Heart Failure in Children

Part II: Diagnosis, Treatment, and Future Directions

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This is the second of a 2-part review of heart failure in children. In Part I, we focused on history, definition, etiology, and pathophysiology.1 In Part II, we review diagnosis, treatment, and future directions. The intention is to highlight key concepts and trends, with the goal of stimulating further interest in research to support evidence-based treatment in pediatric cardiovascular disease.

Diagnosis of Heart Failure in Children

In Part I, we described heart failure as a progressive clinical and pathophysiological syndrome that results from a complex interplay among circulatory, neurohormonal, and molecular derangements. The diagnosis of heart failure in children is based on a combination of clinical signs and symptoms, with assessment of severity of cardiac status augmented by information obtained from laboratory findings such as exercise testing, noninvasive imaging, and biomarker profiling. In symptomatic children without known heart disease, a large part of the evaluation will involve identifying the underlying cardiac diagnosis.

Symptoms

The characteristic signs and symptoms of heart failure include growth failure, respiratory distress, and exercise intolerance and are present in children with heart failure regardless of the cause. Age-adjusted modifications of heart failure scores can quantify the symptoms of heart failure in children and have been used both as inclusion criteria and as end points in several studies of heart failure in children.2,3 Unfortunately, heart failure class at presentation is a poor predictor of worsening clinical outcome.4,5 The scenario of a child with few symptoms who suddenly develops decompensated heart failure is well known and highlights the limitations of heart failure class as a predictor or outcome in children.

In patients with right heart dysfunction, as may occur in tetralogy of Fallot (TOF) or Ebstein anomaly, or in patients with single ventricle physiology, the predominant clinical findings are those of systemic venous congestion, decreased exercise capacity because of abnormal functioning of the subpulmonary ventricle or poor filling of the systemic ventricle, conduction disturbances or arrhythmias, or increasing hypoxemia. In the case of the Fontan patient, protein losing enteropathy is another important manifestation of the failing heart.6

Noninvasive Imaging

Echocardiography, the primary imaging modality in pediatric cardiology, provides excellent structural and functional detail in children. Highly informative subcostal windows often yield a structural diagnosis within the first few minutes of imaging. Echocardiography also permits detailed assessment of ventricular size and function, albeit more robust for the left ventricle than right or single ventricles. Normalized values have been developed for most pediatric measures of ventricular performance, size, mass, and volume to account for variations by age and body size.

Echocardiographic assessment of right and single ventricular (SV) function is more complicated because of altered geometry. Right ventricular (RV) tissue Doppler imaging correlates with measurements of RV end-diastolic pressure obtained during cardiac catheterization,7 and the Doppler myocardial performance index has been used to assess function in children with SVs8 and abnormal RVs.9 The geometric challenges of assessing RV and SV function have led to increased use of cardiac magnetic resonance imaging in children. The role of 3D echocardiography for this purpose is not clear; its chief use to date has been in providing additional detail of intracardiac anatomy.

There have been few pediatric studies correlating ventricular performance and outcome. Worse ejection fraction and fractional shortening at presentation have been correlated with poor outcome in children with dilated cardiomyopathy (DCM) in 2 large epidemiological studies.4,5 The prognostic value of degree of dysfunction at presentation, however, can be affected by underlying cause of the DCM. Particularly, in the case of myocarditis, children can present with severely depressed ventricular function but recover normal function within a few weeks to months. Therefore, a lack of improvement in ejection fraction over time has been a more consistent correlate of worse outcome.4,5 Left ventricular (LV) remodeling to a more spherical shape has been shown in a small retrospective study to predict a poorer prognosis in children with DCM,10 consistent with data from studies in adults.11
Table. Therapeutic Recommendations From the ISHLT Guidelines for Management of Heart Failure in Children With Level of Evidence B

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>No structural disease</td>
<td>Digoxin should be employed for patients with ventricular dysfunction and symptoms of HF, for the purpose of relieving symptoms. For the treatment of moderate or severe degrees of left ventricular dysfunction with or without symptoms, ACE inhibitors should be routinely employed unless there is a specific contraindication. Given the limited information available concerning the efficacy and safety of β-blockers in infants and children with HF, no recommendation is made concerning the use of this therapy for patients with left ventricular dysfunction. If a decision is made to initiate β-blocker therapy, consultation, or comanagement with a heart failure or heart transplantation referral center may be desirable.</td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunction</td>
<td>Patients with diastolic dysfunction that is refractory to optimal medical or surgical management should be evaluated for heart transplantation as they are at high risk of developing secondary pulmonary hypertension and of sudden death.</td>
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<tr>
<td>Systemic right ventricle</td>
<td>Patients with a right ventricle in the systemic position are at risk of developing systemic ventricular dysfunction and should undergo periodic evaluation of ventricular function.</td>
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<tr>
<td>Acute heart failure</td>
<td>Institution of mechanical cardiac support should be considered in patients with or without structural congenital heart disease, who have acute decompensation of end-stage heart failure, primarily as a bridge to cardiac transplantation. Institution of mechanical cardiac support may be considered in patients who have experienced cardiac arrest, hypoxia with pulmonary hypertension, or severe ventricular dysfunction with low cardiac output after surgery for congenital heart disease, including “rescue” of patients who fail to wean from cardiopulmonary bypass or who have myocarditis.</td>
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Data from Rosenthal et al.24

early studies of single (left) ventricle physiology, remodeling to a spherical shape occurred over time and was associated with deterioration in ventricular function and in arterial oxygen saturation. Earlier age at volume-unloading surgery was associated with improved odds of reversing the abnormal ventricular mechanics.12 Studies have also begun to link cardiac magnetic resonance measurements with clinical variables. For example, in children after repair of TOF, RV ejection fraction but not degree of pulmonary regurgitation or stenosis, has been shown to correlate with exercise capacity.13

Exercise Testing

In adults, measurement of maximal oxygen consumption is useful for risk stratification, including need for heart transplantation. However, exercise testing cannot be performed in infants and young children. Furthermore, maximal oxygen consumption varies by age in children, which complicates linking this measurement to outcome. In infants, feeding offers an informal exercise test, because of the energy expenditure necessary. Growth failure, therefore, is often an indication that intervention is necessary. In complex congenital heart disease, factors such as cyanosis, rhythm abnormalities, and abnormal circulatory physiology make maximal oxygen consumption difficult to measure and interpret, and studies of its prognostic value in these settings have not been performed. Declines in performance on serial exercise testing are used clinically as criteria for intervention or reintervention in congenital heart disease such as TOF (timing of pulmonary valve replacement) or aortic stenosis (AS; timing of relief of obstruction).

Neurohormonal Activation

Guidelines for the use of brain natriuretic peptide (BNP) and N-terminal pro-BNP levels in adult patients14 are not generalizable to children, because the type of ventricular impairment, underlying cardiac morphology, age, gender, and assay method may affect the reference values for these markers.15 The role of BNP and N-terminal pro-BNP in the diagnosis and management of children with heart failure remains controversial. BNP levels can distinguish between cardiac and pulmonary causes of respiratory distress in neonates and children16,17 and, in acute decompensated heart failure due to cardiomyopathy, are increased and related to severity of symptoms.18–20 A BNP level >300 pg/mL has been shown to predict death, transplantation, or heart failure hospitalization and was more strongly correlated with poor outcome than symptoms or echocardiographic findings.20 BNP levels can be different in children with DCM and congenital heart disease, despite similar New York Heart Association class, ejection fraction, and maximal oxygen consumption.21 If replicated in a larger study, this finding has implications for the interpretation of information on neurohormonal activation in different pediatric populations.

Treatment

The treatment of heart failure in children depends on the underlying cause and the child’s age. Treatment goals are similar to those for adult patients with heart failure: correct underlying problems, minimize morbidity and mortality, and improve functional status and quality of life. Unfortunately, few of the gains made in evidence-based treatment of heart failure in adults in the past 2 decades have translated to children because of the difficulty of conducting trials in a sufficient number of pediatric patients. Cardiologists taking care of adults with heart failure have 2 major sets of guidelines to consult;22,23 and the recommendations are often based on a high level of evidence (level A; multiple randomized trials). In contrast, in the single set of practice guidelines for pediatric heart failure, developed by the International Society for Heart and Lung Transplantation (ISHLT),24 none of the 49 recommendations is based on level A evidence and only 7 are level B (a single randomized trial or multiple nonrandomized trials); the remainder are level C (expert consensus). The Table summarizes the level B recommendations.
Medical Therapy
A more fundamental difference between adult and pediatric therapy for heart failure is that few of the drugs with demonstrated evidence-based efficacy in adults with heart failure have received regulatory approval for use in children. Although the 1997 Food and Drug Administration Modernization Act and the subsequent 2002 Best Pharmaceuticals for Children Act extended patent exclusivity for pediatric testing, nearly 80% of hospitalized children who have congenital and acquired heart disease receive at least 1 medication off-label during their hospital stay. Unusual pediatric dosing is necessary because pharmacokinetics and pharmacodynamics vary in children with age and developmental maturation. Scaling adult doses for pediatric use solely based on weight can result in either inadequate or excessive drug levels.

Congenital Heart Disease: Volume Overload
A category of heart failure unique to pediatrics is volume overload lesions in the setting of normal ventricular function, typically left-to-right shunt lesions, such as large ventricular septal defects (VSDs), patent ductus arteriosus, or endocardial cushion defects. Symptoms usually develop at ∼6 weeks of age, after the pulmonary vascular resistance has dropped. The general therapeutic approach is to minimize symptoms and optimize growth until a definitive procedure can be performed. The mainstays of medical therapy have historically been digitalis and diuretics. Digitalis was considered an essential component of pediatric heart failure therapy by the 1960s. Subsequently, it became clear that the evidence for efficacy was at best contradictory, especially in volume-overload lesions with normal function, where the mild inotropic effect of digitalis was unnecessary. However, digitalis also has sympatholytic properties, which may modulate pathological neurohormonal activation.

The first “large” study of loop diuretics in 62 children with heart disease of varying etiology was reported in 1978. Furosemide improved clinical symptoms on a background of digitalis administration. There have been no pediatric studies of thiazide monotherapy. Furosemide continues to be used in volume-overload conditions to decrease pulmonary congestion and thus decrease the work of breathing. It is one of the least toxic diuretics in pediatrics, although it has been associated with sensorineural hearing loss after long-term administration in neonatal respiratory distress.

When the first trial data on the benefits of angiotensin-converting enzyme (ACE) inhibition and β-adrenergic blockade in adults with heart failure began to be reported in the late 1980s, pediatric cardiologists began to investigate these medications in infants and children with heart failure because of volume overload lesions. A recent excellent review of ACE inhibition in pediatric patients with heart failure summarizes 4 small nonrandomized therapeutic studies in children with left-to-right shunting that include a total of 49 children. The results were mixed: improved growth was seen in some children with both captopril and enalapril, but a concerning incidence of renal failure occurred, particularly in premature and very young infants. A single small randomized study evaluated the addition of propranolol to the combination of digoxin and diuretics in 20 children with volume overload from left-to-right shunting. In the 10 patients who received propranolol, the Ross heart failure score, assessed by nonblinded reviewers, was reported to be significantly better.

It was not until the mid-1970s that intracardiac repair in infants became a reality. Since then, improvements in surgery and perioperative care have permitted a paradigm shift to earlier transcatheter or surgical intervention, often before age 6 months. This strategy minimizes the time that the infant has significant symptoms or requires medication and minimizes the risk of pulmonary vascular disease. Contemporary data indicate that early repair of a ventricular septal defect, even in the first month of life and at weights <4 kg, does not confer increased risk compared with older, larger infants. Transcatheter device closure of muscular ventricular septal defects has been possible in the United States since September 2007, when the Food and Drug Administration approved a catheter-delivered device in patients who weigh at least 5.2 kg.

Definitive therapy for heart failure in children with large left-to-right shunts and normal ventricular function is prompt resolution of the hemodynamic problem. This strategy is consistent with the ISHLT Guidelines recommendation on volume-overload conditions. Despite their widespread use, there are no systematic data that identify benefit from any of the medications reviewed.

Congenital Heart Disease: Pressure Overload
The ventricular response to pressure overload is determined by the severity and duration of the load, and treatment strategies follow suit. AS is the most common cause of obstruction of LV outflow in pediatrics; severe pulmonary stenosis and coarctation can also cause heart failure. In the neonate, critical AS can cause acute LV failure in early infancy if not recognized immediately and treated. “Critical” implies a requirement for maintaining patency of the ductus arteriosus with prostaglandin infusion to supply the systemic circulation by pulmonary artery-to-aorta blood flow. Treatment of heart failure in this circumstance requires optimizing hemodynamics until urgent intervention can occur. Balloon valvuloplasty, first described in neonates in 1986, has all but replaced surgical valvotomy, as the first-line intervention in uncomplicated AS, including critical AS. Ventricular function improves and usually normalizes after catheter-based or surgical intervention.

For less severe forms of AS, the management goal is preventive: to intervene before ventricular dysfunction occurs. The Natural History Study provides the only systematic evidence on which to base recommendations. Children and young adults with ventricular septal defects, pulmonary stenosis, and AS were enrolled between 1958 and 1969 and reevaluated between 1983 and 1989. Follow-up data were obtained on 371/462 (80.3%) patients in the original cohort with AS. Higher aortic valve gradients were associated with lower fractional shortening, decreased exercise capacity, increased risk of sudden death, and increased risk of serious arrhythmias. The authors concluded that patients with severe AS (Doppler mean gradient ≥50 mm Hg; later authors...
suggest mean gradient ≥ 40 mm Hg as the threshold for intervention to prevent or ameliorate symptoms, and patients with mild AS (Doppler mean gradient ≤ 25 mm Hg) could be followed up. These criteria continue to guide contemporary management along with other criteria such as symptoms, exercise capacity, ventricular hypertrophy, wall stress, and evidence of arrhythmia.

**Congenital Heart Disease: Complex Conditions**

Complex malformations can affect the systemic and pulmonary circulations and can combine volume and pressure overload characteristics. The RV is often abnormal in congenital heart disease and can fail as a result of volume and pressure overload in a variety of malformations such as TOF, where there is often RV outflow tract obstruction and pulmonary valve regurgitation after repair. Recent data on genetic responses in the RV in children with TOF have demonstrated that the ability to upregulate adaptive pathways to chronic hypoxia is impaired in these children. This finding has implications for long-term RV function in patients with TOF, and further study may identify therapeutic targets for early intervention. There is no systematic clinical evidence for anticongestive therapy in RV failure in children. One basis for diuretic use comes from a 1972 report in a rhesus model of RV failure in which diuretic agents, including furosemide, relieved the clinical symptoms. For young adults with RV dysfunction after repair of TOF, β-blocker therapy (bisoprolol) did not reduce circulating cytokines or improve ventricular function in asymptomatic or minimally symptomatic patients after 6 months of therapy. These results, and the findings of altered RV gene regulation, may suggest a different pathophysiological process in RV failure and thus a requirement for novel treatment strategies. When the RV is functioning as the systemic ventricle and symptomatic ventricular dysfunction occurs, the ISHLT Guidelines recommend diuretics, digitalis, and ACE inhibition based solely on expert consensus.

Approximately 1000 infants are born each year with malformations resulting in SV physiology, because of a single RV or LV, or one of indeterminate morphology. After a series of palliative surgeries usually culminating in the Fontan procedure by the age of 4 years, the systemic and pulmonary circulations are separated, and the single ventricle is pumping to the systemic circulation. A trial recently concluded in the Pediatric Heart Network (PHN) randomized 230 infants with single ventricle physiology to enalapril or placebo to evaluate growth, heart failure symptoms, and ventricular function. A report of main trial results is expected by the end of 2009. A large, cross-sectional study of 546 Fontan survivors aged 6 to 18 years found normal ejection fraction in 73% of subjects but abnormal diastolic function in 72%. Diastolic function was significantly worse in the group with RV morphology compared with those with LV or mixed ventricular morphology. Overt heart failure after the Fontan operation is relatively infrequent in the pediatric population, but increases in the adult years. Identifying and treating underlying causes of heart failure, such as conduction or rhythm abnormalities or residual structural lesions, is the initial strategy. There are no compelling data to guide medical treatment when heart failure does occur in pediatric SV patients. When medical therapy seems indicated in symptomatic patients with ventricular dysfunction, the ISHLT guidelines recommend diuretics, digitalis, and ACE inhibition but not β-blockade, based on expert consensus.

**Cardiomyopathies**

Therapy for heart failure in children with cardiomyopathy is largely directed to those patients with primary or acquired forms of DCM. In end-stage hypertrophic cardiomyopathy and some cases of restrictive cardiomyopathy, ventricular systolic function is impaired and the therapies described below have also been used. Therapies for the treatment of primary diastolic heart failure in children with hypertrophic or restrictive cardiomyopathy are limited to the judicious use of diuretics to decrease the degree of pulmonary congestion. Primary or acquired DCM is the cause of pediatric heart failure that is most similar to heart failure in adults. However, as with other causes of pediatric heart failure, there are no robust trial data to guide therapy. The largest pediatric heart failure trial to date enrolled 161 children and adolescents into a multicenter randomized trial of comparing low- and high-dose carvedilol to placebo on a background of conventional therapy. Of the 161 enrolled, 95 (59%) had DCM; the remainder had congenital heart disease. No treatment effect of carvedilol on the primary composite end point of clinical heart failure outcomes was detected. Shortening fraction improved significantly over time in all 3 study groups, and carvedilol therapy significantly improved shortening fraction compared to placebo. Ejection fraction improved significantly over time in all 3 groups as well, but there was no cross-group treatment effect, perhaps because of the strength of the within-group temporal trends. A prespecified analysis demonstrated a significant interaction effect between ventricular morphology and response to carvedilol, with a trend toward better clinical outcome in the subjects with DCM who received carvedilol and worse outcome in subjects with congenital heart disease who received carvedilol.

In the absence of data on children, the ISHLT Guidelines reflect only data from studies in adults in recommending both digitalis and diuretics only for symptomatic LV dysfunction in children. Consideration of digitalis is based on the modest symptomatic improvement seen in trials of adult patients with heart failure, even at relatively low doses. A recent prospective nonrandomized study in 102 children with congenital heart disease and DCM found that torasemide, a newer loop diuretic with potassium-sparing properties, significantly improved the New York University Pediatric Heart Failure Index, decreased BNP levels, and improved fractional shortening, with no change in potassium or sodium levels in children who had not previously received diuretic therapy.

The largest improvements in clinical outcomes in studies of adults with heart failure have come from therapies that modify the neurohormonal milieu. Aside from the carvedilol trial described earlier, the only pediatric data for any of these drugs is for ACE inhibitor and other β-blockers. The studies on ACE inhibitor and β-blockers are primarily case series, retrospective analyses, and small noncontrolled trials in
children with a mixed group of diagnoses. For children with heart failure due to DCM, the weight of the evidence suggests potential improvement in ventricular function and symptoms for both classes of drugs. On the basis of data from studies of adult patients, accompanied by this limited but promising pediatric evidence, the ISHLT Guidelines recommend ACE inhibition for moderate or severe degrees of LV dysfunction, regardless of symptoms; and angiotensin receptor blocker therapy if ACE inhibitor is indicated but not tolerated. These guidelines, published before the carvedilol trial was concluded, do not recommend β-blocker therapy. A recent Cochrane review specifically of the use of β-blockers in children concluded that there are not enough data to recommend or discourage the use of β-blockers in children with heart failure and recommended further investigations in well-defined populations with standardized research methods. Although the carvedilol trial did not demonstrate efficacy based on the primary end point, the improvement in shortening fraction and clinical outcome seen in the DCM patients who received carvedilol has led to the empirical use of carvedilol in this group of patients. The long-term responses to β-blocker therapy have not been studied in children or adolescents and close monitoring of potential adverse effects is essential.

Surgical and Device Therapy

Pacemaker and Implantable Defibrillator Therapy

The AHA/ACC/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities include recommendations for children with heart failure and congenital heart disease. All recommendations are based on expert consensus. Indications for pacemaker therapy in children with heart failure due to congenital heart disease include symptomatic bradycardia, loss of atrioventricular synchrony, or intraatrial re-entrant tachyarhythmias. Implantable cardiac defibrillators are recommended in patients with congenital heart disease with documented ventricular tachycardia or syncope, most commonly after repair of TOF, atrial switch procedure, or the Fontan procedure. In a large multicenter series of children with heart failure awaiting heart transplantation, the incidence of sudden death was 1.3%, so routine implantation of an implantable cardiac defibrillator in children with LV dysfunction is not indicated.

Biventricular Pacing

In most children with DCM, the QRS duration does not meet the criteria used in adults for resynchronization therapy. In addition, patients with congenital heart disease often have a right bundle branch block, rather than the left bundle branch block commonly seen in adults with DCM and ischemic cardiomyopathy. There is considerable interest in the use of newer echocardiographic techniques to demonstrate evidence of mechanical dyssynchrony as an indication for biventricular pacing in children, but no validation studies have been conducted. There is some evidence from observational studies that biventricular or multisite pacing improves functional status in children with heart failure; however, no long-term trials have been performed to establish efficacy.

Ventricular Assist Devices

The use of mechanical assist devices for the treatment of end-stage heart failure in children awaiting transplant has been increasing as the device design has allowed for lower pump volumes. In the older child and adolescent, use of a mechanical assist device results in successful bridge to transplantation in 80% of cases. The options for mechanical support in the infant and young child are more limited. Improved outcomes have been reported using a paracorporeal pulsatile device in small children with survival from 60% to 85%. Since 2004, National Heart, Lung, and Blood Institute has supported the Pediatric Mechanical Circulatory Support Program designed to develop a family of pediatric mechanical circulatory support devices suitable for use in children between 5 and 25 kg in weight. To evaluate the efficacy and adverse events associated with the available mechanical circulatory devices currently available for use in children, pediatric data are being collected by the Interagency Registry for Mechanically Assisted Circulatory Support.

Heart Transplantation

Heart transplantation remains the therapy of choice for end-stage heart failure in children refractory to surgical and medical therapy. Current 1-year survival after heart transplantation in children is 85%; overall survival 20 years after transplantation is 40%. The Pediatric Heart Transplant Study, a prospective event-driven registry, has collected extensive information on children listed for heart transplant since 1993 in the United States, the Canada, and the United Kingdom. Analyses performed by the Pediatric Heart Transplant Study have identified risk factors for poor outcome after listing and transplantation in both cardiomyopathy and congenital heart disease patients, some of which are amenable to intervention. One example was the finding of unacceptably high mortality in infants with unpalliated hypoplastic left heart syndrome compared with those listed who had undergone the first palliative surgical procedure. This led to a change in practice and a decrease in the mortality. A novel approach to expanding the donor pool has been demonstrated by the success of ABO incompatible transplants in young infants whose immature immune systems do not yet produce the relevant antibodies.

Comprehensive Heart Failure Programs

Specific medical and surgical interventions may improve outcomes of heart failure, but how overall medical care is organized and delivered to patients with complex conditions such as chronic heart failure will also influence outcomes. In adults, heart failure disease management programs are a key component of care, and have decreased hospitalization rates, led to increased adherence to guidelines, and may improve survival. Programs vary but can include extensive patient and family education, dietary, exercise, and smoking cessation counseling, early discharge planning and medication review, intensive follow-up by a trained cardiac nurse educator, home visits, and social services consultation.

In several childhood diseases, comprehensive care programs have been shown to have a beneficial effect on disease outcomes. Pediatric asthma outreach programs improve...
health outcomes and decrease costs,\textsuperscript{67} as do intensive case management programs for children with diabetes.\textsuperscript{68} In children with hypoplastic left heart syndrome, Ghanayem et al\textsuperscript{69} reported improved survival between the first 2-staged surgical procedures with the use of an intensive home monitoring program. In the past decade, several pediatric cardiac centers have established heart failure clinics, but few have comprehensive heart failure programs. Developing such programs on a broader scale for children with heart failure has the potential to improve care of this complex condition.

**Nutrition and Exercise in Pediatric Heart Failure**

Nutritional support may be at least as important as medical therapy, particularly in infants. The limited data available consistently support increasing the caloric density of feeds as soon as a diagnosis of a cardiac condition that is associated with growth failure is made.\textsuperscript{70,71} Even if the next stop is the operating room, the few weeks that it may take to get the procedure scheduled can result in significant nutritional “cost” to infants who are trying to both grow and cope with the increased metabolic demands of heart failure symptoms. In contrast to management strategies for heart failure in adults, sodium restriction is not recommended in infants and young children. Sodium restriction may not be necessary, as many of the formulas and other nutritional supplements used to augment caloric intake in children control sodium intake, and because sodium is an important growth factor. Sodium restriction can result in impaired body and brain growth.\textsuperscript{72}

There has been a tendency in pediatric cardiology to overrestrict physical activity, especially, in the face of complex congenital heart disease. Current practice is guided by the 2005 ACC Eligibility Recommendations for Competitive Athletes with Cardiovascular Abnormalities, which balance the desirability of physical activity against what is known about potential risk.\textsuperscript{73} In the adult patient with heart failure, exercise training has been shown to normalize autonomic derangement and neurohumoral activation\textsuperscript{74}; there are no comparable data in children. There is evidence that regular physical activity can result in sustained improvements in physical functioning even in children with complex congenital heart disease. Rhodes et al\textsuperscript{75} enrolled 15 patients aged 8 to 17 years in a 12-week cardiac rehabilitation program, measuring their performance before, immediately after, and 1 year after the program. They found significant, sustained improvements in exercise function, behavior, self-esteem, and emotional state.

**Outcomes of Heart Failure in Children**

Outcomes of heart failure in children depend on the underlying cause. Because of advances in surgical and other interventional strategies, morbidity, and mortality associated with structural heart disease have declined significantly. However, little progress has been made in improving the significant mortality and morbidity associated with symptomatic heart failure in children with cardiomyopathy. In the 1980s, 1-year mortality rates were 20% to 30%, reaching 40% by 5 years.\textsuperscript{76,77} With the advent of pediatric heart transplantation, mortality in the first year after presentation has declined. However, in the carvedilol trial, where most subjects were in New York Heart Association or Ross heart failure class II, and only 2 patients were in class IV, the mortality rate was still high at 7%, with another 11% undergoing heart transplantation over an 8-month follow-up period. On the other hand, symptomatic improvement was reported in 55% of the subjects with improved ventricular ejection fraction.\textsuperscript{3} This dichotomy of end points illustrates the need for further research to identify patients at risk for poor outcome and patients with the potential for full recovery. The mortality rate among children listed and waiting for heart transplantation has also declined but remains unacceptably high at 17%.\textsuperscript{78}

**Future Directions**

There is no shortage of new therapies in the heart failure armamentarium for adults who may have a role in children. These include nesiritide and a reconsideration of nitrates, and newer drugs such as adenosine receptor agonists and phosphodiesterase inhibitors.\textsuperscript{79} Surgical and other interventional therapies to correct the anatomic problems leading to heart failure in congenital heart disease will continue to be refined. Cell-based therapy has been gaining increasing prominence for cardiovascular diseases in adults but has received little attention in pediatrics. Potential indications for stem cell use in pediatric heart failure include repair of ventricular myocardium and creation of biological heart valves, tissue-engineered vessels, and biological pacemakers.\textsuperscript{80} Increasing knowledge about genetic and genomic aspects of pediatric heart disease is also expected to inform treatment and help to risk stratify.

A major future direction to improve treatment of heart failure in children is to obtain sufficient data from well-designed trials with adequate power to support treatment recommendations. The National Heart, Lung, and Blood Institute-supported PHN (www.PediatricHeartNetwork.com)\textsuperscript{81} is a principal resource leading this effort. Since it was established in 2001, the PHN has initiated 4 trials and 4 observational studies, covering a variety of topics including issues related to heart failure. The PHN has demonstrated the effectiveness of having a sustained infrastructure, including a data coordinating center, biorepository, central pediatric echocardiographic laboratory, protocol review committee, data and safety monitoring board, medical monitor, and study coordinators in conducting pediatric cardiovascular studies. In September, National Heart, Lung, and Blood Institute will launch a comprehensive Bench to Bassinet program (http://www.nhlbi.nih.gov/funding/initis/faq-ptc.htm; Figure). This program will create many opportunities to advance pediatric cardiovascular research.

It is clear from this review that a paradigm shift is required in how data are obtained and perhaps interpreted to support therapeutic decisions. Children, and the providers responsible for their care, cannot accept hand-me-downs from research designed for and conducted in adults any more. Children are different, and their heart failure is different.

Catherine Neill and Edward Clark, in their 1995 book on the history of pediatric cardiology described 4 eras of pediatric cardiology: the pretherapeutic era, therapeutic era, infant cardiology era, and cardiac development era.\textsuperscript{37} We
Figure. National Heart, Lung, and Blood Institute Bench to Bassinet Program. The Bench to Bassinet Program consists of the Cardiac Development Consortium, the Pediatric Cardiac Genomics Consortium, and the PHN. This family of translational and clinical strategies will link academic research groups together with a shared vision, approach, and resources to optimize opportunities for leveraging and mutually reinforcing laboratory and clinical findings. ACC indicates Administrative Coordinating Center; Cmte, Committee; DCC, Data Coordinating Center; DSMB, Data and Safety Monitoring Board; PRC, Protocol Review Committee; T1, Translational research stage 1.

believe the next era should be the evidence-based medicine era in which we continue to solidify a culture of systematic investigation into therapy for pediatric heart failure.

Disclosures

Dr Hsu reports being a collaborator on 2 National Institutes of Health research grants that include aims related to pediatric heart failure, the PHN (HL 068290), and the Pediatric Cardiomyopathy Registry (HL 053392) and is a consultant for Berlin Heart Inc. It should be noted for Dr Pearson that the information contained in this article represents her personal views and is not the official opinion of the National Heart, Lung, and Blood Institute.

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