

# **Congestive heart failure in pediatric patients**

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Pediatric patients with congestive heart failure (CHF) are characterized by tremendous heterogeneity with respect to age, mechanisms of disease, and the number of children affected by CHF in various regions of the world. This heterogeneity complicates the assessment of the effectiveness of therapy in this population; consequently, only the use of digitalis and diuretics has been reported in large numbers of pediatric patients with heart failure. Moreover, the use of these agents is based on practices in adult cardiology rather than on evidence from controlled clinical trials in infants and children. Newer treatments such as angiotensin-converting enzyme (ACE) inhibitors and  $\beta$ -adrenergic receptor blockers are currently being administered to small numbers of patients in all categories of pediatric heart failure, but neither the efficacy nor the safety of these agents has been demonstrated in infants and children.

The attempt is often made to extrapolate the results of adult trials of a heart failure therapy to pediatric patients, but such extrapolation may be misleading. The causes and mechanisms of heart failure in pediatric patients are usually quite different from those in adults, in whom ischemic heart disease and hypertension predominate. In addition, the demonstrated safety of a treatment in adults cannot be assumed automatically to apply to pediatric patients. Trials of potentially useful agents should thus be conducted in a pediatric population to determine their effectiveness and safety. Furthermore, such trials should be multicentered because the numbers of pediatric patients with CHF are limited and the etiologies of the disease are diverse. To design effective studies, it is necessary to understand the causes and manifestations of heart failure in the pediatric population and to know the characteristics of the treatments currently used.

## **Causes of congestive heart failure in children and young adults**

The main causes of CHF in children who live in developed countries are (1) congenital heart defects that pro-

duce an excessive workload on the myocardium as a result of pressure or volume overload with or without chronic cyanosis, (2) cardiomyopathies, both genetically determined and acquired, that result from inherited metabolic and muscle disorders, infectious diseases, drugs and toxins, and Kawasaki disease, and (3) myocardial dysfunction after repair or palliation of heart defects.

In developed countries structural heart defects are the most common cause of heart failure in infants and children. The incidence of congenital heart disease in children is approximately 8 per 1000 live births, or 0.8%.<sup>1</sup> About one third to one half of these defects are severe enough to produce symptoms that prompt treatment, catheterization or surgery, or to cause death in the first year of life. Only about one half of these severe defects results in CHF; interventions are performed in the remaining defects because of cyanosis or potential or actual circulatory collapse related to closure of the ductus arteriosus. Thus the yearly incidence of heart failure from structural defects is about 0.1% to 0.2% of live births. The defects most likely to cause heart failure include left-to-right shunt lesions (eg, ventricular septal defect, common atrioventricular canal defect, patent ductus arteriosus, aorticopulmonary window, truncus arteriosus), left heart obstructive lesions (eg, critical aortic stenosis, severe aortic coarctation, congenital mitral stenosis), and congenital atrioventricular or semilunar valve regurgitation.

The incidence of cardiomyopathy in infants and children is difficult to assess, in part because of the variation in diagnostic criteria in different regions of the world and in part because of the heterogeneous etiologies of the disease. Arola et al<sup>2</sup> carried out a large population study in Finland between 1980 and 1991 to determine the incidence of idiopathic cardiomyopathy among infants, children, and adolescents. In this study, subjects with an identifiable cause of the cardiomyopathy (eg, metabolic disorder or muscular dystrophy) were excluded. These authors found an annual incidence of 0.34 cases per 100,000 of the age-specific population, with 52% occurring in the first year of life. The prevalence of idiopathic dilated cardiomyopathy at the end of 1991 was 2.6 per 100,000.<sup>1</sup> If all causes of dilated cardiomyopathy are included, the incidence and prevalence appear to be substantially higher. The Baltimore-Washington Infant Study found an annual incidence of cardiomyopathy in the first year of life of 4 cases per 100,000 live births, including all forms.<sup>3</sup> The Pediatric Cardiomyopathy Registry reported regional data from 2 areas of the United States and found an annual incidence of 0.6 per 100,000 persons for dilated

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cardiomyopathy in children aged 0 to 18 years.<sup>4</sup> The incidence was 16 times as high in persons <1 year old than it was in those older than 1 year and was nearly 3 times greater in African American and Hispanic children than in white children.<sup>4</sup> Each of the above studies focused primarily on idiopathic cardiomyopathy, thereby excluding cardiomyopathy resulting from anthracycline therapy for childhood cancer. Although comprehensive data concerning the incidence of doxorubicin cardiomyopathy are not available, the agent is clearly a significant etiologic factor. Indeed, at Boston Children's Hospital anthracycline therapy accounts for more than 50% of the prevalent cases of congestive cardiomyopathy.

The prevalence of heart failure among patients with repaired or palliated structural heart defects is unknown. It has been estimated that between 10% and 20% of patients with common transposition of the great arteries who have undergone a Mustard or Senning operation have failure of the systemic right ventricle by the time of young adulthood.<sup>5-9</sup> At least as high a percentage of patients with a functionally single ventricle who have undergone long-term palliation with a Fontan-type operation have symptoms of heart failure. After the repair of other types of defects, the occurrence of heart failure appears to be much less common.

## Manifestations of heart failure in infants, children, and adolescents

In infants, the symptoms of heart failure most commonly exhibited include tachypnea, tachycardia, poor feeding, and failure to thrive.<sup>10</sup> Other signs of heart failure in this group of patients include hepatomegaly, diastolic gallop on physical examination, and cardiac enlargement with or without pulmonary edema on chest radiograph. Toddlers and older children may also exhibit tachycardia and tachypnea but typically manifest symptoms of fatigue and exercise intolerance; poor appetite and growth failure are typical of this age group as well. In older children, venous distension and peripheral edema may be apparent as well. Adolescents have complaints similar to those in adults, including breathlessness, fatigue, exercise intolerance, orthopnea, nocturnal dyspnea, and gastrointestinal symptoms. The class measures developed by the New York Heart Association are a useful means by which to quantify severity of heart failure in older children and adolescents. The Ross scale<sup>10</sup> has been developed to evaluate heart failure in infants, but verification of its prognostic importance is lacking.

## Treatment of heart failure in infants, children, and adolescents

Medical management has a limited role in pediatric patients with structural heart defects because, for most

defects, effective surgical therapy is available. Digitalis, diuretics, and ACE inhibitors are used as temporizing therapy to improve the condition of patients before surgical repair, which is generally accomplished in the first weeks or months of life so that medical therapy is generally of short duration. Only in the cases of a few defects is longer-term medical therapy attempted, either because of the propensity for the defect to regress spontaneously (eg, ventricular septal defect) or because the treatment itself is problematic (as is the case, for example, in congenital mitral stenosis). In these instances, surgical repair is usually postponed as long as the infant is growing normally and the risk of pulmonary vascular disease or ventricular dysfunction is minimal.

The pharmacologic therapy of pediatric patients with cardiomyopathy is more variable than surgical therapy and is based on a smaller body of experience and age-relevant evidence. Specific drug treatment is lacking for most forms of cardiomyopathy. Inborn errors of metabolism rarely have an effective treatment, although carnitine replacement therapy has been reported to be beneficial in some cases of carnitine deficiency and a structured dietary regimen may be beneficial in some patients with specific enzyme deficiencies. Muscle diseases such as Duchenne's disease and myotonic dystrophy, mitochondrial diseases, and most genetic disorders have no effective specific treatment. Symptom management with digitalis and diuretics forms the basis of therapy in most patients. More recently, afterload reduction therapy has been used with increasing frequency.

In pediatric patients with acute myocarditis the variety of treatment options is broader but remains supported primarily by clinical experience and anecdotal evidence. Supportive therapy with inotropic agents, mechanical ventilation, antiarrhythmic drugs, and antithrombotics is generally accepted. Although a role has been suggested for corticosteroids, intravenous immunoglobulin, and immunosuppressive agents,<sup>11-13</sup> the evidence to support each of these is based on case reports or uncontrolled retrospective trials.

Anthracycline drugs used to treat childhood cancer are toxic to the myocardium in a dose-related fashion that usually manifests during or soon after the course of treatment. Digitalis, diuretics, and vasodilators have been used to treat heart failure symptoms. Use of anthracyclines in very young children appears to limit the potential for myocardial growth so that the myocardial mass does not increase adequately to keep pace with somatic growth.<sup>14</sup> The reduced thickness/dimension ratio leads to excessive myocardial afterload and diminished function. Afterload-reducing agents such as ACE inhibitors would appear to be specific therapy for this late form of anthracycline cardiotoxicity. However, a cogent argument can also be made in support of the concept that a reduction in the hypertrophic stimulus

may exacerbate the problem over time. Again, specific therapeutic trials to address this issue are lacking.

The treatment of children, adolescents, and young adults with heart failure symptoms after repair or palliation of a congenital heart defect includes the use of digitalis, diuretics, and usually ACE inhibitors. Aldosterone antagonists or  $\beta$ -receptor blockers have not been used consistently despite evidence of efficacy in adults with heart failure from other causes. In many instances, perioperative myocardial depression is transient and full recovery is possible. Nonetheless, heart failure can progress in some patients early or late after repair, which may lead to the necessity for heart transplantation or to death in some patients.

There is a much larger cohort of individuals who manifest asymptomatic systemic ventricular dysfunction, for whom there is even less consensus as to whether and what type of therapy is indicated. There are excellent data indicating that therapy can reduce the incidence of CHF and the rate of related hospitalizations in adults with asymptomatic left ventricular dysfunction.<sup>15</sup> On the basis of these observations, many pediatric cardiologists routinely treat their patients with asymptomatic left ventricular dysfunction, and even patients they consider at risk for ventricular dysfunction, primarily with ACE inhibitors, although some clinicians use digoxin in this situation as well. The etiologies of ventricular dysfunction in these children (hemodynamic overload, systemic right ventricle, postoperative congenital heart disease, primary or familial cardiomyopathies, anthracycline-induced cardiomyopathy) were not among those included in prior trials and in most instances would be expected to have a completely different pathophysiologic mechanism. For example, patients studied by the Study of Left Ventricular Disease (SOLVD) investigators<sup>15</sup> had a 4-year cumulative incidence of death or CHF of 45%, a time course vastly accelerated compared with the clinical impression of the natural history of asymptomatic left ventricular dysfunction in children.

## Evidence for efficacy of treatment

### Digoxin

In the United States, digoxin has remained one of the cornerstone therapies for CHF since colonial times. Aside from anecdotal reports of efficacy, few trials have provided evidence for clinical efficacy of this drug in either adults or children. No study has shown a reduction in mortality from digoxin in CHF, and only the recent Digoxin Investigators Group trial has provided strong evidence of clinical benefit (fewer hospitalizations) in the treatment group.<sup>16</sup> The only studies published that evaluate the therapeutic efficacy of digoxin in children show modest benefits in small nonrandomized or unblinded trials.<sup>17-19</sup> Evidence of increased con-

tractility does not consistently correlate with clinical improvement. There is evidence of increased parasympathetic cardiac and arterial baroreceptor activity with cardiac glycosides, which decrease central sympathetic outflow and thus exert a favorable neurohormonal effect. This may explain the evidence of efficacy of digoxin in patients with normal systolic function. Because of the potential for toxicity and the limited evidence for the efficacy of this treatment, randomized controlled trials are needed to determine whether the risk/benefit ratio is positive.

### Diuretics

Because of the clear clinical benefit from chlorothiazide, ethacrynic acid, and furosemide, little has been published in the last 30 years regarding the efficacy of these agents. Most of what has been published pertains to pharmacologic properties and interactions with other medications. Spironolactone, however, has recently attracted renewed attention because of the Randomized Aldactone Evaluation Study (RALES) trial, which showed reduced mortality and hospitalizations in adults with severe CHF when treated with low doses of this agent.<sup>20</sup> A small, randomized trial in children has demonstrated spironolactone's safety and diuretic efficacy,<sup>21</sup> but the potential impact on mortality has not been examined.

### Angiotensin inhibitors

The evidence is overwhelming that ACE inhibitors improve symptoms and prolong life in adults with CHF. However, in 2 large-scale adult trials, patients with non-ischemic cardiomyopathy did not consistently derive the same mortality benefit from ACE inhibitors as did patients with ischemic cardiomyopathy.<sup>22,23</sup> In addition, all of these large, randomized trials in adults with CHF excluded patients with significant valvular heart disease. Therefore these trials provide little information as to whether children with heart failure from causes that are more typical of congenital heart disease, such as volume overload lesions, can derive the same benefit as patients with ischemic heart disease. In addition, little is known about the long-term developmental effects of ACE inhibitors on growing children. This class of medication has been evaluated more than any other medical therapy for pediatric CHF. Several small trials have shown clinical stabilization and improvement in infants with heart failure secondary to left-to-right shunts.<sup>24-29</sup> Two small case studies have shown at least a short-term reduction in neurohormonal markers as well as clinical improvement in children treated with ACE inhibitors.<sup>30-32</sup> One retrospective study showed reduced mortality in children with dilated cardiomyopathy treated with ACE inhibitors compared with the standard treatment (digoxin and diuretics).<sup>33</sup> One study showed that after 2 months of therapy with enalapril

there was no hemodynamic or exercise improvement in patients who had previously undergone a Fontan procedure.<sup>34</sup> Another retrospective study failed to show any benefit from captopril in preventing post-Fontan pleural drainage,<sup>35</sup> although the patients studied were not treated in the immediate postoperative period. More recently, in a prospective trial of ACE inhibitor therapy in patients undergoing bidirectional cavopulmonary anastomosis and in whom therapy was initiated immediately after surgery, a significant reduction in postoperative pleural effusions was demonstrated.<sup>36</sup> No studies to date have evaluated the efficacy of ACE inhibitors in slowing progression of systemic right ventricular failure.

### $\beta$ -Blockers

Multiple trials in adults with CHF have shown a benefit from  $\beta$ -blockers with the primary end points of improvement in ejection fraction, reduction in overall mortality, reduction in the need for hospitalization, improved New York Heart Association heart failure class, and improved exercise tolerance (in some studies).<sup>37-45</sup> In children, 2 nonrandomized trials have shown improvement in left ventricular function, improved exercise tolerance, and a decreased need for heart transplantation in patients with idiopathic, drug-induced, or inherited dilated cardiomyopathy.<sup>46,47</sup> One small case series showed that the addition of propranolol to diuretics and digoxin improved the clinical symptoms and reduced neurohumoral markers in infants with CHF from large left-to-right shunts.<sup>48</sup> No studies have reported the use of  $\beta$ -adrenergic blockers in patients prone to development of ventricular failure (eg, those with a systemic right ventricle or those with chronic semilunar valve regurgitation, such as older patients after correction of tetralogy of Fallot).

## The need for and obstacles to age-specific trials

The dearth of age-specific pediatric pharmacologic trials is a well-recognized problem and one that is certainly not unique to cardiology.<sup>49</sup> Nearly all current heart failure treatments such as vasodilators and  $\beta$ -adrenergic blockers are being used in children largely because of the results of trials in adults. Unfortunately, the very different causes and mechanisms of heart failure in pediatric patients make extrapolation from adult data risky. For example, on the basis of existing data in adults it would be predicted that afterload reduction in patients after a Fontan operation would be beneficial. However, the small trial performed by Kouatli et al<sup>34</sup> suggests that Fontan patients treated with ACE inhibitors have worse exercise capacity than do untreated patients in the control groups. Similarly, the effectiveness of  $\beta$ -adrenergic blockers in heart failure

has been convincingly demonstrated in adults with ischemic or hypertension-related heart failure. The role of these agents in children with metabolic errors, inflammatory or intrinsic muscle disease, or structural heart defects is unknown and could not be easily extrapolated from the results in ischemic heart disease.

Despite the fact that large-scale, well-controlled trials in pediatric populations need to be performed, there are significant obstacles to their implementation. Compared with clinical trials in adults, the conduct of clinical trials in children introduces an additional layer of ethical complexity and significant impediments to recruitment. The debate as to the need and morality of placebo controls is even more contentious when informed consent must be provided by proxy. Under the ethical guidelines that govern human experiments, children are considered unable to provide informed consent for their participation in clinical studies. Thus parents of children who participate in studies and the investigators who perform the studies typically require a substantial pre-existing body of evidence, acquired in subjects able to provide consent, that indicates that the agent to be investigated is safe and efficacious. This situation often creates the paradox that studies in children are difficult to justify without significant preliminary data, at which time it can be argued that these prior data render placebo-controlled trials unethical. On a practical level, very real barriers to research on CHF in children limit the available options for study design. Invasive procedures are more difficult in children and incur greater risk than in adults. In small children even noninvasive procedures such as echocardiograms and magnetic resonance imaging require sedation or anesthesia to enable accurate data acquisition. The wide variety of etiologies for CHF and the small number of patients within each category requires a multicenter approach to clinical trials if meaningful end points are to be achieved. Ultimately, however, it is generally the selection of valid study end points that presents the most problematic issue in study design.

Mortality from heart failure is uncommon in pediatric patients, and trials using this end point will consequently require large numbers of patients. Only acute myocarditis has a mortality rate (25% to 35%) high enough to enable mortality to be used as an end point in moderate-sized trials. The use of surrogate end points is hampered by the fact that none have been validated as predictors of survival in adult or pediatric patients. Ventricular function correlates with outcome in some forms of pediatric cardiomyopathy,<sup>50</sup> but the predictive capacity is weak. Additional obstacles interfere with the use of ventricular function as a study outcome in patients with congenital heart disease, obstacles related to abnormal ventricular configuration and right ventricular hypertension. New York Heart Association class (or Ross score for infants) and self-assessment scales

permit objective assessment of symptoms and lifestyle but have not been validated in pediatrics as a predictor of outcome. Exercise capacity, especially when expired gases are analyzed for assessment of maximal oxygen consumption or ventilatory threshold, is a reasonably objective measure of functional capacity but cannot be obtained in younger patients. Changes in neurohormones such as atrial natriuretic peptide, brain natriuretic peptide, or norepinephrine can be used to monitor the response to therapy of CHF, but again, the relationship to long-term outcome of pediatric congestive heart failure is unknown.

## Suggested approach

Moving treatment of CHF in children into the realm of evidence-based medicine requires cooperation and innovation within the pediatric cardiology community. Retrospective analysis of a single-center experience is useful for safety considerations but will not adequately address issues concerning efficacy, as shown by other experts in the field.<sup>51</sup> Although identification of the most promising agents for long-term therapy is straightforward, including the ACE inhibitors, high- versus low-dose ACE inhibitors, angiotensin receptor blockers, and  $\beta$ -blockers, each of the many decisions in study design beyond that identification will be controversial and difficult. The group that would have the greatest chance of designing protocols that would be acceptable to the pediatric cardiology community at large would be a multicenter consortium of interested investigators who could initiate the design of such trials independent from particular institutional biases and interests. The recent National Institutes of Health initiative, Pediatric Heart Disease Clinical Research Network (RFA HL-00-013), represents the type of organizational infrastructure needed for the pediatric cardiology community to move forward in terms of evidence-based pediatric therapies. Whether clinical trials of treatments for CHF are on the agenda for this particular clinical research network is not currently known, but there can be little doubt that a program such as this one will be required for genuine progress in pediatric CHF to occur.

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