INTRODUCTION
The Need for Pediatric Guidelines

Heart failure (HF) in the United States is well recognized as a major public health problem, with over 900,000 hospital admissions annually in the United States, and greater than 250,000 deaths per year. The great majority of heart failure occurs in adults. In children, the scope of the problem is less well defined, but recent data from the Pediatric Cardiomyopathy Registry suggest an annual incidence of 1.13 cases of cardiomyopathy per 100,000 children. While some of this represents asymptomatic disease, the burden of disease overall is nonetheless quite high. In the Pediatric Cardiomyopathy Registry, the majority of children with cardiomyopathy also had HF, with mortality rates of 13.6% at 2 years in dilated forms of cardiomyopathy.

The etiology of heart failure differs greatly between children and adults. Children in the Pediatric Cardiomyopathy Registry had a recognizable syndrome or genetic diagnosis in 27% of cases, with an additional 5% of cases due to myocarditis. Furthermore, a large percentage of children with end-stage HF (between 25% and 75%, depending upon the age group) have an underlying diagnosis of congenital heart disease. In contrast to adult patients, ischemic heart disease is rare in children.

There is a large, and rapidly growing literature addressing HF treatment for adult patients, with a much smaller literature concerning HF therapy in children. Excellent guidelines for adult patients have recently been published, but given the significant differences between adult and pediatric patients with HF, there is little reason to believe that these guidelines are directly applicable to children. Accordingly, in this document we have attempted to summarize the relevant literature and synthesize management guidelines for children with HF. The document that follows has been prepared in a consensus fashion, with input from pediatric cardiologists at multiple sites throughout the United States and Canada.

Levels of Evidence and Strength of Recommendations

Each recommendation in this document is ranked with regard to the level of supporting evidence:

- **Class I**: Conditions for which there is general agreement that a given therapy is useful and effective.
- **Class II**: Conditions for which there is conflicting evidence or a divergence of opinion concerning the usefulness and effectiveness of a therapy.
- **Class IIa**: Weight of evidence/opinion favors usefulness/effectiveness.
- **Class IIb**: Weight of evidence/opinion is less in favor of usefulness/effectiveness.
- **Class III**: Conditions for which there is general agreement that a therapy is not useful and (in some cases) may be harmful.

From the International Society for Heart and Lung Transplantation, Addison, Texas.

Reprint requests: David Rosenthal, MD, (W) 725 Welch Road, room 1751, Stanford, California 94304, Telephone: 650-497-8676, Fax: 650-497-8422. E-mail: david.rosenthal@stanford.edu

Copyright © 2004 by the International Society for Heart and Lung Transplantation. 1053-2498/04/$-see front matter. doi:10.1016/j.healun.2004.03.018
DEFINITIONS AND CLASSIFICATION

Definition of Heart Failure

Heart failure is a complex clinical syndrome, with multiple etiologies and diverse clinical manifestations. Many definitions have been offered, but we prefer that set forth by Arnold Katz, which not only describes the clinical aspects of HF, but also reflects a growing understanding of the cellular processes which accompany this condition:4

“...heart failure is a clinical syndrome in which heart disease reduces cardiac output, increases venous pressures, and is accompanied by molecular abnormalities that cause progressive deterioration of the failing heart and premature myocardial cell death.”

It is important to note that at present, this definition is not clinically applicable as a diagnostic roadmap. In fact, there is no gold standard diagnostic approach to HF. Rather, the recognition of HF depends on a thorough characterization of the patient from a clinical, hemodynamic, and – increasingly – neurohumoral perspective. In specific cases, the weight of the diagnosis may stem from elements of the medical history, while in other cases, echocardiography or cardiac catheterization may provide essential data. Perturbations in circulating hormones such as the natriuretic peptides are coming to play a substantial role in the diagnosis of HF in the adult population, but are less widely used for this purpose in children.

Additionally, there is often ambiguity concerning the use of the term HF for children with uncorrected structural lesions resulting in left to right shunting with preserved systolic function. In this manuscript, we do not address the clinical issues posed by such patients, which are very different from HF associated with myocyte dysfunction.

NYHA Classification

The New York Heart Association (NYHA) classification is widely used for grading HF in adult patients because of its simplicity in providing a practical assessment of functional limitation. It is an ordinal scale defined by the degree to which symptoms of HF limit a patient’s physical activity. However, the applicability to younger children and infants is limited.

Ross Classification

The Ross Classification was developed for grading HF in infants and younger children (Table 1).5 In 1994 the Ross Classification was adopted by the Canadian Cardiovascular Society as their official system for grading HF in children,6 and the system is currently used in the national Cardiomyopathy Registry and in a multicenter study of carvedilol. A direct correlation between the Ross class and plasma norepinephrine concentrations5 and an inverse relationship between the Ross class and β-receptor density support the validity of the Ross classification system.7

Other Scoring Systems

Several other scoring systems have been proposed for grading HF in children. One such system developed for infants has a 12-point scale based on variables assigned by 4 pediatric cardiologists blinded to the patient’s diagnosis.8 These variables were: quantity and duration of feeding, respiratory rate and pattern, heart rate, peripheral perfusion, presence of a diastolic filling sound, and degree of hepatomegaly. Another recently proposed system is the New York University Pediatric Heart Failure Index.9 In this system, a total score from 0 to 30 is obtained by adding together points based on physiologic indicators and the patient’s specific medical regimen. Items scored are signs and symptoms, HF medications, and ventricular pathophysiology. None of these systems have been validated in large numbers of children nor tested against biological markers of HF or exercise capabilities.10 Ohuchi and colleagues have recently published a detailed analysis of the relationship between changes in neurohumoral indices and clinical status of children and young adults with congenital heart disease.11

Staging System

Both the NYHA and Ross HF scales concentrate on current symptomatology. Neither of these scales discriminates well among patients with early stages of disease, nor between stable and decompensated stages of illness. Overt HF symptoms occur late in the disease process, indicating a failure of compensatory mechanisms. The ACC/AHA 2002 HF guidelines therefore advocate a HF classification schema that addresses these deficiencies and complements the NYHA scale.12 The ACC/AHA staging identifies patients at risk for HF who require early intervention to prolong the symptom-free state; it also delineates patients who require aggressive management of symptoms once they become manifest.

Table 1. Ross Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>II</td>
<td>Mild tachypnea or diaphoresis with feeding in infants. Dyspnea on exertion in older children.</td>
</tr>
<tr>
<td>III</td>
<td>Marked tachypnea or diaphoresis with feeding in infants. Prolonged feeding times with growth failure due to heart failure. In older children, marked dyspnea on exertion.</td>
</tr>
<tr>
<td>IV</td>
<td>Symptoms such as tachypnea, retraction, grunting, or diaphoresis at rest.</td>
</tr>
</tbody>
</table>

Ross class and plasma norepinephrine concentrations5 and an inverse relationship between the Ross class and β-receptor density support the validity of the Ross classification system.7
The system advocated by the ACC/AHA for HF staging in adults can be readily applied to infants and children as well, with minor modifications as shown in Table 2. The writing committee of this document has adopted this nomenclature due to the advantages enumerated above.

### Table 2. Proposed Heart Failure Staging for Infants and Children*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients with increased risk of developing HF, but who have normal cardiac function and no evidence of cardiac chamber volume overload. Examples: previous exposure to cardiotoxins, family history of heritable cardiomyopathy, univentricular heart, congenitally corrected transposition of the great arteries.</td>
</tr>
<tr>
<td>B</td>
<td>Patients with abnormal cardiac morphology or cardiac function, with no symptoms of HF, past or present. Examples: aortic insufficiency with LV enlargement, history of anthracycline with decreased LV systolic function.</td>
</tr>
<tr>
<td>C</td>
<td>Patients with underlying structural or functional heart disease, and past or current symptoms of HF.</td>
</tr>
<tr>
<td>D</td>
<td>Patients with end-stage HF requiring continuous infusion of inotropic agents, mechanical circulatory support, cardiac transplantation or hospice care.</td>
</tr>
</tbody>
</table>

*HF, heart failure; LV, left ventricular.

Left Ventricular Systolic Dysfunction

**Pharmacotherapy.**

**Digitalis.**

*Clinical Data in Adult Patients with HF.* Digoxin improves symptoms in adults with HF. However, despite large study cohorts, digoxin has not been shown to improve survival in HF. Adams and colleagues have recently shown that low doses of digoxin are as effective as higher doses in preventing further HF, and may reduce the incidence of side effects and toxicity, especially when other medications are instituted which can increase digoxin levels. In one recent post-hoc analysis of the DIG trial, higher serum digoxin levels were associated with increased mortality in men with HF, independent of glomerular filtration rate.

*Clinical Data in Pediatric Patients.* Although only scant pediatric data are available, digoxin is widely used to treat HF in infants and children. Recommendations can only be extrapolated from those for adult patients with left ventricular systolic dysfunction and HF.

**Diuretics.**

*Clinical Data in Adult Patients.* Few data are available concerning the appropriate use of diuretics, but their use is widespread. Current guidelines in adult patients recommend the use of diuretics in all patients with HF and fluid retention in order to achieve a euvolemic state.

Spironolactone, specifically, has been shown to improve survival in adults with advanced HF. This does not appear to represent a diuretic effect, but rather is specifically due to blockade of aldosterone; the benefit has also been demonstrated with another aldosterone antagonist, eplerenone. The activation of the renin-aldosterone-angiotensin system (RAAS) is thought to be critical in the pathogenesis of HF, and interruption of the RAAS is a foundation of modern HF therapy. Although this is primarily accomplished in current management by administration of ACE inhibitors, spironolactone has an additive effect in adults with severe HF.

*Clinical Data in Pediatric Patients.* No published clinical studies are available concerning the effectiveness of diuretics in reducing mortality or improving symptoms in pediatric patients.

**Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers.**

*Clinical Data in Adult Patients.* HF is associated with chronic activation of the RAAS and increased symp-
thetic drive. These alterations, which may be beneficial acutely, contribute to the progression of HF over time. Increased adrenergic tone increases afterload and myocardial oxygen demand. Angiotensin II is a vasoconstrictor which causes myocyte hypertrophy and fibrosis as well as aldosterone secretion. Increased concentrations of both aldosterone and angiotensin II are associated with a poor outcome in HF patients. The efficacy of ACE inhibitor therapy in HF is related to disruption of the activation of the renin-angiotensin axis and to decreased cardiac adrenergic drive.

Multiple large clinical trials have shown that therapy with ACE inhibitors improves symptoms and survival in adult patients (primarily middle-aged men) with HF, and reduces the rate of disease progression in asymptomatic patients. In the majority of trials, ACE inhibitors were well tolerated. Symptomatic hypotension can occur; careful titration of these agents and adjustment of diuretic dosages is necessary. Cough, which is often associated with pulmonary edema, is present more frequently in patients treated with ACE inhibitors.

A frequent observation in the literature evaluating treatment of patients with HF concerns the underutilization of ACE inhibitors. On the one hand, only a minority of eligible adults receives an ACE inhibitor. Of equal importance, those patients who are treated with ACE inhibitors are often treated with doses considerably lower than the doses for which efficacy has been established in clinical trials. Although there is some controversy regarding appropriate dosing of ACE inhibitors for HF, most studies suggest a more robust response to higher doses of ACE inhibitors when hemodynamics, symptoms or neurohumoral profiles are considered. The ATLAS trial compared the effects of low and high dose lisinopril on the morbidity and mortality of 3164 subjects with NYHA class II-IV. No survival benefit was seen from high dose therapy as compared to low dose, but high dose therapy reduced the composite outcome of death or hospitalization by 12%, and reduced hospitalization by 13%. Although dizziness, hyperkalemia and hypotension were all more common in the high dose group, these side effects did not require withdrawal from therapy more commonly than in the lower dose group. The ATLAS trial confirmed that certain benefits of ACE inhibition are greater at higher doses, and that these agents are clinically tolerated at higher doses. It is also noteworthy that the effect on symptoms was not associated with dose level, suggesting that titration of ACE inhibitors according to clinical endpoints is not a viable strategy.

Data concerning administration of ACE inhibitors to patients with structural heart disease is understandably limited. However, the beneficial effects of ACE inhibition on LV volume, dimensions, mass index, wall stress and reduction in the volume-loaded ventricle have been demonstrated for adult patients with aortic regurgitation.

There are important differences between the ACE inhibitors and the angiotensin receptor blockers (ARB’s). The ARB’s are competitive antagonists for the angiotensin II receptor that is responsible for mediating all the known actions of angiotensin II. ARB’s block the cell surface receptor for angiotensin, rather than acting through blockade of angiotensin converting enzyme. Unlike ACE inhibitors, ARB’s do not inhibit bradykinin breakdown, which has been implicated in causing the troublesome cough that is a prominent side effect of ACE inhibitors. ARB’s are not nephrotoxic, affording these drugs a theoretical advantage over ACE inhibitors.

Despite these mechanistic differences, trials in adult patients with HF have not shown any important differences in hemodynamic effects, efficacy and safety between ARB’s and ACE inhibitors. Currently ARB’s are recommended in adults intolerant to ACE inhibitors. The addition of ARB’s to ACE inhibitor therapy may increase efficacy and is often recommended in adult HF patients intolerant to β-blockade.

Clinical Data in Pediatric Patients. Although ACE inhibitors have been used in the pediatric population for two decades, relatively few studies concerning the administration of ACE inhibitors to children with HF are available. Numerous small observational studies have shown that ACE inhibitors benefit children with HF caused by systemic ventricular systolic dysfunction. Effects on mortality have not been described, with the exception of one retrospective report, in which survival was improved by administration of ACE inhibitors during the first year of treatment but not subsequently.

The use of ACE inhibitors in patients with structural heart disease is less well understood. However, a single controlled study in children with preserved ventricular function and volume-overloaded ventricles from valvar insufficiency showed a reduction in both LV volume overload as well as hypertrophy in the ACE inhibitor treated group over an average of 3 years of follow-up.

No safety or efficacy data regarding the use of ARB in children with HF are available. There is very limited experience with ARB therapy for pediatric patients with hypertension.

β adrenergic Blockers.

General Remarks. Initial compensatory mechanisms in the failing heart include activation of the sympathetic nervous system and increased levels of circulating catecholamines. In the long term the increased levels of
catecholamines, particularly norepinephrine, contribute to the progression of HF through multiple mechanisms, including myocardial fibrosis and apoptosis, peripheral vasoconstriction, and salt/water retention by the kidneys. The rationale for the use of adrenergic antagonists in HF is to antagonize the deleterious effects of sympathetic activation on the myocardium.

The risks associated with the use of beta-blockers include hypotension and worsening HF. Usually these symptoms occur in the first 48 hours after initiation of treatment or at the time of up-titration of the drug. Fluid retention may cause an increase in symptoms and adjustment in diuretic dosage may be needed. Bradycardia is seen with the use of beta-blockers, is usually asymptomatic, but may require dose reduction if there is associated hypotension. Beta-blockers are contraindicated in patients with severe bradycardia, sick sinus syndrome and second or third degree heart block, unless a pacemaker is in place. Beta-blockers are also contraindicated in patients with bronchial asthma and in patients with cardiogenic shock.

Clinical Data in Adult Patients. Metoprolol was the first beta-blocker studied in placebo-controlled trials in patients with HF. Early studies failed to show a statistically significant decrease in the risk of death or listing for transplantation. Eventually, in a trial involving 3991 patients with ischemic and non-ischemic cardiomyopathy and mild to moderate CHF, administration of metoprolol reduced mortality by 34%, which was statistically significant. In addition to metoprolol, carvedilol has been studied extensively in adult patients with HF resulting from left ventricular dysfunction. Several placebo-controlled trials have shown that carvedilol therapy decreases the risk of clinical progression of HF and decreases all-cause mortality. Of particular interest, the COPERNICUS study (Carvedilol Prospective Randomized Cumulative Survival Trial) evaluated the effects of carvedilol in 2289 patients with severe HF from either ischemic or non-ischemic cardiomyopathy. Patients treated with carvedilol had a 24% reduction in combined risk of death and hospitalization for any reason and a 35% reduction in mortality, showing that even these severely compromised patients benefited from carvedilol therapy.

Clinical Data in Pediatric Patients. The reported use of beta-blockers in children with HF is very limited, and no large placebo-controlled trials are available. In a multi-institutional experience Shaddy, et al. reviewed the results with metoprolol in 15 children with cardiomyopathy of different etiologies. Metoprolol was started at 0.2-0.4 mg/kg/day and slowly increased to a maximum dose of 1.1 mg/kg/day. There was no significant difference in ejection fraction on conventional therapy from the time of diagnosis to the time when metoprolol was started, but after a mean of 23 months on metoprolol there was a statistically significant and clinically important increase in ejection fraction from 27% to 41%.

The experience with carvedilol in pediatric patients with HF is similarly limited. Bruns, et al. reviewed the use of carvedilol in 46 infants and children with cardiomyopathy (80%) or congenital heart disease (20%) at 6 centers. Patients were on standard treatment with digoxin, diuretics, and ACE inhibitors for at least three months before the start of beta-blocker therapy. Carvedilol was initiated at an average dose of 0.08 mg/Kg/day and titrated to a mean maximum dose of 0.92 mg/kg/day. After 3 months of therapy, modified NYHA class improved in 67% of patients and worsened in 11%. Shortening fraction improved slightly, from 16.2% to 19.0%. Side effects, mainly dizziness, hypotension, and headache, occurred in 54% of patients and were well tolerated overall.

In a single center study Rusconi, et al. reviewed the results in 24 pediatric patients with dilated cardiomyopathy. Carvedilol was added to standard treatment at a mean of 14 months after the diagnosis of cardiomyopathy was made, with an average maximum dose of 1.0 mg/kg/day. Adverse effects occurred in 5 patients. The medication was tolerated in 22 patients. The mean left ventricular ejection fraction improved from 25% to 42% (p<0.001). The NYHA class improved in 15 patients, 1 patient died and 3 were transplanted. Lower doses of carvedilol may also be effective, as suggested by Azeka and colleagues. In this study of 22 children with DCM, improvement of both ejection fraction and clinical status was seen at 6 months with treatment dose of 0.2 mg/kg day of carvedilol, which was tolerated in all patients.

Therapeutic Recommendations: No structural Disease.

Recommendation 1: The underlying cause of new-onset ventricular dysfunction (HF Stages B, C or D) should be evaluated thoroughly in all patients. The evaluation may include metabolic and genetic evaluation in selected cases, as indicated by the available history and physical findings. Invasive assessment, including myocardial biopsy, may be considered in selected cases. In infants, particular care should be paid to the exclusion of coronary artery anomalies and other anatomic causes. (Level of Evidence C; Strength of Recommendation I)

Recommendation 2: Screening of first-degree relatives should be considered in patients with new-onset ventricular dysfunction due to DCM (HF Stages B, C or D). (Level of Evidence C; Strength of Recommendation I)

Recommendation 3: Patients with fluid retention
associated with ventricular dysfunction (HF stage C) should be treated with diuretics to achieve a euvolemic state using clinical criteria of fluid status and cardiac output. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 4:** Digoxin is not currently recommended for patients with asymptomatic forms of left ventricular dysfunction (HF Stage B) because this agent did not alter survival in large trials of adult patients with HF. (Level of Evidence C; Strength of Recommendation IIb)

**Recommendation 5:** Digoxin should be employed for patients with ventricular dysfunction, and symptoms of HF (HF Stage C), for the purpose of relieving symptoms. Lower doses of digoxin are preferred for this purpose. (Level of Evidence B; Strength of Recommendation I)

**Recommendation 6:** For the treatment of moderate or severe degrees of left ventricular dysfunction with or without symptoms (HF Stage B and C), ACE inhibitors should be routinely employed unless there is a specific contraindication. These medications should be started at low doses, and should be up-titrated to a maximum tolerated safe dose. Up titration may require a reduction in the dose of diuretics. (Level of Evidence B; Strength of Recommendation I)

**Recommendation 7:** For the treatment of decompensated left ventricular dysfunction (HF Stage D), the use of ACE inhibitors as initial therapy is not recommended. (Level of Evidence C; Strength of Recommendation IIb)

**Recommendation 8:** Patients who have an indication for ACE inhibitors therapy, but are intolerant of ACE inhibitors should be considered for ARB therapy. (Level of Evidence C; Strength of Recommendation IIA)

**Recommendation 9:** Given the limited information available concerning the efficacy and safety of β agonist receptor blockade in infants and children with HF, no recommendation is made concerning the use of this therapy for patients with left ventricular dysfunction (HF Stage B or C). If a decision is made to initiate β-blocker therapy, consultation or co-management with a heart failure or heart transplantation referral center may be desirable. (Level of Evidence B; Strength of Recommendation IIA)

**Recommendation 10:** Use of β-blocker therapy is not indicated for patients in HF Stage D. (Level of Evidence C; Strength of Recommendation IIb)

**Therapeutic Recommendations: Volume or Pressure Overload Conditions. Recommendation 11:** In all cases of HF associated with structural heart disease (HF Stage B, C or D), consideration should be given to surgical repair of significant lesions, as the long-term outlook may be more favorable than with medical management alone. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 12:** In pressure-induced left ventricular hypertrophy, with normal myocardial function, ACE inhibitors are not recommended in the absence of a non-cardiac indication such as hypertension. (Level of Evidence C; Strength of Recommendation III)

**Left Ventricular Diastolic Dysfunction**

**Overview.** Diastolic dysfunction is a syndrome characterized by impaired filling of one or both ventricles. Diastolic heart failure refers to a clinical syndrome of HF with preserved systolic function. Diastolic dysfunction is the sole or primary cause of HF in as many as 1/3 of adult patients with HF. No published estimates of the prevalence of diastolic dysfunction in the pediatric population are available.

There are 2 fundamental types of diastolic abnormality: impaired ventricular relaxation (affecting early diastole), and increased myocardial stiffness (affecting late diastolic filling). The hemodynamic consequences of diastolic dysfunction include increased ventricular filling pressures leading to elevation in atrial and venous pressures, and in the case of left ventricular dysfunction, leading also to an increase in pulmonary arterial pressure.

Conditions that cause diastolic dysfunction are varied and include pericardial as well as myocardial etiologies. Of note, patients with chronic diastolic dysfunction are at risk for sudden death, as well as for developing pulmonary hypertension, which further complicates treatment and limits survival.

**Pharmacotherapy.** There are no large-scale, randomized controlled trials of diastolic HF therapy in the adult or pediatric population.

**Diuretics.**

**Clinical Data.** Diuretics are the first line of therapy for diastolic dysfunction. Diuretics reduce pulmonary congestion and relieve symptoms such as orthopnea, cough and dyspnea. Injudicious or excessive use will reduce preload and result in diminished cardiac output.

**ACE Inhibitors and Angiotensin Receptor Blockers.**

**Clinical Data in Adult Patients.** Therapy with ACE inhibitors may benefit some forms of diastolic dysfunction as tissue ACE levels are increased in models of hypertrophy, and angiotensin II is known to induce myocyte hypertrophy as well as fibrosis. ACE inhibitors may be employed to obtain regression of left ventricular hypertrophy, reverse vascular hypertrophy and fibrosis, and improve endothelial function.
retically, ACE inhibitors and perhaps angiotensin receptor blockers may be a reasonable treatment option.\textsuperscript{70}

In the PRESERVE study, enalapril had moderately beneficial and statistically indistinguishable effects on regression of left ventricular hypertrophy compared with nifedipine.\textsuperscript{81} There are currently no mortality data to support the use of ACE inhibitors for patients with chronic HF and preserved ejection fraction in the absence of another indication for ACE inhibitors therapy (such as hypertension).

Limited experience in the adult population demonstrates improved exercise tolerance with ARB therapy in patients with diastolic dysfunction.\textsuperscript{82}

**Clinical Data in Pediatric Patients.** Captopril was deleterious in 1 small study with 4 pediatric patients with restrictive cardiomyopathy who demonstrated systemic hypotension without an improvement in cardiac output.\textsuperscript{41}

**Calcium Channel Blockers.**

**Clinical Data in Adult Patients.** Much of the literature regarding calcium channel blockers is in the elderly population and in patients with hypertrophic cardiomyopathy. There are no prospective randomized trials. Benefit may be achieved by cardiac slowing, prolonging filling time, and improving myocardial relaxation.\textsuperscript{73,79} Prolonged administration of calcium channel blockers may lead to regression of left ventricular hypertrophy.\textsuperscript{81} Calcium channel blockers may also directly improve ventricular relaxation or compliance, but there are few data to indicate that this is a clinically important effect.\textsuperscript{74}

When compared to enalapril, nifedipine had moderately beneficial and statistically indistinguishable effects on regression of left ventricular hypertrophy compared with nifedipine.\textsuperscript{81} Some patients may deteriorate after administration of calcium channel blockers; this is likely the result of a decrease in afterload.\textsuperscript{73}

**Clinical Data in Pediatric Patients.** There are no data on the use of calcium channel blockers for the treatment of diastolic dysfunction in children.

**β Blockers.**

**Clinical Data.** Use of β-blockers has been reported for diastolic dysfunction in elderly patients with hypertrophic cardiomyopathy but no prospective randomized study has been performed. The rationale for use includes reduced heart rate leading to a prolonged filling time and relief of cardiac ischemia.\textsuperscript{73,74} It is recognized that some patients deteriorate with institution of β blockade.\textsuperscript{73} β-blockers are proposed to directly improve diastolic dysfunction by augmenting ventricular relaxation or improving compliance, but there are few data to indicate that these agents exert a clinically important effect by this mechanism.

**Nitrates.**

**Clinical Data.** Nitric oxide or drugs that enhance NO release (sodium nitroprusside, nitroglycerin) improve diastolic dysfunction when administered locally to the coronary arteries.\textsuperscript{69,83} Systemic use of nitrates may result in decreased systemic venous preload, increased pulmonary venous filling, reduced systemic afterload, hypotension and clinical deterioration.\textsuperscript{73} Patients with chronic restrictive disease may have typical or atypical anginal pain, which may respond to nitrate therapy.

**Therapeutic Recommendations.**

**Recommendation 13:** Clinical management of diastolic dysfunction should address symptoms and attempt to address the underlying cause of the diastolic dysfunction, if known. This should include a careful evaluation for pericardial disease, and coronary insufficiency with attendant myocardial ischemia. Systemic hypertension, if present, should be controlled aggressively. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 14:** Fluid management to control symptoms remains a cornerstone in the management of symptomatic diastolic dysfunction (HF Stage C). Diuretics can be very useful to control symptoms but must be used cautiously as cardiac output depends on the elevated filling pressures. Renal function should be followed closely with care taken not to over-diurese a patient. Finally, sodium and fluid restriction may be helpful in controlling symptoms. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 15:** Patients with marked atrial dilatation due to diastolic dysfunction (HF stage B or C) have a propensity for the formation of thrombi and prophylactic anticoagulation may be considered in this setting. (Level of Evidence C; Strength of Recommendation Ia)

**Recommendation 16:** Atrial arrhythmias are not infrequent in patients with diastolic dysfunction due to atrial enlargement. However, atrial contribution to ventricular filling is particularly important for this group of patients (HF Stage B and C). Therefore, efforts should be made to maintain sinus rhythm by use of antiarrhythmic therapy and pacemaker therapy. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 17:** Asymptomatic diastolic dysfunction (HF Stage B) should be followed closely, but does not require pharmacotherapy. (Level of Evidence C; Strength of Recommendation IIa)

**Recommendation 18:** Treatment with agents which reduce afterload, such as ACE inhibitors, β
blockers, calcium channel blockers and nitrates, should be cautiously undertaken with close monitoring. Abrupt decreases in afterload in patients with restrictive or constrictive disease may be deleterious. (Level of Evidence C; Strength of Recommendation IIb)

**Recommendation 19**: Patients with diastolic dysfunction that is refractory to optimal medical/surgical management should be evaluated for heart transplantation as they are at high risk of developing secondary pulmonary hypertension, and of sudden death (HF Stage C). (Level of Evidence B; Strength of Recommendation I)

---

**The Systemic Right Ventricle**

**Overview.** The morphologic right ventricle (RV) is connected to the aorta and is thus the systemic ventricle in 2 main groups of patients with biventricular circulation: patients born with d-transposition of the great arteries who were treated with atrial baffle surgery (Mustard or Senning repair) and patients born with congenitally-corrected transposition of the great arteries. RV dysfunction has been described in both these groups of patients and may lead to HF. Although RV performance at rest is often normal, exercise ability is often limited in patients who have undergone atrial baffle surgery because of both chronotropic incompetence and limited stroke volume reserve.85-92

The mechanism of systemic right ventricular dysfunction is poorly understood. Various theories include: (a) a sub-optimal myocardial fiber arrangement and mechanics in the right ventricle, (b) adverse pattern and reduced heterogeneity of ventricular strain, (c) tricuspid insufficiency and, (d) myocardial fibrosis secondary to prolonged hypoxemia during infancy while awaiting atrial baffle surgery.93 Perfusion defects with associated wall motion abnormalities have been described using single photon emission computed tomography, suggesting a role for chronic subendocardial ischemia.

The clinical course in patients with congenitally-corrected transposition of the great arteries is often determined by associated structural (ventricular septal defect, pulmonary stenosis) or electrophysiologic abnormalities (AV block). Although there are reports of patients without such abnormalities whose right ventricles have continued to function normally well into adulthood, systemic RV dysfunction and HF occur with increasing prevalence with advancing age. By 45 years of age, 25% of patients without and 67% of patients with associated lesions have HF.97

There is a limited surgical experience with conversion of the atrial baffle to a systemic left ventricle (“double-switch”), with baffle takedown accompanied by arterial switch procedure. Early results indicate that surgery is feasible, but surgical risk may be substantial for this approach, and the long-term results are not known.98 A similar procedure has been performed in small numbers of patients with corrected transposition, although again, long-term outcomes are not yet defined.

**Pharmacotherapy.**

**Clinical Data.** Data specifically addressing the medical therapy of systemic right ventricular dysfunction are exceptionally scanty. Administration of ACE inhibitors to 14 survivors of the Mustard operation did not affect exercise tolerance or right ventricular ejection fraction.99 However, selected patients did show benefit. In the absence of more specific data, the management guidelines below are based on clinical experience and the effectiveness of these regimens in adult patients with systemic LV failure.

**Special Considerations.** Although β-blockers are now considered an important part of HF therapy in adult patients with cardiomyopathy, specific problems may be encountered in administration of these agents to patients with a systemic RV. These difficulties relate to the high prevalence of sinus node dysfunction in survivors of atrial baffle repair and AV node dysfunction in patients with congenitally corrected transposition of the great arteries. The administration of β-blockers in these patients may be particularly problematic, and may result in symptomatic bradycardia and exacerbation of HF.

**Therapeutic Recommendations.**

**Recommendation 20**: Patients with a right ventricle in the systemic position are at risk of developing systemic ventricular dysfunction (HF Stage A) and should undergo periodic evaluation of ventricular function. (Level of Evidence B; Strength of Recommendation I)

**Recommendation 21**: Patients with fluid retention associated with systemic right ventricular dysfunction (HF stage C) should be treated with diuretics to achieve a euvolemic state. In patients receiving chronic diuretic therapy, electrolyte balance and renal function should be evaluated periodically. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 22**: Digoxin should be employed for patients with symptomatic systemic RV dysfunction (HF Stage C), for the purpose of relieving symptoms. Digoxin is not currently recommended for patients with asymptomatic systemic right ventricular dysfunction (HF Stage B). (Level of Evidence C; Strength of Recommendation Ia)

**Recommendation 23**: For the treatment of asymptomatic systemic right ventricular dysfunction (HF Stage B), ACE inhibitors should be routinely employed unless there is a specific contraindication. These medications should be employed at standard doses. (Level of Evidence C; Strength of Recommendation Ia)
**Recommendation 24:** For the treatment of symptomatic systemic right ventricular dysfunction (HF Stage C), ACE inhibitors should be routinely employed, as above. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 25:** Patients who have an indication for ACE inhibitors therapy, but are intolerant of ACE inhibitors should be considered for ARB therapy. (Level of Evidence C; Strength of Recommendation IIa)

**Recommendation 26:** Consideration of surgical revision of the tricuspid valve should be given where both systemic right ventricular dysfunction and severe tricuspid valve regurgitation are present, particularly when the regurgitation is due to an intrinsic abnormality of the tricuspid valve (HF Stage B and C). (Level of Evidence C; Strength of Recommendation IIa)

**Recommendation 27:** Anatomic revision (“double-switch”) or cardiac transplantation should be considered for patients with advanced systemic right ventricular failure (HF Stage C) that is refractory to medical therapy. (Level of Evidence C; Strength of Recommendation IIa)

**CHRONIC HEART FAILURE IN THE UNIVENTRICULAR CIRCULATION**

**Overview**

For most patients with single ventricle anatomy, surgical management is the primary treatment path, and may include a variety of early palliative procedures followed by bi-directional Glenn (superior cavopulmonary connection, SCPC), and ultimately the Fontan procedure (total cavopulmonary connection, TCPC). Early palliation with complete mixing of systemic and pulmonary venous flow requires that ventricular output must be maintained at a level that is 2 to 3 times normal. This chronic volume overload places the myocardium at considerable risk. Ventricular anatomic type and the specifics of early management are important determinants of ventricular outcome after the SCPC or TCPC. In particular, patients with a prior aortopulmonary shunt typically have larger postoperative ventricular size than those with a prior pulmonary artery band. In some series, systemic left ventricles are more dilated than systemic right ventricles at the time of volume-unloading surgery, although other reports have found no difference in size or function between morphologically single right or left ventricles. The durability of the systemic right ventricle is in question, with reports suggesting this may or may not be a problem. In one series, early postoperative survival was better in patients with a morphologic left ventricle but by 6 months after completion of the Fontan procedure, ventricular morphology did not influence survival.

In patients who have completed the bi-directional Glenn or Fontan palliation, the manifestations of HF do not include the typical symptoms that occur in patients with 2 ventricles. After SCPC, TCPC, or Fontan palliation, systemic venous pressure is by necessity higher than pulmonary. These patients experience peripheral edema, pleural and pericardial effusions, cyanosis, and symptoms related to reduced cardiac output such as chronic fatigue, loss of appetite, and extreme exercise intolerance. These symptoms can clearly be related to factors other than myocardial dysfunction, many of which are common in this patient population. The basic physiology of the post-Fontan circulation is not intrinsically distinguishable from HF: activation of the renin-angiotensin system is usual if not universal, neurohumoral activation does not correlate with hemodynamic variables, and increased levels of catecholamines do not track well with severity of symptoms.

Reduction in exercise capacity may be helpful in making this distinction; however exercise performance in children with successful or optimal Fontan palliation may be quantitatively identical to that in children with mild HF. Reduced exercise capacity may in part be explained by diminished resting stroke volume and stroke volume reserve compared with normal hearts. The impact of reduced stroke volume in patients who have had the Fontan operation is compounded by chronotropic incompetence, with most series reporting maximum achieved heart rate to be about 75% of the age-predicted normal value, and in some series, though not all, peak heart rate correlates with the percent of predicted VO₂max that is achieved. Exercise-induced hypoxia may also be a limiting factor. Arterial saturation typically falls during exercise in Fontan patients and correlates with exercise capacity. The cause of the exercise-related hypoxia is not clear. Vital capacity and functional residual capacity are reduced, consistent with a restrictive pattern of pulmonary abnormality. Adult patients after Fontan have been reported to have sufficient restriction so as to manifest severely diminished maximum ventilation with secondary reduction in aerobic capacity.

The role of ventricular dysfunction and myocardial insufficiency in limiting exercise capacity in these patients remains unclear. This highlights the importance of identifying other potentially treatable sources of exercise intolerance before classifying the patient as having cardiogenic HF.

**Diagnostic Approach.** In patients who have previously undergone Fontan-type repair, thorough evaluation and management of circulatory insufficiency is essential. Significant systemic or pulmonary venous obstruction is unlikely to be tolerated. Valve regurgitation is common and may be progressive, causing persistent volume overload, and is associated with a poorer outcome.
Atrial arrhythmias increase in frequency with age and may be associated with tachycardia-induced ventricular dysfunction. Chronotropic incompetence may be more poorly tolerated than in other forms of heart disease. Residual right-to-left shunts may augment during exercise, severely limiting exercise capacity. In general, invasive hemodynamic investigation is needed both to document that myocardial dysfunction is primarily responsible and that other potentially treatable contributing factors are not present.

Pharmacotherapy.

Diuretics. Use of diuretics is common in the early post-operative period and in many instances becomes a permanent component of therapy, even in the absence of specific findings that clearly point to fluid overload. Peripheral edema, pleural and pericardial effusions, and other evidence of elevated systemic venous pressure occur frequently and often respond favorably to diuretics. However, the absence of a pulmonary pumping chamber renders the Fontan circulation particularly vulnerable to an inability to maintain an adequate systemic ventricular preload. Reduction of systemic venous pressure through diuresis reduces systemic ventricular preload in a more direct fashion than in patients with a biventricular circulation. Although the beneficial use of diuretics for HF invariably represents a balancing act with regard to maintenance of cardiac output, the margin of safety is far narrower in these patients and requires a greater degree of vigilance with regard to electrolyte disturbances, pre-renal azotemia, and exacerbation of exercise intolerance.

Digoxin. Digoxin is in common use for post-Fontan patients despite the absence of specific evidence of safety or benefit in this setting. There are no theoretical concerns that would make this population more or less likely to benefit from this agent than other groups with ventricular dysfunction.

ACE Inhibitors. In patients with single ventricles, activation of the RAAS contributes to the increased vascular resistance that typically occurs after the Fontan procedure, and a favorable response to ACE inhibitors or ARB might therefore be anticipated. However, in a study of Fontan patients who did not have HF, administration of enalapril for 6 weeks did not alter systemic resistance, resting cardiac index, or exercise capacity. Although these agents were well tolerated, and clinical experience confirms that ACE inhibitors can be safely administered to patients who have had the Fontan operation, the efficacy and risks of long-term ACE inhibitor therapy in this setting are not known.

β Blockers. The utility of β-blockers in patients after Fontan-type operations is unknown. Specific clinical data in this population are absent. There is a reasonable probability that β-blocker therapy may impair exercise tolerance in these patients because of the pervasive finding of chronotropic incompetence in post-Fontan patients and the generally adverse impact of β-blocker therapy on VO_{2,max}.

Therapeutic Recommendations. Recommendation 28: In patients with a univentricular circulation who undergo deterioration in clinical status (HF Stage B and C), consideration should be given to invasive assessment of hemodynamics, due to the heightened sensitivity of this group to elevations of filling pressure. (Level of Evidence C; Strength of Recommendation I)

Recommendation 29: A clinical decision as to the severity or presence of HF symptoms in patients with a univentricular circulation must include consideration of the patient's prior status and underlying anatomic defects. Longitudinal evaluation is of great importance in this regard. (Level of Evidence C; Strength of Recommendation I)

Recommendation 30: Maintenance of atrioventricular synchrony should be a priority in the management of patients with a univentricular circulation and HF (HF Stages B and C). (Level of Evidence C; Strength of Recommendation I)

Recommendation 31: Patients with fluid retention associated with systemic ventricular dysfunction in a univentricular circulation (HF stage C) should be treated with diuretics to achieve a euvolemic state. In patients receiving chronic diuretic therapy, electrolyte balance and renal function should be periodically evaluated. (Level of Evidence C; Strength of Recommendation I)

Recommendation 32: Digoxin should be employed for patients with systemic ventricular dysfunction in a univentricular circulation (HF Stage C), for the purpose of relieving symptoms. Digoxin is not currently recommended for patients with asymptomatic systemic ventricular dysfunction in a univentricular circulation (HF Stage B). (Level of Evidence C; Strength of Recommendation I)

Recommendation 33: For patients with a univentricular circulation after SCPC or TCPC, in whom systolic function is normal (HF Stage A), ACE inhibitors should not be employed routinely. (Level of Evidence C; Strength of Recommendation III)

Recommendation 34: For the treatment of asymptomatic systemic ventricular dysfunction in a univentricular circulation after SCPC or TCPC (HF Stage B), ACE inhibitors should be employed unless there is a specific contraindication. These medications should be...
employed at standard doses (Level of Evidence C; Strength of Recommendation IIa).

**Recommendation 35:** For the treatment of symptomatic systemic ventricular dysfunction in a univentricular circulation after SCPC or TCPC (HF Stage C), ACE inhibitors should be employed, as above. (Level of Evidence C; Strength of Recommendation IIa)

**Recommendation 36:** Use of β-blocker therapy is not routinely recommended for patients with systemic ventricular dysfunction in a univentricular circulation after SCPC or TCPC (HF Stage B and C). (Level of Evidence C; Strength of Recommendation IIb)

**ACUTE HEART FAILURE**

**Pharmacologic Support**

In adult studies, it has been recognized that inotropes may be required in the management of refractory acute HF exacerbations that are accompanied by hypoperfusion and hypotension. Currently available inotropic agents increase contractility through a common pathway of increasing intracellular levels of cyclic adenosine monophosphate (cAMP). Increased cytoplasmic levels of cAMP cause increased calcium release from the sarcoplasmic reticulum and increased contractile force generation by the contractile apparatus. Increases in cAMP occur by two different mechanisms: β-adrenergic-mediated stimulation (increased production) or phosphodiesterase III (PDE III) inhibition (decreased degradation).

The catecholamines are the most potent positive inotropic agents available; however, effects are not limited to inotropy. They also possess chronotropic properties and complex effects on vascular beds of the various organs of the body. Consequently, the choice of an agent may depend as much on the state of the circulation as it does on the myocardium.

Amrinone and milrinone belong to a class of nonglycoside, nonsympathomimetic inotropic agents (phosphodiesterase III inhibitors). Intravenous administration of amrinone or milrinone increases cardiac output and reduces cardiac filling pressures, pulmonary vascular resistance, and systemic vascular resistance with minimal effect on the heart rate and systemic blood pressure of adult patients. These drugs are particularly useful in the treatment of cardiogenic shock because they increase contractility and reduce afterload by peripheral vasodilatation without a consistent increase in myocardial oxygen consumption. Milrinone has been well studied in the pediatric population. A recently completed randomized, controlled trial demonstrated that milrinone infusion reduced the incidence of low cardiac output following cardiac surgery.

Both of these agents require careful bolus dosing prior to initiating an infusion – a rapid infusion of the bolus dose may cause hypotension. An alternative approach, which may be preferred in unstable patients, is to begin infusion without an initial bolus. Since both of these drugs have relatively long half-lives, they should be used cautiously in the presence of significant hypotension. However, recent data indicate that the half-life of milrinone may be shorter than originally extrapolated from adult data.

Nesiritide, a recombinant B-type natriuretic peptide, is the first new drug approved by the U.S. Food and Drug Administration in 14 years for the treatment of acutely decompensated HF in adults. Endogenous B-type natriuretic peptide is a cardiac hormone produced by the failing heart to counteract the maladaptive hemodynamic, neural, and hormonal compensations associated with the syndrome of CHF. Nesiritide is identical to the naturally occurring peptide, and like this peptide, Nesiritide reduces preload and afterload, leading to increases in cardiac index without reflex tachycardia or direct inotropic effect, increased diuresis and natriuresis, and suppression of the renin-angiotensin-aldosterone axis and sympathetic system. In a large randomized controlled clinical trial of 489 patients, nesiritide was found to be faster and more effective than IV nitroglycerin plus standard care at improving hemodynamic and symptomatology in patients with acutely decompensated CHF who have hypoxia at rest. Because of its unique mechanism of action and greater safety compared to both standard inotropic therapy with dobutamine and vasodilator therapy with nitroglycerin, the availability of nesiritide may alter the current algorithms for CHF management. However, no pediatric data are currently available.

Infants and children with low blood pressure and adequate cardiac function after cardiac surgery refractory to standard cardiopressors respond well to the pressor action of exogenous vasopressin and permit withdrawal or significant lowering of epinephrine dose. In a study of 11 children with vasodilatory shock after cardiac surgery, all 9 children with adequate cardiac function improved with vasopressin and survived; the 2 patients that received vasopressin in the setting of poor cardiac function died, despite transient improvement in blood pressure. Plasma vasopressin levels were decreased before treatment in 3 patients in whom blood levels were tested indicating that deficiency of the hormone may contribute to this hypotensive condition.

**Mechanical Support**

**Overview.** Mechanical circulatory support has become an important addition to the treatment armamentarium for the infant or child with acutely decompensated HF and low cardiac output unresponsive to pharmacologic maneuvers. Options for mechanical circulatory support include total heart-lung bypass (Extracorporeal Membrane Oxygenation [ECMO]), or more limited cardiac...
support with a left ventricular assist device (LVAD), right ventricular assist device (RVAD), or intra-aortic balloon pump (IABP). In pediatric patients, most experience has been with ECMO, primarily because size limitations have generally precluded extensive use of other modalities. However, with the development of smaller ventricular assist devices (primarily in Europe) and the adaptation of existing devices, mechanical ventricular assistance has been applied to infants as young as 5 days of age. The choice of modality in a given patient will depend on the specific pathophysiology of HF in that patient, on the availability of support devices and on the expertise of the child’s physicians.

**Risks and Benefits.** Mechanical assist in children can be life saving in low cardiac output situations where there is a reversible underlying abnormality that would benefit from short-term cardiac support. Mechanical support maintains end-organ function and reduces myocardial oxygen requirements during a critical period of recovery from a cardiac insult. Preliminary evidence indicates that cardiac remodeling, on both a structural and molecular level, occurs during mechanical support. Studies with small number of patients have demonstrated rates of survival to hospital discharge ranging from 25 to 65%. Ibrahim and colleagues reviewed a 10-year experience in 96 cardiac patients requiring ECMO (67 patients) or ventricular assist devices (29 patients). Of these patients, 40% and 41%, respectively, survived to hospital discharge. The use of mechanical support in patients with single ventricle physiology has been associated in some studies with a poorer outcome, although recent data from Jaggers et al. and others support the use of ECMO after Norwood palliation. Overall hospital survival in the 35 patients in that series was 61%. Mechanical assist can also be used a bridge to transplant when cardiac recovery is not expected. In this case, mechanical support extends the period over which a patient can wait for a donor organ. End-organ function may be preserved, or perturbations in function may reverse with improved perfusion, thus improving transplant suitability and outcome.

**Therapeutic Recommendations.** Recommendation 37: Institution of mechanical cardiac support should be considered in patients with or without structural congenital heart disease, who have acute decompensation of end-stage HF, primarily as a bridge to cardiac transplantation (HF Stage D). (Level of Evidence B; Strength of Recommendation I)

**Recommendation 38:** Institution of mechanical cardiac support should be considered in patients with or without structural congenital heart disease, who have acute decompensation of end-stage HF, primarily as a bridge to cardiac transplantation (HF Stage D). (Level of Evidence B; Strength of Recommendation I)

**Recommendation 39:** 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 (HF Stage D). However, the outcomes in this group are less satisfactory than for other indications for mechanical support. (Level of Evidence B; Strength of Recommendation IIa)

**Recommendation 40:** Mechanical cardiac support is not indicated in those cases in which there is evidence of a severe and irreversible defect (e.g. catastrophic intracranial hemorrhage, or advanced multisystem organ failure). However, in practice, the determination of the severity and/or irreversibility of the associated condition may be difficult to determine, so the decision concerning eligibility for mechanical support is a difficult clinical judgment. (Level of Evidence C; Strength of Recommendation IIb)

**ELECTROPHYSIOLOGY CONSIDERATIONS**

**Overview**

Arrhythmia is a major cause of morbidity and mortality in pediatric patients with end-stage HF. Myocardial scars and stretching associated with pressure or volume overload, previous heart surgery or intrinsic myocardial disease provide a ripe substrate for arrhythmogenesis. Multiple triggers for arrhythmia are prevalent in patients with HF and include electrolyte imbalance, blood gas and pH abnormalities, ischemia and administration of potentially pro-arrhythmic drugs such as digoxin, positive inotropes, phosphodiesterase inhibitors and anti-arrhythmic drugs themselves. Although it is controversial whether ventricular arrhythmias are independent risk factors for sudden death in this population, sustained tachycardia may cause hemodynamic collapse, and complex non-sustained ventricular ectopy reflects potential electrical instability of the myocardium. Atrial arrhythmias may also impair cardiac output and aggravate HF by eliminating the atrial contribution to filling and/or causing a rapid ventricular response.

In patients with dilated cardiomyopathy, between 50 and 63% of those patients who die have ventricular arrhythmias at presentation. In pediatric patients awaiting transplantation, 62% had life-threatening arrhythmias, most commonly ventricular tachycardia.
Arrhythmia management is an important component in the overall care of the pediatric patient with HF.

Treatment can be broken down into the management of acute arrhythmias causing hemodynamic collapse and chronic arrhythmias requiring long-term suppression because they lead to impaired cardiac performance or may pose a significant risk factor for sudden death.

**Pharmacotherapy**

**Acute Arrhythmia Management.** Arrhythmias likely to require acute treatment in patients with HF include atrial tachyarrhythmias with a rapid ventricular rate, paroxysmal supraventricular tachycardia, junctional ectopic tachycardia and sustained ventricular tachycardia. Synchronized DC cardioversion/defibrillation should be considered for treatment of either supraventricular or ventricular arrhythmias if hemodynamic collapse is imminent.167,168

Atrial tachycardia, flutter or fibrillation can be initially managed by controlling the ventricular rate with AV nodal blocking agents. For rate control, digoxin is not likely to be useful primarily because of its delayed onset of action. Intravenous diltiazem is a reasonable first choice, but hypotension is a major concern in a setting of impaired ventricular function. An intravenous β-blocker, such as esmolol can be useful in decreasing the ventricular rate but hypotension is likely to preclude its use.

The treatment of the atrial rhythm itself includes intravenous amiodarone, procainamide or ibutilide. However, side effects such as hypotension and torsade de pointes occur frequently and elective cardioversion is often preferable. There is very little experience using IV ibutilide for the acute conversion of atrial flutter or fibrillation in pediatric patients with significant myocardial dysfunction. Paroxysmal supraventricular tachycardia is best treated with intravenous adenosine, but a longer acting agent such as procainamide or amiodarone may be necessary for control of recurrent episodes.

Junctional ectopic tachycardia responds best to IV amiodarone and to minimizing the dose of any intravenous inotropes or phosphodiesterase inhibitors. The pharmacologic treatments for ventricular tachycardia, include intravenous lidocaine, amiodarone and procainamide.169,170 Lidocaine is the first line drug because of its rapid onset of action and limited toxicity if drug levels are kept in the therapeutic range. If this is unsuccessful, either intravenous amiodarone or procainamide can be utilized, but amiodarone is preferable because of a lower incidence of hypotension and tendency for arrhythmia aggravation.

**Chronic Arrhythmia Management.** Chronic drug suppression of arrhythmias in patients with HF can be very problematic. For atrial arrhythmias, many drugs have been shown to have a modest success rate including those in the category of IA, IC and III. However, amiodarone stands out as the most appropriate drug because of its somewhat higher success rate and lesser tendency for pro-arrhythmia.171,172 For ventricular tachycardias, the superiority of amiodarone over the other drugs is even more evident. This medication is usually well tolerated, even in patients with very poor contractility. The major limiting factor in the short-term is bradycardia and hypotension, while longer use requires monitoring for thyroid and liver dysfunction as well as pulmonary interstitial disease.

As an alternative to pharmacotherapy in the setting of chronic atrial arrhythmias, ablation therapy can be considered. The safety of radiofrequency or surgical ablation is well established, and there are significant data attesting to its efficacy.172–174 Triedman and colleagues report a 73% procedural success rate for radiofrequency ablation, with approximately 50% success at 1 year, for a mixed population including Fontan and Mustard patients.172 In a population of Fontan patients, short-term control of atrial tachycardia was achieved in 14/15 patients using a modified RA maze intraoperatively, with no recurrences after 43 months of follow-up.175

**Therapeutic Recommendations.**

**Recommendation 41:** In patients with significant arrhythmias in the setting of HF associated with structural heart disease (HF Stages B, C or D), consideration should be given to surgical repair of important uncorrected or residual defects, as this is likely to be essential to achieve adequate rhythm control. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 42:** In patients with significant arrhythmias in the setting of HF associated with structural heart disease (HF Stages B, C or D), consideration should be given to improving or optimizing the medical treatment for HF and correcting aggravating factors such as electrolyte abnormalities, as this is likely to be a key determinant of the successful control of arrhythmias. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 43:** In patients with significant arrhythmias in the setting of HF associated with structural heart disease (HF Stages B, C or D), maintenance of atrio-ventricular synchrony is of great importance in optimizing hemodynamics, and management of intratrial arrhythmias should be oriented towards restoration of sinus rhythm rather than on ventricular rate control alone. (Level of Evidence C; Strength of Recommendation I)

**Recommendation 44:** In patients with impaired ventricular function (HF Stages B, C or D), many forms
of tachycardia can precipitate acute hemodynamic collapse, and many of the available pharmacotherapies can precipitate hypotension. Therefore, consideration should be given to early utilization of electrical cardioversion/defibrillation for treatment of both atrial and ventricular tachycardias. (Level of Evidence C; Strength of Recommendation IIa)

Recommendation 45: For acute treatment of clinically significant junctional ectopic tachycardia, the first line of therapy should usually be amiodarone because of its superior efficacy as compared to alternative medications. (Level of Evidence C; Strength of Recommendation IIa)

Recommendation 46: For chronic suppression of atrial arrhythmias in children with HF (HF Stages B, C or D), the first line of therapy should usually be amiodarone because of its superior efficacy as compared to alternative medications. (Level of Evidence C; Strength of Recommendation IIa)

Recommendation 47: Patients with potentially significant atrioventricular tachycardias who are scheduled to undergo completion of the Fontan procedure, should be considered for definitive ablation therapy, prior to the Fontan surgery, to reduce the risk of serious arrhythmia during the postoperative period and beyond. Ablation, in these circumstances, might be accomplished by transcatheter technique or by intraoperative Maze procedure. (Level of Evidence C; Strength of Recommendation IIa)

Device Therapy.

Pediatric ICD and Resynchronization Experience. The development of the ICD has improved survival in the adult HF population. Recent multicenter trials in adult HF patients have shown that ICD therapy is more beneficial than antiarrhythmics in both ischemic and idiopathic cardiomyopathies. Data from Bocker and colleagues suggest that ICD therapy prolongs life in NYHA classes I–III, with greatest initial benefit in class II and III but longest benefit in class I. However, no multicenter prospective trials of ICD therapy in children with any heart disease have been performed.

In a study of the use of defibrillator therapy in adult patients awaiting cardiac transplant, 71% received appropriate discharge with no inappropriate discharges. In a multicenter retrospective review of ICD therapy in pediatric patients awaiting heart transplantation, 45% of the patients had appropriate discharges with an inappropriate discharge rate of 27%. Freedom from appropriate discharge at 100 days was 63%. This may be due to the higher rate of complications and the technical difficulties associated with placing ICD in the pediatric population. Berul and colleagues found a significantly higher complication and infection rate when comparing a pediatric group of ICD recipients to an adult group. However, this issue may be diminishing with the development of newer leadless ICD systems for smaller children.

In adult patients with HF associated with LV dysfunction and left bundle branch block, LV resynchronization has proven valuable in improving hemodynamics and clinical status, which is thought to be the result of improved mechanical efficiency within the left ventricle. This therapy has not been validated in children, but Dubin and colleagues have shown that resynchronization of the right ventricle in patients with right ventricular dysfunction can produce favorable hemodynamic changes in an acute setting. In addition, Janousek et al have shown improved blood pressure in patients with acute heart failure following repair of congenital heart disease, by combining atrioventricular optimization with ventricular resynchronization of the right ventricle. While these results are intriguing, their implications are not yet clear.

Special Considerations in Structural Heart Disease. Patients with structural heart disease offer unique challenges in arrhythmia management that may not need to be considered when treating the patient with dilated cardiomyopathy alone. The negative inotropic properties of anti-arrhythmic therapy may be accentuated in patients with congenital heart disease such as those with single ventricle physiology, multiple ventricular scars, or significant dysfunction of either the atrioventricular or semilunar valves. A second area of concern is that patients with significant ventricular dysfunction may require an elevated heart rate to help maintain an adequate cardiac output. Antiarrhythmic medications may lead to a relative bradycardia, and impair cardiac output. This is compounded in patients with congenital heart disease who have underlying sinus or atrioventricular node dysfunction.

There are also issues encountered with the use of device therapy in patients with congenital heart disease that are not seen in those with structurally normal hearts. The use of transvenous pacing and defibrillator leads is impossible in some forms of palliated congenital heart disease. Patients who have undergone superior vena cava to pulmonary artery anastomosis have no access to the heart from above. In patients who have undergone a Fontan procedure there is typically no direct venous access to the heart. Transvenous pacing and defibrillator leads are contraindicated in patients with residual right to left shunting such as seen in Eisenmenger’s syndrome. The inability to use transvenous systems in these patients necessitates the place-
ment of epicardial systems with their risks of morbidity and mortality in a hemodynamically compromised patient.

Although ventricular arrhythmias are the most worrisome type of arrhythmias seen in patients with HF, supraventricular arrhythmias also can lead to significant hemodynamic compromise. Patients with significant myocardial dysfunction will be compromised with relatively modest increases in their heart rates and are at risk for the rhythm to degenerate into a life threatening arrhythmia. In a study by Rosenthal et al. of 96 patients listed for cardiac transplantation, 2 of 5 patients with VT only 1 had congenital heart disease.166 Atrial tachyarrhythmias are frequently seen in patients with congenital heart disease that have had atrial level surgery such as Fontan, Senning, or Mustard procedures.

Ventricular arrhythmias are common in patients with HF. It is well known that patients who have undergone surgery for congenital heart disease will often develop ventricular arrhythmias from scars and suture lines in the heart. Although there would seem to be an increased prevalence of these arrhythmias in patients with congenital heart disease and HF, Rosenthal and colleagues found that of 8 pre-transplant patients with VT only 1 had congenital heart disease.166 In the same study one patient with congenital heart disease developed VF.

Therapeutic Recommendations. Recommendation 48: At this time, clinical criteria for ICD placement in children are in flux and are not well defined. ICD placement may be considered as a bridge to cardiac transplantation in selected patients with advanced HF (HF Stage C and D), on a case-by-case basis. (Level of Evidence C; Strength of Recommendation IIa)

Recommendation 49: In patients with structural heart disease, particularly including those with a univentricular circulation, pacemaker implantation should be considered as possible adjunctive therapy, to maintain atrioventricular synchrony and chronotropic competence, and to permit administration of other pharmacotherapies that are needed for treatment of HF. (Level of Evidence C; Strength of Recommendation IIa)

REFERENCES

3. Heart Failure Society of America (HFSA) practice guidelines. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunc-


81. Devereux RB, Palmieri V, Sharpe N, et al. Effects of once-daily angiotensin-converting enzyme inhibition and...
calcium channel blockade-based antihypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension: the prospective randomized enalapril study evaluating regression of ventricular enlargement (preserve) trial. Circulation 2001;104:1248-54.


84. Redington AN, Rigby ML, Shinebourne EA, Oldershaw PJ. Changes in the pressure-volume relation of the right ventricle when its loading conditions are modified. Br Heart J 1990;63:45–9.


143. Williams MR, Quagebeur JM, Hsu DT, Addonizio LJ, Kichuk MR, Oz MC. Biventricular assist device as a


