Carvedilol in Children With Cardiomyopathy: 3-Year Experience at a Single Institution

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Background: Carvedilol reduces mortality and hospitalization in adults with congestive heart failure. Limited information is available about its use in children.

Methods: We reviewed the medical records of 24 children with dilated cardiomyopathy and left ventricular ejection fraction of $\leq 40\%$, who were treated with carvedilol as adjunct therapy to angiotensin-converting enzyme inhibitors, digoxin and diuretics.

Results: Carvedilol was initiated 14.3 ± 23.3 (mean $\pm$ SD) months after the diagnosis of cardiomyopathy. Mean age at initiation of therapy was 7.2 ± 6.4 years. The mean initial and maximum doses were 0.15 ± 0.09 and 0.98 ± 0.26 mg/kg/day. Adverse effects occurred in 5 patients (21%). Two patients (8%) required discontinuation of the drug within 5 weeks of the initial dose. The remaining 22 patients tolerated carvedilol for a mean follow-up period of 26.6 ± 14.7 months. Among these 22 patients, mean left ventricular ejection fraction improved from $24.6 \pm 7.6\%$ to $42.2 \pm 14.2\%$ ($p < 0.001$), and mean sphericity index from 0.86 ± 0.11 to 0.74 ± 0.10 ($p < 0.001$). New York Heart Association functional class improved in 15 patients (68%). One patient (4%) died and 3 (14%) were transplanted.

Conclusions: Carvedilol, in addition to standard therapy for dilated cardiomyopathy in children improves cardiac function and symptoms; it is well tolerated, with minimal adverse effects, but close monitoring is necessary as it might worsen congestive heart failure and precipitate asthma. Control studies are necessary to assess the effect of carvedilol on mortality and hospitalization rates.

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Cardiomyopathy (CMP), which accounts for only 1% of patients with pediatric cardiac disease,¹ remains a major cause of morbidity and mortality. The outcome of medical treatment for children with severe heart failure is variable. Patients with severely impaired systolic function for 1 to 3 months have the highest mortality, 54% at 1 year, despite the use of standard therapy with diuretics, digoxin and angiotensin-converting enzyme (ACE) inhibitors.^{2,3} The overall mortality in patients with dilated CMP has been reported to be as high as $\geq 50\%$.^{4,5} Although complete recovery of left ventricular function is possible in children with dilated CMP, it

may take >1 year.⁶ For children with severe, persistent cardiac dysfunction the only hope for survival remains cardiac transplantation. Unfortunately, approximately 20% of patients listed for heart transplantation die while waiting for a new heart.⁷

More aggressive pharmacologic treatments for severe heart failure in children are needed to arrest the progression of the disease, prevent or reverse remodeling of the myocardium, and improve the patient's clinical and functional condition. Recent studies^{8–10} in adult patients have suggested that sympathetic activation plays an important role in the genesis and progression of heart failure. This, combined with the results of several clinical trials,^{11–16} has led to the addition of β -sympathetic antagonists to the armamentarium of pharmacologic treatments for heart failure in adults. Carvedilol is a third generation non-selective β -antagonist with α_1 -adrenergic blocking and anti-oxidant activity.^{17–21} When combined with diuretics, digoxin and ACE inhibitors, carvedilol has been shown to be effective in decreasing hospitalization rates and improving survival in adults with congestive heart failure (CHF).^{8,10,11} The efficacy and safety of carvedilol in pediatric patients with CHF due to either dilated CMP or end-stage congenital heart defects has not been fully established. The purpose of this study is to report our

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experience using carvedilol in managing children with dilated CMP, and to evaluate its dosing, safety and efficacy.

METHODS

A systematic approach for the treatment of dilated CMP was established at our institution in 1998. Since then, patients with left ventricular ejection fraction (LVEF) $\leq 40\%$ have been referred to our pediatric heart failure program where a single designated physician evaluates and follows the referred children. At each follow-up visit, symptoms, level of physical activity, growth and development are assessed and documented. Pharmacologic treatment with digoxin, ACE inhibitors and diuretics are optimized, along with the child's nutritional status. Carvedilol is initiated in patients who, despite optimization of standard treatment, have persistent LVEF $\leq 40\%$. Patients with acute CHF, second or third degree heart block and history of long-term therapy for asthma are not eligible for treatment with carvedilol. Carvedilol is initiated at a low dose (extrapolated from adult initial doses) with in-hospital monitoring of heart rate and blood pressure for at least 12 hours. The dose is then increased by 50% to 100% every 1 to 2 weeks in an ambulatory setting with monitoring of blood pressure for 2 hours after each change in dose. Target dose is 1.0 mg/kg/day (extrapolated from adult maximum doses). Routine echocardiograms are performed periodically to assess LVEF measured using a biplane method.²² Left ventricular geometry is assessed measuring the sphericity index (SI), calculated as the ratio between the left ventricular transverse and longitudinal diameter in diastole.

From March 1998 to December 2001, 41 patients were referred to the pediatric heart failure program at the University of Miami/Jackson Memorial Hospital. Carvedilol was initiated as adjuvant treatment in 34 patients: 24 had dilated CMP; 7 had congenital heart disease; and 3 had CMP associated with muscular dystrophy. After obtaining approval from the institutional review board of our institution, we reviewed the hospital charts of the 24 patients with dilated CMP treated with carvedilol. Data collected included: age at diagnosis; therapy prior to carvedilol; time period between diagnosis and initiation of carvedilol; age, weight and symptoms at carvedilol initiation and last follow-up; time, dosage and number of increments required to reach the maximum dose; and adverse effects of the drug. Modified New York Heart Association (NYHA) class was assigned retrospectively according to the Bruns classification (Table 1).²³ LVEF was assessed at diagnosis, and at pre- and post-carvedilol. Changes in LVEF were also analyzed: Pre-carvedilol values refer to values obtained before initiation of carvedilol, whereas post-carvedilol values refer to those obtained at the last

Table 1. New York Heart Association Class Modified for Use in Children^a

Class I	Cardiac disease with no limitation of physical activity. School-age child takes gym class and keeps up with peers.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary activity can cause fatigue, palpitations or dyspnea. School-age child takes gym class but does not keep up with peers. Secondary growth failure is likely.
Class III	Marked or severe limitation of physical activity. Less than ordinary activity, such as walking <1 block, can cause fatigue, palpitations or dyspnea. School-age child is unable to take gym class. Secondary growth failure is likely.
Class IV	Unable to perform any physical activity without discomfort. Symptoms are present at rest and increase with any activity. Secondary growth failure is likely.

^aFrom Bruns et al.²³

follow-up visit (just before surgery for the patients who had heart transplant). Intermediate measurements of LVEF were available for patients who were on carvedilol for at least 9 months. SI values and changes pre- and post-carvedilol were also analyzed.

Statistical Methods

Statistical methods included descriptive statistics and calculation of 95% confidence intervals. Changes from pre- to post-carvedilol were assessed using paired *t*-tests for continuous variables, when the differences were approximately normally distributed, and by using Wilcoxon rank tests for differences with skewed distributions. Changes in binary variables were assessed using McNemar's test. For patients with multiple EF and SI measurements, growth curve analysis techniques were used to ascertain trends over time. *p* < 0.05 was considered statistically significant.

RESULTS

Study Population

The study population consisted of 24 pediatric patients, 12 girls and 12 boys, and included 15 children who had been referred for cardiac transplant evaluation. Age at diagnosis ranged from 1 day to 16.5 years, with a mean ($\pm$ SD) of 6.0 ± 6.3 (median 3.0) years.

All patients had idiopathic dilated cardiomyopathy and LVEF $\leq 40\%$; in 16 patients (67%) LVEF was $< 30\%$. Carvedilol was added as adjunct therapy to digoxin, ACE inhibitors and diuretics. After carvedilol initiation, all patients remained on their standard therapy, except for 1 in whom enalapril was discontinued because of a severe allergic reaction.

Table 2. Frequency Distribution of Age and Weight at Initiation of Carvedilol for 24 Children with Cardiomyopathy

Characteristic	Patients (N)	%
Age (years)		
0–0.9	7	29
1–4.9	3	12.5
5–9.9	5	21
10–14.9	6	25
15–18	3	12.5
Weight (kg)		
5–10	10	42
11–20	3	12
20–40	5	21
>40	6	25

Carvedilol was initiated at a mean of 14.3 ± 23.3 months after the diagnosis of CMP (range 0.1 to 83.1, median 5.4 months). The mean age at the initiation of carvedilol was 7.2 ± 6.4 years (range 0.25 to 18.1, median 6.4 years) with 11 of the 24 patients <18 months of age. The pre-carvedilol mean weight was 28.9 ± 30.1 kg (range 5.3 to 136.0, median 16.1 kg). The age-gender-specific percentile for weight pre-carvedilol ranged from the 3rd to the 95th percentile (mean 30.9 ± 32.7 , median 18.8). Nine patients (38%) had a weight at or below the 5th percentile for age. The frequency distributions of age and weight of the study participants at the initiation of carvedilol treatment are shown in Table 2.

Carvedilol Dosing and Safety

The mean initial carvedilol dose was 0.15 ± 0.09 mg/kg/day (range 0.04 to 0.36, median 0.13 mg/kg/day) in 2 divided doses. For those patients requiring doses less than the smallest available dose strength (3.125 mg), carvedilol tablets were diluted in water to make a solution of 1 mg/ml. The dose was then increased to a mean maximum dose of 0.98 ± 0.26 mg/kg/day (range 0.6 to 1.8, median 0.96 mg/kg/day). The median time to reach the maximum dose was 14 weeks (range 3.3 to 45 weeks), with a mean of 4 increments.

Adverse Effects

Adverse effects occurred in 5 (21%) of the 24 patients initiated on carvedilol treatment (Table 3). One patient with a medical history of sporadic asthma (not requiring long-term treatment) had 2 episodes of asthma necessitating hospitalization and temporary discontinuation of the drug. The drug was resumed at a lower dose with no further asthma recurrences. This same patient experienced transient bradycardia (heart rate between 50 and 69 bpm), first-degree heart block with a PR interval of 360 milliseconds, and occasional Mobitz Type I second-degree heart block. Two patients experienced dizziness: 1 with emesis and headache that required a

Table 3. Frequency Distribution of Adverse Effects Among 24 Children Initiated on Carvedilol

Adverse effects	Patients (N)	%
None	19	79
Worsening congestive heart failure	1	4
Reactive airway disease ^a	2	8
Hypotension ^{b,c}	2	8
Bradycardia ^a	1	4
Emesis ^c	1	4
Headache ^c	1	4
Mobitz Type I heart block ^a	1	4
Dizziness ^{b,c}	2	8

^aThe same patient had reactive airway disease, bradycardia and Mobitz Type I.

^bThe same patient had hypotension and dizziness.

^cThe same patient had emesis, headache, dizziness and hypotension.

decrease in the carvedilol dosage. Both of these patients tolerated carvedilol, but required slower titration to the maximum dose.

Discontinuation of carvedilol therapy was necessary in 2 patients, 1 as a result of asthma and the other secondary to worsening CHF. In these 2 patients, drug discontinuation occurred within 5 weeks of initiation of therapy, thereby excluding them from assessment of changes in clinical status and indexes of cardiac function.

Carvedilol Efficacy

In the 22 patients who tolerated carvedilol no significant changes in mean LVEF were seen from the time of diagnosis to initiation of carvedilol (pre-carvedilol) despite maximization of standard medical treatment, with a mean change of $2.2 \pm 11\%$ ($p = 0.5$ non-significant). However, mean LVEF increased significantly from $24.6 \pm 7.6\%$ before carvedilol initiation to $42.2 \pm 14.2\%$ at the latest follow-up, with a mean increase of $17.6 \pm 11.1\%$ (95% confidence interval [CI] 12.6% to 22.5%, $p < 0.001$).

Mean SI decreased significantly from 0.86 ± 0.11 before carvedilol to 0.74 ± 0.10 at the last follow-up, with a mean change of -0.12 ± 0.12 (95% CI -0.17 to -0.07 , $p < 0.001$).

Group Analysis

Patients with CMP may show spontaneous improvement in systolic function, especially in the first few months after diagnosis.²⁴ To differentiate those patients with spontaneous improvement in LVEF and SI from those whose improvement could be attributed to carvedilol, the 18 patients who survived without a heart transplant were divided into 3 groups according to the time period from diagnosis to initiation of carvedilol. Changes in LVEF from diagnosis to pre-carvedilol as well as changes in LVEF and SI from pre-carvedilol to post-carvedilol are shown in Table 4. The time periods

Table 4. Changes in Ejection Fraction and Sphericity Index by Length of Time from Diagnosis to Initiation of Carvedilol in the 18 Patients who Survived without a Heart Transplant

Time from Diagnosis to Carvedilol Initiation	N	Change in EF from Diagnosis to Carvedilol Initiation	p-value	Change in EF Pre- and Post-Carvedilol	p-value	Change in SI Pre- and Post-Carvedilol	p-value
0–2.9	6	4.5 ± 4.5 [–0.3, 9.3]	0.060	29.7 ± 5.4 [24.0, 35.4]	<0.001	–0.16 ± 0.14 [–0.31, –0.01]	0.038
3–5.9	5	4.8 ± 17.0 [–16.4, 26.0]	0.563	17.4 ± 11.0 [3.8, 31.1]	0.024	–0.15 ± 0.08 [–0.28, –0.01]	0.039
≥6	7	–2.3 ± 8.6 [–11.4, 6.7]	0.538	15.7 ± 5.5 [10.7, 20.8]	<0.001	–0.15 ± 0.12 [–0.26, –0.04]	0.017
Total	18	2.2 ± 10.7 [–3.3, 7.7]	0.414	20.8 ± 9.5 [16.1, 25.5]	<0.001	–0.15 ± 0.11 [–0.21, –0.09]	<0.001

Data expressed as mean ± SD [CI].

CI, confidence interval; EF, ejection fraction; N, number of patients; SI, sphericity index.

were 0 to 2.9, 3.0 to 5.9 and ≥6 months. None of the groups showed statistically significant changes in EF from diagnosis to initiation of carvedilol despite being on standard medical treatment. Statistically significant changes in EF and SI from initiation of carvedilol to final measurement were noted for each of the groups (Table 4 and Figure 1). The overlapping of the 95% CIs corresponding to each group indicates that changes in LVEF and SI are not associated with the length of time on standard treatment.

The largest improvement in LVEF (30 units) occurred in those patients who were initiated on carvedilol within 3 months of diagnosis. Patients who were on standard treatment for >6 months before initiating carvedilol also showed significant improvement (Figure 1).

Five patients reached a 50% LVEF within 6 months after reaching the maximum dose of carvedilol.

In 1 patient, discontinuation of carvedilol on 2 separate occasions was associated with a subsequent fall in LVEF.

Figure 1. Left ventricular ejection fraction (LVEF) in the 18 pediatric patients surviving without a heart transplant. Patients were divided into 3 groups according to length of time (in months) on standard treatment before initiation of carvedilol. The 4 points on each curve represent: LVEF at time of diagnosis (negative value); initiation of carvedilol (time 0); LVEF at a mean of 5 months after reaching maximum dose of carvedilol; and LVEF at last follow up, respectively.

Clinical Improvement

Clinical improvement was assessed by the change in age-gender-specific weight percentile (Table 5) and NYHA classification pre- and post-carvedilol (Table 6). Pre- and post-carvedilol values for age-gender-specific weight percentile are shown by patient's final status: deceased, transplanted, and alive without a transplant. Of the 18 patients with no cardiac transplant, 6 had a weight at or below the 5th percentile pre-carvedilol. Post-carvedilol, 4 of these patients improved to the 25th percentile or above. All patients with unfavorable outcome (death or cardiac transplant) were initially at or below the 25th age-gender-specific percentile for weight (Table 5).

NYHA class improvement occurred in 15 (68%) of the 22 patients: 9 improved by ≥2 classes, and 6 improved by 1 class. NYHA class remained unchanged in 7 patients, including 3 patients who remained in Class I (Table 6).

Patient Outcome

The overall mean follow-up period for the 22 patients who tolerated carvedilol was 26.6 ± 14.7 months (range 2.5 to 47.8, median 27.9 months). During the follow-up period, 1 patient died of ventricular tachycardia while awaiting cardiac transplant, and 3 patients underwent cardiac transplantation. These 3 patients were already on the transplant list before initiating carvedilol and they did not show improvement in systolic function while on carvedilol. NYHA class improved in only 1 patient, from Class IV to Class III; however, because of this patient's recurrent ventricular tachycardia and pulmonary hypertension, a transplant was necessary. The mean follow-up for surviving patients without a transplant was 30.4 ± 13 months.

DISCUSSION

One of the most deleterious effects of congestive heart failure is activation of the sympathetic system.²⁵ Stimulation of β1-receptors by catecholamines leads to in-

Table 5. Pre- and Post-Carvedilol Age–Gender-Specific Weight Percentiles by Patient's Final Status

Alive, No Cardiac Transplant			Cardiac Transplant			Deceased		
N	Pre	Post	N	Pre	Post	N	Pre	Post
1	3	3	1	5	5	1	3	3
3	3	25	1	17.5	37.5			
1	4	10	1	25	5			
1	5	75						
1	6	50						
1	10	75						
1	20	30						
1	25	95						
1	37.5	37.5						
7	≥50	≥50						

N, number of patients.

creases in heart rate and contractility.²⁶ Stimulation of α 1-receptors causes peripheral and coronary vasoconstriction,²⁷ increases oxygen consumption of the myocardium by increasing the afterload,²⁵ and contributes to remodeling of the heart with fibrosis and hypertrophy.²⁸ Norepinephrine stimulation of β 1-receptors results in accumulation of calcium in the myocyte leading to cell death.²⁸ The effects from the stimulation of these receptors ultimately leads to increased cardiotoxicity and progression of heart failure.

Compared with other β -blockers, carvedilol has the advantages of blocking both β and α -receptors²⁶ and having an anti-oxidant effect, which provides myocardial protection.^{20,21,29} β -Receptor blockade can prevent myocardial structural changes and cell death.²⁹ Left ventricular hypertrophy can be reduced by the peripheral and coronary vasodilating effect of α -blockade.^{11,28,30}

The beneficial effect of adrenergic suppression on mortality and hospitalization rates in adults has been demonstrated in several large-scale studies with metoprolol^{13,14} and bisoprolol.^{15,16} In adults with CHF who were treated with digoxin, diuretics and ACE inhibitors, the addition of carvedilol significantly reduced mortality and hospitalization rates.⁸ Carve-

dilol is well tolerated and effective even in advanced (Class IV) CHF.¹¹

The present study of a relatively small number of children treated with carvedilol suggests that the drug is safe and effective in the pediatric population. Carvedilol was initiated at a mean of 0.15 ± 0.09 mg/kg/day given in 2 divided doses and titrated every 1 to 2 weeks to a mean of 0.98 mg/kg/day. The median time to reach the maximum dose of carvedilol was 14 weeks. The wide range in the initial and maximum dose from our data reflects the lack of pediatric dosing information at the beginning of our experience. Thirteen of the 22 patients have been followed for >2 years with minimal adverse effects. Most of these adverse effects resulted only in dosage decreases or slowing the rate of dosage increments, although precipitation of asthma and worsening CHF necessitated the discontinuation of carvedilol in 2 patients. Monitoring patients closely for these adverse effects is crucial.

The lack of significant hypotension upon initiation of carvedilol in our patients may allow for initiation of this medication in an outpatient setting with monitoring of blood pressure for at least 2 hours.

In the 22 patients who tolerated carvedilol, there was a statistically significant improvement in mean LVEF of

Table 6. Pre- and Post-Carvedilol NYHA Classification by Patient's Final Status

Alive, No Cardiac Transplant			Cardiac Transplant			Deceased		
N	Pre	Post	N	Pre	Post	N	Pre	Post
3	1	1	1	2	2	1	4	4
3	2	1	1	4	3			
1	2	2	1	4	4			
5	3	1						
1	3	2						
3	4	1						
1	4	2						
1	4	3						

N, number of patients; NYHA, New York Heart Association.

17 units and mean SI of 0.12 units. Ten of these patients (45%) reached an LVEF of $\geq 50\%$. The significant change noted in SI is an indication of the reversal of left ventricular remodeling that occurs in dilated cardiomyopathy.

Lack of a control group in this study makes it difficult to establish that the improvement in systolic function is secondary to the carvedilol. Therefore, a sub-group analysis in the 18 patients who survived without a heart transplant was performed to depict the changes in LVEF and SI according to the time period from diagnosis to initiation of carvedilol. The longer the time period between the diagnosis to the initiation of carvedilol, without significant change in systolic function, the more likely that improvements seen after the initiation of carvedilol were secondary to this therapy. In patients who had initiation of the drug within 3 months from diagnosis of CMP (Group 1) there was an improvement in mean LVEF of 30 units and improvement in SI. Because of the short time that this group was on standard treatment we cannot exclude that they improved independently of carvedilol. However, statistically significant improvement in LVEF and SI was evident in the Groups 2 and 3 as well, with a mean change in LVEF of ≥ 15 units. The improvement in LVEF is shown in Figure 1 by the increase in steepness of the line, representing the change in mean LVEF in the 3 groups, and suggests a positive effect of carvedilol on improvement of cardiac function in children. This is particularly evident in those patients who had been on standard treatment the longest (Group 3) without showing any improvement in systolic function. Lack of significant improvement in LVEF occurred in both the patient who died and in the 3 patients who had a heart transplant.

The beneficial effect of carvedilol is suggested by the improvement in weight percentile and NYHA class after initiation of the drug (Tables 5 and 6). Although NYHA class was assigned retrospectively, the task was facilitated by the fact that the level of activity was indicated in details at each follow-up visit and inter-observer variability was avoided by having a single physician follow the patients. Improvement in functional class occurred in 68% of our patients.

Factors that may have contributed to improvement in outcome were the frequent follow-up visits every 1 to 2 weeks, which allows for close monitoring of compliance and adjustment in medications, and supplementing caloric intake in children whose weight fell below the appropriate percentile for age and gender.

In conclusion, the present results suggest a beneficial effect of carvedilol in addition to standard therapy for treatment of dilated CMP in children. Doses of up to 1 mg/kg/day are well tolerated, with minimal adverse effects, but close monitoring is necessary as it might

worsen CHF and precipitate asthma. Placebo-controlled studies are necessary to determine the true efficacy of carvedilol on the progression of CHF, hospitalization rate and mortality.

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