Challenges and Opportunities in Pediatric Heart Failure and Transplantation

Update on Pharmacological Heart Failure Therapies in Children

Do Adult Medications Work in Children and if Not, Why Not?

Joseph W. Rossano, MD; Robert E. Shaddy, MD

Heart failure is a serious problem in children with acquired and congenital heart disease (CHD). In 2006, there were nearly 14,000 hospitalizations related to heart failure in pediatric patients. The disease is also costly, not only in terms of lives lost with a 20-fold increase in hospital mortality compared with children without heart failure but also in terms of morbidities, prolonged hospitalizations, and dramatically high hospital charges. However, it is not clear that there has been an overall improvement in the outcomes of children with heart failure. Although the risk-adjusted hospital mortality has declined, several single-center and multicenter studies with heart failure have not been proven to be effective in children. There are many potential reasons for this. One potential reason is that the medications are actually beneficial, but the design and populations included in prior studies were not sufficient to demonstrate the benefit. However, there are other problems that may have more to do with the potential differences between adults and children with heart failure and their response to medications that treat heart failure. These issues are the focus of this review.

Challenges in Study Design in Pediatric Heart Failure

One potential explanation for the negative findings of many pediatric heart failure studies is that the medications actually work, but the challenges in study design and study implementation make it difficult, if not impossible, to see the beneficial treatment effect. Prospective pediatric heart failure drug trials are almost universally underpowered to detect a difference between treatment arms, particularly if the study is using a primary end point of symptoms or survival rather than a surrogate end point such as a biomarker or an echocardiographic end point. Many of the problems related to this underpowering of these types of trials are unavoidable and related to the markedly lower incidence of heart failure in children.

The pediatric carvedilol study, a multicenter, randomized, controlled trial, involved 161 children with chronic symptomatic heart failure from systemic ventricular dysfunction, with enrollment from 26 centers over 5 years. Approximately 60% of these patients had DCM, and the remainder had some form of CHD. Most were in New York Heart Association or Ross heart failure class II, and very few were in class IV. The primary end point, which was a composite measure of clinical heart failure, was no different between carvedilol- and placebo-treated patients, although more than half of the patients in both groups improved. Secondary end points such as death or transplantation were also similar in both groups. Importantly, only 8 patients (5%) suffered cardiovascular mortality.

Conversely, a large, prospective, randomized trial of carvedilol in adult heart failure patients included 2289 patients with New York Heart Association class III or IV. In this study, mortality was observed in 320 patients (14%). Only 70% of the patients were alive by 21 months after randomization in the placebo group. In the adult trial, the large number of patients combined with a high event rate allowed the differences between carvedilol and placebo to be readily apparent, and trial enrollment was stopped early secondary to benefit noted on interim analysis. Because of the differences in events and the number of patients enrolled, it is not surprising that the pediatric study failed to observe a difference even if there is a difference in reality (type II error). Assuming that carvedilol is beneficial for the patient population studied in the pediatric trial, it would take >6000 patients followed up for 2 years (assuming a 10% mortality in placebo-treated patients at 2 years) to demonstrate a 20% improvement in survival. Given that <200 patients were enrolled from 26 US centers in 5 years, it is very unlikely that the study will be repeated with a larger cohort of patients. These challenges with prospective, randomized, controlled trials highlight the issue of relying on these types of studies as the sole evidence of therapeutic efficacy. Comparative effectiveness research using observational studies from well-designed registries or large databases can provide complementary data to randomized, controlled
trials and, in some cases, replace randomized, controlled trials when the trials would be unethical or impractical.18–20 For example, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has served as the platform for US Food and Drug Administration postapproval studies.21 Thus, for many pediatric diseases, including heart failure, assessment of therapeutic efficacy should not rely solely on randomized, controlled trials but rather should take into account the totality of evidence from well-conducted preclinical and clinical studies.

The use of surrogate end points is common in pediatric trials secondary to the low number of clinically important events such as death. However, there is a real risk of error in concluding the benefit or lack thereof of therapies on the basis of these surrogate end points. Early trials of β-blockers in adult heart failure patients failed to meet the primary end point of improvement in exercise tolerance, although an improvement in ejection fraction was noted.22,23 Although it may be tempting to conclude that an improvement in symptoms or exercise tolerance from a medication would be sufficient to reasonably conclude that mortality would also be improved, this should be done with caution. Inotropic medications such as dobutamine and milrinone improve cardiac output and heart failure tolerance from a medication would be sufficient to reasonably conclude that mortality would also be improved, this should be done with caution. Inotropic medications such as dobutamine and milrinone improve cardiac output and heart failure symptoms.24–28 However, these medications have also been associated with increased mortality in heart failure patients from multiple studies in adults.29–33 There are limited data on the association of inotropic medications with mortality in pediatric heart failure, and these medications are often used as a bridge to transplantation.34–37

Another significant issue in trials of medications for pediatric heart failure patients is deciding which patients should be included. The carvedilol study included patients with cardiomyopathy and CHD and patients with systemic left ventricles (LVs) and systemic right ventricles. As detailed below, there are significant differences between the right ventricles and LVs in heart failure that may account for some of these differences. Additionally, DCM is a heterogeneous disorder that can arise from a variety of sources, including infections, inflammatory disorders, metabolic disorders, mitochondrial disease, and mutations in a variety of myocardial genes.38 Some of these sources may respond well to angiotensin-converting enzyme inhibitors and β-blockers, whereas others may not. For example, patients with Duchenne muscular dystrophy, who have an abnormality of the cytoskeletal protein dystrophin, seem to have a favorable response to angiotensin-converting enzyme inhibitors and β-blockers from several observational studies and small clinical trials.39–42 Although it would be ideal to perform large-scale clinical trials in children with DCM of the same underlying origin, the majority of pediatric patients with DCM are idiopathic. Thus, trials finding no overall net benefit in all patients with DCM may be overlooking an important subset of patients who do benefit from the medications but are not discernible because they represent a relatively small proportion of patients in the study.

### Different Responses to Medications

One’s response to a drug depends on many factors. These factors are compounded when one considers the variable responses that can be seen in a growing child at different stages of development. There are age- and development-dependent changes in how medicines are distributed in and eliminated from the body (pharmacokinetics). There are also age- and development-dependent changes in the response to medicines (pharmacodynamics). Furthermore, there are age- and development-dependent changes in the adverse effects of medicines, both short and long term. With the use of population pharmacokinetics in the pediatric carvedilol trial, it was demonstrated that steady-state concentrations of carvedilol

### Table. Summary of Trials of β-Blockers, Angiotensin-Converting Enzyme Inhibitors, and Angiotensin II Antagonists in Patients With a Systemic Right Ventricle

<table>
<thead>
<tr>
<th>β-Blocker</th>
<th>Agent</th>
<th>TGA/ccTGA</th>
<th>n</th>
<th>Follow-Up, mo</th>
<th>MRI*</th>
<th>V₀,max</th>
<th>NYHA Class</th>
<th>Pro/Retro</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindenfeld et al51</td>
<td>Carvedilol</td>
<td>ccTGA</td>
<td>1</td>
<td>7</td>
<td>↑</td>
<td>ND</td>
<td>ND</td>
<td>Pro</td>
</tr>
<tr>
<td>Giardini et al52</td>
<td>Carvedilol</td>
<td>Both</td>
<td>8</td>
<td>12</td>
<td>↑</td>
<td>–</td>
<td>↑</td>
<td>Pro</td>
</tr>
<tr>
<td>Josephson et al53</td>
<td>Various</td>
<td>TGA</td>
<td>8</td>
<td>36</td>
<td>ND</td>
<td>ND‡</td>
<td>↑</td>
<td>Retro</td>
</tr>
<tr>
<td>Doughan et al54</td>
<td>Various</td>
<td>TGA</td>
<td>31</td>
<td>4</td>
<td>ND</td>
<td>ND</td>
<td>↑</td>
<td>Retro</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hechter et al55</td>
<td>Various</td>
<td>TGA</td>
<td>14</td>
<td>24</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>Retro</td>
</tr>
<tr>
<td>Robinson et al56</td>
<td>Enalapril</td>
<td>TGA</td>
<td>9</td>
<td>12</td>
<td>ND</td>
<td>–</td>
<td>ND</td>
<td>Pro</td>
</tr>
<tr>
<td>Therrien et al57</td>
<td>Ramipril</td>
<td>TGA</td>
<td>17</td>
<td>12</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>Pro</td>
</tr>
<tr>
<td>ATII antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dore et al58</td>
<td>Losartan</td>
<td>Both</td>
<td>29</td>
<td>3.5</td>
<td>ND</td>
<td>–</td>
<td>ND</td>
<td>Pro</td>
</tr>
<tr>
<td>Lester et al59</td>
<td>Losartan</td>
<td>TGA</td>
<td>7</td>
<td>2</td>
<td>↑‡</td>
<td>ND</td>
<td>ND</td>
<td>Pro</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ATII, angiotensin II; ccTGA, congenitally corrected transposition of the great arteries; MRI, magnetic resonance imaging; ND, not determined; NYHA, New York Heart Association; Pro, prospective study design; Retro, retrospective study designs; ↑, significant improvement; –, no significant change.

*Right ventricular ejection fraction as determined by MRI.
‡Determined in a minority of patients.
†Right ventricular ejection fraction as determined by echocardiography.

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appeared to be lower in this group of pediatric patients compared with historical data in adult patients, suggesting that higher doses of carvedilol in children may be needed to achieve the same effect as in adults. A subsequent formal pharmacokinetic study of carvedilol in children found that significantly higher doses and possibly more frequent dosing are necessary to reach the same exposure as in adults. Thus, one reason that heart failure drugs may not work the same in children and adults is attributable to differences in absorption, metabolism, or excretion. A joint statement from the US Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research recommends the following: (1) a combined pharmacokinetic and pharmacodynamic approach to ensure that achieving a given exposure to a medication results in the desired therapeutic effect; (2) the development, validation, and use of different end points for specific age and developmental subgroups; and (3) long-term studies to determine possible effects on skeletal, behavioral, cognitive, sexual, and immunity maturation and development.

Different Diseases

As noted above, the causes of heart failure in children are diverse, including CHD and structurally normal hearts with heart muscle disease (cardiomyopathy). Overall, 60% to 70% of heart failure admissions in children occur with some form of CHD. For the purposes of this review, we limit the discussion of heart failure to those patients with signs or symptoms of heart failure resulting from systemic ventricular systolic dysfunction. In the pediatric carvedilol trial, in a comparison of those with a systemic LV with those whose systemic ventricle was not a morphological LV, there was a statistically significant difference between the percentage of patients who had an improved outcome (64%) in the systemic LV groups compared with those without a systemic LV (35%), suggesting a differential response to carvedilol on the basis of the morphology of the systemic ventricle.

Thus, it is possible that children with heart failure caused by systolic LV dysfunction may benefit from carvedilol or other β-adrenergic receptor blocker therapy. However, this would assume that the causes of systolic LV dysfunction in a child are similar to those in an adult. This assumption may not be correct. In adults with nonischemic cardiomyopathy, there is a high incidence of comorbidities, including atrial fibrillation (20%–35%), diabetes mellitus (25%–47%), and hypertension (40%–70%). In contrast, these comorbidities are virtually nonexistent in pediatric nonischemic cardiomyopathies. It is certainly possible, even likely, that the response to heart

Figure 1. The 10 most abundantly expressed microRNAs (miRs) in the right ventricle (RV) of sham and pulmonary artery–constricted animals compared with the RV of sham and serum response factor–induced left ventricular (LV) hypertrophy (LVH) ventricles. RVH indicates RV hypertrophy. Reproduced from Reddy et al58 with permission from the publisher. Copyright © 2012 American Physiological Society.
failure medications will be very different in a hypertensive, diabetic adult with atrial fibrillation than in a child with idiopathic DCM, despite the fact that both patients have heart failure caused by systolic LV dysfunction.

In addition to systolic LV dysfunction as a cause of heart failure in children, systolic dysfunction of a systemic ventricle that is not of LV morphology is becoming increasingly common in pediatric patients. Now that a higher percentage of patients are surviving surgery for CHD, many of whom have a systemic right or single ventricle, systolic dysfunction is becoming increasingly common as they age. An early prospective, randomized trial of enalapril compared with placebo in a group of patients after the Fontan operation failed to show any benefit of enalapril over placebo with respect to exercise capacity. However, more concerning was the finding that the mean percent change in cardiac index from rest to maximal exercise was significantly decreased in the enalapril group compared with the placebo group, suggesting potential deleterious effects of angiotensin-converting enzyme inhibitors in patients with Fontan circulation. Other studies in adults with a systemic right ventricle have failed to demonstrate improvement in right ventricular ejection fraction with enalapril or to demonstrate improvement in exercise capacity or N-terminal pro-brain natriuretic peptide levels with losartan (Table). Most recently, a double-blind, randomized, placebo-controlled pilot study in a group of young adults with a systemic right ventricle showed no benefit of valsartan over placebo with regard to right ventricular ejection fraction, exercise capacity, or quality of life. Moreover, there are data to suggest that the right ventricles and LVs may be different in terms of gene expression, microRNA expression, and adaptation to fibrosis (Figure 1).58-60

Although it is possible that these studies were also underpowered to detect a difference between groups, they clearly raise the question of whether the proven standard treatments for heart failure in those with a systemic LV can be extrapolated to those with a systemic ventricle that is not an LV. Similarly, there are no randomized trials demonstrating clear benefit of β-blockers in this subgroup of pediatric and young adult patients with a systemic ventricle that is not an LV.

Different Substrate

In addition to potential differences in drug metabolism and differences in morphology, the underlying substrate of the systemic ventricle may be very different between children and adults. In the first pharmacogenetic analysis of angiotensin-converting enzyme inhibition in children with CHD, Mital and colleagues showed that renin-angiotensin-aldosterone system upregulation genotypes are associated with unfavorable remodeling and a deleterious effect of enalapril on growth. Using an explanted human heart biorepository, Miyamoto and colleagues have shown that the molecular characteristics of pediatric heart failure may be markedly different from those in adults (Figure 2), including downregulation of β1- and β2-adrenergic receptors in children but no downregulation of β2-adrenergic receptors in adults, upregulation of connexin 43 in children compared with downregulation in adults, no differences in phosphatase expression in children whereas upregulation occurs in adults, and no decrease in phosphorylation of phospholamban in children with heart failure, a known characteristic of adult heart failure. This difference in β-adrenergic receptor expression between adults and children may have important implications for β-receptor blockade therapy in heart failure. Data from Bernstein and other investigators suggesting that there are

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![Figure 2](http://circ.ahajournals.org/)
differential effects of cardiac β1-adrenergic receptors (as being more cardiotoxic) and β2-adrenergic receptors (as being more cardioprotective) imply that the response to β-blockade may depend at least partially on the ratio of each receptor type in pediatric versus adult myocardium. Furthermore, Stauffer and colleagues have recently shown differences in microRNA and SMAD4 expression in pediatric failing human heart, suggesting changes unique to children. These studies suggest that there may be important developmental differences between pediatric and adult heart failure among cardiomyopathy patients that may account for at least some of the differential treatment effects.

Conclusions

Currently, it is difficult to conclude with any degree of certainty whether the medications that have been well established to be beneficial for adult heart failure patients are also beneficial for children. An adequately powered study with a pediatric population with sufficiently long follow-up for important clinical outcomes such as death is unlikely to happen in the current funding environment and would be difficult in any funding environment. Thus, it will continue to be difficult to properly interpret negative studies. However, there are important differences in the pediatric and adult heart failure populations in terms of underlying diseases, pharmacokinetic/pharmacodynamic characteristics, and gene expression that provide a plausible explanation of why these medications may not work in children. Extrapolating evidence from adult patients to children with heart failure may have limited utility. This presents a challenging dilemma for the practitioner having to decide to use or not use these medications for pediatric heart failure patients without the guidance of evidence-based recommendations and highlights the need for ongoing research in the field.

Disclosures

None.

References


**Key Words:** heart failure ■ pediatrics ■ pharmaceutical preparations
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Circulation. 2014;129:607-612
doi: 10.1161/CIRCULATIONAHA.113.003615

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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