriate therapies.

Working Group

In April 2013, the National Heart, Lung, and Blood Institute convened a Working Group (WG) of experts in pediatric and adult cardiology, HF, CM, cardiomyocyte proliferation, genomics, pediatric cardiac surgery, gene therapy, and imaging. Although the WG acknowledged the need to improve clinical care and quality of life for children with HF, its purpose was to identify promising research targets, or mechanistic areas related to the unique pathogenesis of pediatric HF with possible therapeutic potential.

Roadmap for Pediatric HF

As a first step, the WG characterized the landscape of pediatric HF research and identified opportunities to advance the field.

Create New Paradigms

Addressing pediatric HF requires approaches that recognize the interdependence of the ventricles and emphasize personalized strategies to understand and treat the heterogeneous pediatric HF population.
Develop and Expand Registries and Databases
The WG recognized the importance of multicenter trials, but also acknowledged the challenges of conducting randomized clinical trials in pediatric HF. Creating a national pediatric HF registry could identify subpopulations that benefit from targeted therapies, link phenotypic and genotypic data, and characterize high-performing centers with model practices.

Existing resources should be leveraged and expanded, including the Pediatric Cardiac Genomics Consortium, Pediatric Heart Network, Cell Therapy Network, Pediatric Cardiomyopathy Registry, and Pediatric Cardiomyopathy Specimen Repository. The increased granularity of registries and databases with genomics, biomarkers, and systematically collected longitudinal data will improve knowledge of mechanisms, outcomes, and therapeutic responses.

Develop Innovative Partnerships
A novel partnership that improved advanced HF treatment is the Interagency Registry for Mechanically Assisted Circulatory Support,11 which is supported by the National Heart, Lung, and Blood Institute, Food and Drug Administration, Centers for Medicare and Medicaid Services, and industry, in cooperation with clinicians, scientists, and hospitals. Adopting similar collaborative models may advance pediatric HF and facilitate the development of pediatric-specific ventricular assist devices (VADs).

The WG also encouraged partnering with industry, focusing on partial extracardiac support, VADs, biological therapeutics for rare diseases, and drug repurposing. Regulatory opportunities could be used to facilitate such partnerships. For example, the Orphan Drug Act of 1983 established a pathway for Food and Drug Administration Orphan Status Designation for promising drugs and biological products for rare diseases.12 Drug repurposing may also be useful for pediatric HF. The Food and Drug Administration’s Rare Disease Repurposing Database13 contains drugs that have received orphan designation status with at least 1 market approval for another condition. The Pediatric Exclusivity Provision of the 1997 Food and Drug Administration Modernization Act and The Best Pharmaceuticals for Children Act of 2002 provide 6 months of additional patent protection for companies conducting pediatric studies.14 This approach was used to grant patent extension to GlaxoSmithKline for sponsoring the placebo-controlled trial of carvedilol in pediatric HF.9

Develop Relevant Models and End Points
Translating basic research requires appropriate models and meaningful study end points. Although animal models exist for several forms of early-onset HF in CM, they are lacking for CHD, including single-ventricle HF. The WG acknowledged the challenges inherent in creating animal models but emphasized their importance.

Focus Research on Molecular Mechanisms Specific to Pediatric HF
Future research should focus on mechanistic targets that reflect the unique pathogenesis of pediatric HF. Some of these targets are discussed below.

Biventricular Interactions
Although left and right heart diseases are commonly discussed separately, there is increasing realization of the important anatomic, physiological, and biological interactions between the 2 sides of the heart. Electrophysiological interactions are well known, and, although the WG endorsed the exploration of resynchronization in children, it concentrated on less well-established avenues of understanding and potential therapeutic benefits of harnessing biventricular interactions.

In the normal heart, important interactions exist between the ventricles that are fundamental to cardiovascular function. The right ventricle (RV) and left ventricle (LV) share a septum, are enclosed by the pericardium, and, importantly, share common myocardial fibers, particularly in the superficial layers of their walls.15 These shared fibers extend from the RV outflow tract to the LV apex and result in powerful cross talk between the ventricles. For example, >40% of the RV’s mechanical work is estimated to result from LV contraction in the normal circulation. Conversely, even modest isolated RV dilation directly impairs LV contractility and reduces cardiac output in the normal heart, even without pericardial constraint.17

Biventricular interactions may play a more prominent role in the diseased heart. In adults, the outcome of LV dilated cardiomyopathy (DCM) is influenced by RV dysfunction,18 and, in idiopathic pulmonary hypertension, functional performance may relate to secondary LV dysfunction.19 Although emphasis has understandably been on RV performance as a predictor of outcomes in tetralogy of Fallot, ventricular arrhythmias and survival are related to the coexistence of LV diastolic20 and systolic21 dysfunction, respectively. Even in hypoplastic left heart syndrome, LV size and morphology may affect outcomes.22

There is increasing appreciation of the potential for biological biventricular interactions in pediatric HF. That is, hemodynamic stress to 1 part of the heart may lead, via parallel signaling, to abnormal myocardial biology in an unaffected part. Circulating neurohumoral responses, biomarkers, and mediators of disease progression in pediatric HF continue to be explored, and the WG endorsed such research.

A complete discussion of the many potential biological interactions is beyond the scope of this report, but a few relevant areas can be highlighted. LV fibrosis identified in the setting of increased RV afterload following pulmonary artery banding23 emphasizes the potential for biological cross talk leading to adverse cardiac remodeling. This may be relevant to disease progression in tetralogy of Fallot, in which fibrosis is recognized as a risk factor for poor outcomes.24 The mechanism of increased fibrosis signaling is unknown, but isolated RV afterload leads to modifications of microribonucleic acid (miRNA) signaling in both ventricles.25

There are intriguing experimental avenues of potential therapeutic modification of biventricular interactions. Friedberg et al examined fibrosis signaling in response to RV afterload in a rabbit model. Having first demonstrated upregulation of pathways in the LV and RV, including transforming growth factor beta (TGFβ) signaling, they showed abrogation of both RV and LV fibrosis with losartan, an angiotensin receptor blocker known to downregulate downstream TGFβ–induced responses.26 The Giessen group explored the potential for
harnessing ventricular cross talk by performing pulmonary artery banding in pediatric DCM. Hypothesizing that the induction of RV hypertrophy would benefit LV performance, as the LV supports normal RV function, Schranz reported early results in 12 children. LV ejection fraction increased from 14.5% ± 5% prebanding to 27 ± 13% at hospital discharge and to 47 ± 10% at 3 to 6 months. There were 2 late deaths in children with LV noncompaction, but 8 of 10 were ultimately debanded, and function was maintained in the majority. These data emphasize the potential for novel therapies that could evolve from increased understanding of biventricular interactions.

The WG recommended:

- exploration of the pathophysiology of biventricular interactions in normal hearts and CHD
- emphasis on basic mechanisms of biventricular responses in terms of myocardial biology, fibrosis signaling, and neurohumoral modulation
- multicenter validation of novel therapeutic interventions, including pulmonary artery banding in DCM and modification of fibrosis signaling in diseases with maladaptive biventricular remodeling, like tetralogy of Fallot.

**Mechanical Circulatory Support**

Mechanical circulatory support (MCS) revolutionized adult HF therapy and is becoming a more common and attractive option for children. However, pediatric MCS is still in its infancy. Besides the Berlin Heart Excor Pediatric VAD and the DeBakey VAD Child, MCS devices have been designed for adults and were not intended for smaller patients or complex circulations. Significant morbidity and mortality have been described in patients with CHD receiving MCS. Approval of pediatric MCS devices has helped, but the technology remains problematic, and there is an ongoing need to reduce morbidity and mortality. Recognizing the importance of designing pediatric-specific MCS devices, the National Heart, Lung, and Blood Institute supported a preclinical pediatric VAD initiative and the Pumps in Kids, Infants, and Neonates Program.

Because myocardial regenerative potential is higher in children, the likelihood of myocardial recovery to device explantation (bridge to recovery) may be higher in children. Improved understanding of the mechanisms of myocardial regenerative potential in pediatric HF and failing single ventricles may inform targeted approaches to MCS use, such as partial extracardiac support.

Patients with single-ventricle CHD who undergo the Fontan operation, which results in passive systemic venous return from the vena cavae directly to the pulmonary arteries, often develop HF in the second and third decades of life. The mechanisms of failure in the Fontan circulation differ from those of biventricular failure in important ways. In Fontan failure, diastolic dysfunction typically predominates, with preservation of systolic function. This pattern may be related to chronic preload deprivation; however, the mechanisms are unclear. The use of devices intended for systemic circulatory support in Fontan failure creates a mismatch between the technologies’ optimal design and the Fontan circulatory needs, resulting in suboptimal performance. Emerging technologies may allow targeted support of the Fontan circulation on the foundation of the more stable biventricular circulation. The increasing number of patients surviving to Fontan palliation emphasizes the need to understand ventricular dysfunction and the remodeling potential of the functional single ventricle with circulatory support. The lack of chronic animal models of the Fontan circulation currently limits our ability to determine the efficacy of technologies intended to support the univentricular circulation.

The WG recommended:

- investigation into myocardial regenerative potential
- application of MCS as a bridge to recovery
- creation of MCS strategies in biventricular failure
- adaptation of MCS strategies to address the needs of single-ventricle failure
- development of animal models of the Fontan circulation.

These structural approaches of optimizing biventricular interactions and MCS may be translated fairly rapidly into clinical practice. Although important, fundamentally, they fail to target the primary events leading to HF. Consequently, the WG identified several areas of myocardial biology that may be important for understanding and treating pediatric HF.

**Myocardial Fibrosis**

Fibrosis is an important determinant of HF outcomes. Basic research has increased our understanding of fibrosis, resulting in the development of antifibrotic therapies. The search for imaging techniques, biomarkers, and genetic risk markers for cardiac fibrosis has been central to these efforts. A major hurdle in the application of antifibrotic therapies to pediatric HF is the knowledge gap regarding the pathogenesis of fibrosis in children with HF.

**Pathogenic Mechanisms**

Fibroblasts account for 50% of cardiac cells and are integral in maintaining structure and function. In the developing heart, fibroblasts arise from differentiation of epicardial cells that migrate into the myocardium through endothelial mesenchymal transformation. Zeisberg et al showed that endothelial mesenchymal transformation can be reactivated in adult hearts during stress. Mouse hearts subjected to pressure overload developed fibrosis through endothelial mesenchymal transformation, resulting in myofibroblast transformation and proliferation with extracellular matrix deposition. This process was prevented by inhibiting TGFβ1. Endothelial mesenchymal transformation may be activated in adult hearts, and in children with hypertrophic cardiomyopathy (HCM) and fetal hearts with hypoplastic left heart syndrome, as well. The pathway of stress-induced fibrosis may therefore be similar in pediatric and adult hearts.

Diseased hearts in children are often exposed to chronic hypoxia and hemodynamic load, which upregulate hypoxia-inducible factor 1-alpha, resulting in an adaptive hypoxia response. However, chronic hypoxia-inducible factor 1-alpha activation may be maladaptive by promoting progressive TGFβ1-mediated fibrosis. Children with an HCM genotype associated with higher hypoxia-inducible factor
1-alpha expression demonstrated more severe LV hypertrophy and diastolic dysfunction and lower freedom from surgical myectomy.34 Yet, children with tetralogy of Fallot with the same genotype had less RV dilation and better RV function despite having more fibrosis,37 suggesting that not all fibrosis is detrimental. Reversible myofibroblast transformation may permit survival in a hostile environment, whereas progressive, irreversible myofibroblast transformation may contribute to adverse ventricular remodeling.38

Fibrosis Imaging

Until recently, the assessment of fibrosis was limited by a lack of noninvasive measures. It is now possible to detect regional myocardial fibrosis noninvasively by using cardiac magnetic resonance imaging (MRI) with late gadolinium enhancement.39 This technique takes advantage of the increased extracellular distribution volume in fibrosis; however, it requires a threshold level of fibrosis. It is useful in evaluating dense regional fibrosis seen in myocardial infarction and CM variants, but is less applicable to the diffuse interstitial fibrosis of nonischemic CM. A newer cardiac MRI technique, T1 mapping, uses the differential pre- and postcontrast magnetic relaxation parameters of fibrotic and normal myocardium and is an accurate noninvasive method for quantifying diffuse fibrosis.40 Another approach is nuclear molecular imaging with the use of molecular probes targeted at specific fibrotic pathway components, including the myofibroblast, TGFβ receptor, angiotensin receptor, αvβ3 integrin, and the frizzled 2 receptor.41 Such nuclear molecular imaging has the potential to target specific elements of the fibrosis pathway rather than the gross histopathology.

Biomarkers

Studies have shown good correlation between echocardiographic ventricular dysfunction and serum levels of myocardial interstitial collagen breakdown products and collagen turnover enzymes.42 In HCM genotype–positive adults, serum C-terminal propeptide of type I procollagen was elevated even in the absence of septal hypertrophy, suggesting that serum levels may be preclinical biomarkers of fibrosis.39

Molecular Targets of Fibrosis

Many antifibrotic compounds for adult noncardiac diseases are in phase 1 or 2 trials.43 Several drug classes that prevent or reverse cardiac fibrosis have been identified, including 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, angiotensin receptor blockers, nephrilysin inhibitor, microRNA-101, TGFβ1 inhibitor, PT23, aldosterone inhibitor, tranilast, angiotensin (1–7), 3,3'-diodothymidine, and the A2B adenosine receptor antagonist GS-6201.44 Clinically approved drugs for adult cardiac fibrosis or other pediatric diseases may allow for drug repurposing in pediatric HF.44 However, safety concerns surrounding antifibrotic therapies must be addressed, including the risk of adverse ventricular remodeling, immune activation and tumorogenesis.

The WG recommended:

- development of imaging protocols for detecting and quantifying fibrosis in pediatric HF
- correlation of imaging findings and clinical outcomes to enable the use of imaging end points as surrogate outcomes
- identification and validation of peripheral biomarkers
- initiation of clinical trials of antifibrotic therapies in pediatric HF.

microRNAs

miRNAs are short, noncoding RNAs that regulate gene expression. They have been suggested as therapeutic targets given their independent regulation in different disease states, including HF.45 The mechanisms of miRNA gene regulation are under investigation, but the most well-understood is down-regulation of gene expression by binding to the 3′-untranslated regions of mRNA and targeting them for degradation or translation repression.46

Tissue miRNA expression contributes to molecular reprogramming in HF.47 In adult HF, differential miRNA regulation has been demonstrated, with at least 50 upregulated and 35 downregulated.48 Although there are similarities between miRNAs regulated in adult HF and those expressed in the normal fetal heart between 12 and 14 weeks gestation,39 there are significant differences in miRNA expression profiles of children50 and adults47,48 with idiopathic DCM (ie, no identifiable cause). Only miRNA-1 expression in pediatric idiopathic DCM50 overlaps with miRNAs involved in cardiac development.51 miRNA expression profiles have been explored in CHD in human fetal hearts with single ventricles52 and in mouse models of RV failure.25 Unfortunately, the miRNAs in the mouse do not always correlate with those in humans; however, research using large animal models may address this discordance. Understanding the differences in miRNA expression profiles in cardiac development, CHD, and adult and pediatric HF may facilitate the identification of therapeutic targets.

Recent attention has focused on circulating miRNAs as biomarkers of disease. Plasma miRNAs are remarkably stable, and expression profiling has diagnostic and prognostic potential in some diseases.53 Several miRNAs have been proposed as markers of acute myocardial infarction and adult HF.54,55 Given the difficulties in tissue sampling in children, circulating miRNAs would be appealing as HF biomarkers.

The pleiotropic effects of miRNAs make them attractive targets for therapeutic exploitation. Although clinical data are lacking, research suggests the potential benefit of miRNAs in the treatment of cardiovascular diseases. For example, in a rat model of hypertension-induced HF, a miRNA-208a antagonist reduced cardiac remodeling and blunted functional decline.56 In human atrial tissue, miRNA-21 was upregulated and correlated with the degree of fibrosis, and systemic delivery of miRNA-21 antagonist prevented fibrosis in transgenic mouse models.57 Other miRNAs influence myocardial function and have therapeutic potential in adult HF,58 but studies in pediatric HF are lacking.

The WG recommended:

- examination of the age and disease specificity of miRNA expression and regulation in pediatric HF and CHD
• profiling circulating miRNA in children with CHD and HF to identify novel biomarkers
• clarification of miRNA’s therapeutic role in pediatric HF.

Myocardial Regeneration
The ability to regenerate heart muscle has the potential to cure HF or improve outcomes. Although stimulating myocardial regeneration in adults is challenging, it may be a more viable strategy in children. Proliferation of differentiated cardiomyocytes is a basic mechanism of myocardial growth during development, and proliferation following injury is an evolutionarily conserved mechanism in lower vertebrates and has been demonstrated in neonatal mice. Although homeostatic cardiomyocyte proliferation is low or absent in healthy adults, children may increase cardiomyocyte numbers by 3.5-fold between birth and 20 years. Cardiomyocyte cell cycle activity in infants with heart disease has been reported, although the alterations of proliferation and differentiation in myocardial diseases remain to be defined.

Cardiomyocyte proliferation has been stimulated in adult HF animal models by modifying transcription factors and miRNAs and by administering recombinant proteins like neuregulin. Such efforts have resulted in functional and measurable, but small structural improvements. Administration of recombinant neuregulin is in clinical testing, and initial results have demonstrated benefit and safety in adult HF. This approach may be applicable to pediatric HF.

Pluripotent Stem Cells
Robust protocols exist for deriving cardiomyocytes and other cardiac lineages from human pluripotent stem cells. There are currently 2 types of human pluripotent stem cells: human embryonic stem cells derived from the inner cell mass of early-stage embryos and induced pluripotent stem cells (iPSCs) reprogrammed from terminally differentiated cells like skin fibroblasts. Because human embryonic stem cell lines are derived from normal embryos, they have been used to study normal cardiomyocyte differentiation. It is important to test if other approaches to producing pluripotent stem cells, such as somatic cell nuclear transfer, can overcome current hurdles like immunogenicity, tumorigenicity, and immaturity of derived cardiomyocytes.

Several studies have used iPSCs derived from patients with CM and long QT syndrome to derive immature but functional cardiomyocytes. Although recapitulation of important aspects of the mature disease phenotypes has been observed in vitro, questions remain about the relevance of these observations to the intact loaded myocardium. Nonetheless, the prospect of generating engineered cardiac tissues from a patient’s own cells, thereby addressing ethical issues related to human embryonic stem cells and avoiding the allogenicity of other cell types, will likely improve the clinical relevance of these models. Developments in genome manipulation also enable gene correction with mutant iPSCs, allowing for the generation of isogenic control lines or more complex genetic models.

As a renewable resource, iPSC-derived cardiomyocytes can also be used to identify novel therapies. Small molecules, either candidate compounds or larger libraries, can be screened for phenotype rescue. Although preclinical work with animal models will be necessary, this approach allows for efficacy screening in human-relevant models before initiating clinical trials. Studies suggest that cardiac fibroblasts may be reprogrammed directly to cardiomyocytes in vivo. Currently, the process requires the introduction of specific genetic factors, but this may someday be practical by using small molecules.

Challenges remain for research on myocardial growth and repair mechanisms. Although access to myocardial samples is limited, this could be overcome with collaborations, networks, and the use of human embryonic stem cell and iPSC models. Development and validation of animal models of pediatric HF would also be required for preclinical development.

The WG recommended:
• exploration of alterations in cardiomyocyte proliferation in myocardial diseases
• attempts to stimulate cardiomyocyte proliferation to promote therapeutic myocardial regeneration.

Cytoskeleton
The cytoskeleton provides mechanical support and contributes to the spatial arrangement of subcellular elements. It preserves structural and functional integrity of the myocardial cell, participates in various cell procedures like division, migration, intracellular and intercellular communication, proper arrangement and function of organelles and receptors, and plays an important role in mechanical signal transduction. The disruption of final common pathways within the cytoskeleton lead to clinical features of CM that cause HF and arrhythmias associated with sudden death. The disrupted final common pathways include the sarcolemma-sarcomere link (DCM and LV noncompaction), the sarcomere (HCM and restrictive CM), the desmosome (arrhythmogenic RV CM), the intercalated disc (hypertrophy), and ion channels (arrhythmias). Understanding the cytoskeleton and its associated proteins is therefore critical to understanding pediatric HF.

The WG recommended:
• creation of genetic and proteomic studies of the cytoskeleton by using human and animal models.

Cardiomyopathy Genetics
Several genetic causes of CM have been elucidated. Although our understanding is more complete for some forms (HCM) than others (restrictive CM), such discoveries have enabled genetic testing, which has become widely available and less costly with newer sequencing approaches. Coverage by the known gene panels for certain forms of CM, such as severe infantile forms of DCM, is less complete than those that present later in life. With current approaches enabling whole exome or genome sequencing, gene discovery is likely to proceed rapidly. Improving diagnostic and prognostic accuracy for pediatric CM via gene discovery will enable the development of rational therapies.

Expression of CM phenotypes occurs in an age-dependent manner, is often incomplete, and is highly heterogeneous, even...
within families. This phenotypic variability is attributed to genetic heterogeneity, as well as the influence of modifier genes (including variants in genes for other structural components), and of environmental factors on phenotype. Because children harboring CM mutations are more likely to be diagnosed at earlier stages of disease and be presymptomatic, preventive strategies may be applied and therapy could be more efficacious. Several strategies based on CM pathogenesis are in development. For instance, gene therapy using adeno-associated virus vectors may enable replacement of missing proteins underlying certain types of CM, as in Duchenne muscular dystrophy.77

The WG recommended:

- use of genomic technology to facilitate rapid discovery of a broader range of CM mutations to promote development of targeted therapies.

Conclusion

These novel research approaches based on the unique pathogenesis of pediatric HF may enhance our understanding and treatment of the heterogeneous causes of pediatric HF.

Disclosures

None. This report represents the authors’ views and does not reflect official National Heart, Lung, and Blood Institute positions.

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