Dose-Response of Chronic β-Blocker Treatment in Heart Failure From Either Idiopathic Dilated or Ischemic Cardiomyopathy

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Background Small-scale clinical investigations have demonstrated that single doses of β-blocking agents can improve left ventricular function in heart failure from idiopathic dilated cardiomyopathy (IDC). The purpose of this multicenter clinical trial was to determine the dose-effect characteristics of β-blockade in a heart failure population that includes ischemic dilated cardiomyopathy (ISCD).

Methods and Results Bucindolol is a nonselective β-blocking agent with mild vasodilatory properties. One hundred forty-one subjects with class II or III heart failure, left ventricular ejection fraction (LVEF) ≤0.40, and background therapy of angiotensin-converting enzyme inhibitors, digoxin, and diuretics were given an initial challenge dose of bucindolol 12.5 mg. One hundred thirty-nine subjects (99 with IDC, 40 with ISCD) tolerated challenge and were randomized to treatment with placebo or bucindolol 12.5 mg/d (low dose), 50 mg/d (medium dose), or 200 mg/d (high dose). At the end of 12 weeks, left ventricular function and other parameters were measured and compared with baseline values. There was a dose-related improvement in left ventricular function in bucindolol-treated subjects. In the high-dose bucindolol group, radionuclide-measured LVEF improved by 7.8 EF units (%) compared with 1.8 units in the placebo group (P<.05), and compared with the placebo group, a greater percentage of subjects had an increase in LVEF by ≥5 units. In contrast, all three bucindolol doses prevented deterioration of myocardial function as defined by an LVEF decline of ≥5 units.

Conclusions In heart failure from systolic dysfunction, β-blockade with bucindolol produces a dose-related improvement in and prevents deterioration of left ventricular function. (Circulation. 1994;89:1632-1642.)

Key Words • heart failure, congestive • receptors, adrenergic, beta • ventricles

In heart failure, the renin-angiotensin and adrenergic nervous systems are activated to maintain central blood pressure and stabilize delivery of cardiac output to organs with autoregulatory control of blood flow.1-3 Activation of the renin-angiotensin system exerts an adverse effect on the natural history of heart failure, inasmuch as in heart failure or left ventricular dysfunction, inhibition of angiotensin II formation reduces mortality related to progressive pump dysfunction.4-6 In contrast, there is only limited clinical evidence7 that β-adrenergic activation of the myocardium produces an adverse effect on the natural history of heart failure.

Early uncontrolled studies with the β1-selective blocking agent metoprolol8,9 suggested a benefit of β-blockade in heart failure from idiopathic dilated cardiomyopathy (IDC), but subsequent attempts to confirm these observations in short-term (<3-month) placebo-controlled trials10,11 failed to confirm the initial Swedish experience. However, recent small-scale, placebo-controlled studies of ≥3 months’ duration using a variety of β-blocking agents12-14 have supported the initial Swedish work. The degree of β-blockade used in the more recent placebo-controlled trials has ranged from low to moderate for metoprolol,12,13 moderate for carvedilol,19-21 and high for bucindolol.14-17 No previous study has examined the dose response of a single β-blocking agent, and as a result it is unclear what degree of β-blockade is desirable in treating heart failure from dilated cardiomyopathy. Furthermore, a large-scale placebo-controlled multicenter experience with β-blockade in a mixed-cause heart failure population that includes ischemic cardiomyopathy (ISCD) has not been previously reported. Finally, the smaller-scale trials have suggested that β-blocker therapy can both impede progression of left ventricular dysfunction and reverse it; however, none of these trials have been large enough to define precisely how these two potentially different effects are influenced by β-blockade.

Low- to moderate-dose β-blockade with metoprolol can restore downregulated β-adrenergic receptors in myocardium failing as a result of IDC22,23 and might be preferable for restoring exercise responses.12 This is because low-level competitive β-blockade may be overcome during exercise by evoked norepinephrine release, allowing for full chronotropic and inotropic stimulation of the reconstituted β-receptor pathway.24 For optimal...
cardioprotection, on the other hand, high-dose β-blockade might be preferable, since undesirable adrenergic stimulation during times of increased adrenergic drive would be prevented. Furthermore, since β-receptors coupled to positive inotropic and chronotropic responses constitute 30% to 40% of the β-adrenergic receptors in the failing human heart,25-27 a nonselective β-blocking agent might be preferable to a selective β-blocker.

In human ventricular myocardium bucindolol is a nonselective, non-ISA β-blocking agent28 whose weak vasodilatory action14,29 renders it well tolerated in heart failure up to full β-blocking doses.14-17 On chronic dosing, moreover, the pharmacological effects of the drug appear to be confined to β-blockade, with no evidence of a primary vasodilator effect.14,17,30 As such, we reasoned that bucindolol is a suitable tool for exploring dose-response aspects of β-blockade in a multicenter trial.

For these reasons we undertook an investigation of the dose response of bucindolol in heart failure from primary or dilated cardiomyopathy. The doses were selected to produce low, medium, and high degrees of β-blockade over a 16-fold range. The design was a four-way randomization among the three doses of β-blockade and placebo in a multicenter study performed in 12 US and Canadian centers.

Methods

Study Design

The purpose of this study was to determine the dose response of bucindolol on left ventricular function, heart failure symptoms, functional capacity, and cardiac rhythm in subjects with heart failure from systolic dysfunction. The primary efficacy criterion was improvement in left ventricular function as assessed by radionuclide ventriculography. The study design is shown in Fig 1. This was a prospective, randomized, double-blind comparison of three doses of bucindolol with placebo in subjects with congestive heart failure from either ISDC or IDC. The bucindolol treatment was divided into three different dosages: low (12.5 mg/d given as 6.25 mg BID), medium (50 mg/d given as 25 mg BID), and high (200 mg/d given as 100 mg BID). The duration of study was 12 weeks.

To be eligible for this study, subjects were required to have heart failure symptoms of at least 1 month’s duration, a left ventricular ejection fraction (LVEF) of <0.40, and a maximum exercise time (see below) between 4 and 16 minutes. Patients with active myocarditis, causes of heart failure other than IDC or ISDC, active ischemia, recent (<30 days) myocardial infarction, symptomatic ventricular tachycardia, heart block, or bradycardia (resting heart rate <50 beats per minute) were excluded. The existence of other compromising conditions such as systolic blood pressure (SBP) persistently <80 mm Hg or a pulmonary vascular resistance >8 Wood units were additional criteria for exclusion.

Enrollment, Randomization, Dose Titration, and Treatment

Patients were required to be on a stable heart failure medical regimen consisting of diuretics with or without angiotensin-converting enzyme (ACE) inhibitors with or without digoxin for at least 2 weeks before beginning the study and to have had heart failure symptoms for at least 1 month. Excluded standard medications included β-blocking agents and calcium antagonists. Once enrolled, patients underwent pretreatment screening that included two modified Naughton maximum exercise treadmill tests,31 radionuclide ventriculography, echocardiography, 24-hour Holter monitoring, and a submaximal exercise test consisting of a 6-minute walk test. Patients then received a challenge dose of one to three doses of bucindolol 12.5 mg PO every 12 hours. If they tolerated the challenge, they were then randomized in a double-blind fashion to one of the four treatment arms. Randomization was stratified by centers in blocks of eight. In subjects in the medium- and high-dose groups, study medication was uptitrated over a 4-week period, and study medication in the placebo and low-dose groups received sham up-titration to preserve the double-blind design. After target dosage was achieved, subjects were continued on a stable dosage of study medication for an additional 8 weeks for a total of 12 weeks of study medication. The protocol was approved by the institutional review boards of each of the various contributing centers. A list of participating institutions and the principal investigators is included in the “Acknowledgments.”

Heart Failure Symptoms

Before randomization and at the end of study, each patient underwent a full history and physical examination performed by the local investigator(s), with estimation of New York Heart Association (NYHA) functional class. In the week before randomization and at 4, 8, and 12 weeks on study, study subjects also filled out a symptom questionnaire (Minnesota Living with Heart Failure [MLHF])32 that reflected symptoms at rest and with exertion, as well as the ability to perform activities of daily living.

Maximal Exercise

Maximal exercise treadmill testing was performed according to a modified Naughton treadmill protocol33 at least twice in the week before randomization (baseline tests) and at the end of study. On two baseline tests, exercise time had to be within 2 minutes or the test was repeated. The last exercise test performed before randomization was taken as the baseline value.

Submaximal Exercise

The ability to perform submaximal exercise was assessed by the 6-minute hall walk method.33 Subjects walked on a specified course within the hospital and were told to travel the maximum distance possible over a 6-minute period. Distance traveled was then recorded in number of feet. Two tests were performed in the week before randomization; the second test was taken as the baseline value. Subsequent tests were then performed at 4 weeks, 8 weeks, and end of study. Data were analyzed in two ways: (1) the change from baseline in all subjects completing the study and (2) from the last test available in subjects who died or withdrew from the study.

Echocardiography

Standard M-mode echocardiograms measuring left ventricular end-systolic and end-diastolic dimensions and percent
TABLE 1. Baseline Characteristics for the Four Treatment Groups

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>Bucindolol 12.5 mg/d</th>
<th>Bucindolol 50 mg/d</th>
<th>Bucindolol 200 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients randomized</td>
<td>34</td>
<td>38</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Age, y</td>
<td>52±2</td>
<td>55±2</td>
<td>56±2</td>
<td>56±1</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>20/14</td>
<td>26/12</td>
<td>18/14</td>
<td>21/14</td>
</tr>
<tr>
<td>NYHA class I/II/III/IV</td>
<td>0/16/16/1</td>
<td>0/16/21/0</td>
<td>0/12/20/0</td>
<td>1/14/20/0</td>
</tr>
<tr>
<td>IDC/ISCDC</td>
<td>24/10</td>
<td>27/11</td>
<td>23/9</td>
<td>25/10</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>25.8±1.3</td>
<td>24.7±1.3</td>
<td>24.1±1.2</td>
<td>23.2±1.1</td>
</tr>
<tr>
<td>LVDD, cm</td>
<td>6.7±0.2</td>
<td>6.8±0.2</td>
<td>7.0±0.2</td>
<td>6.9±0.2</td>
</tr>
<tr>
<td>ETT, s</td>
<td>549±33</td>
<td>548±34</td>
<td>566±27</td>
<td>511±29</td>
</tr>
<tr>
<td>6-Min walk, ft</td>
<td>1512±46</td>
<td>1467±54</td>
<td>1449±65</td>
<td>1479±48</td>
</tr>
<tr>
<td>HR (resting, from ECG), bpm</td>
<td>86±3</td>
<td>85±3</td>
<td>84±6</td>
<td>86±2</td>
</tr>
<tr>
<td>Treadmill HR (resting), bpm</td>
<td>97±3w</td>
<td>92±3</td>
<td>94±4</td>
<td>97±4</td>
</tr>
<tr>
<td>Treadmill HR (max), bpm</td>
<td>151±4</td>
<td>143±3</td>
<td>151±7</td>
<td>147±5</td>
</tr>
<tr>
<td>SBP (resting), mm Hg</td>
<td>116±4</td>
<td>114±3</td>
<td>122±4</td>
<td>117±3</td>
</tr>
<tr>
<td>Treadmill SBP (max), mm Hg</td>
<td>142±6</td>
<td>137±4</td>
<td>145±5</td>
<td>139±4</td>
</tr>
<tr>
<td>HR, average/24 h (Holter), bpm</td>
<td>87±2</td>
<td>86±2</td>
<td>87±2</td>
<td>88±2</td>
</tr>
<tr>
<td>PVCs/h (Holter), n</td>
<td>221±69</td>
<td>179±46</td>
<td>131±33</td>
<td>152±35</td>
</tr>
<tr>
<td>VT/24 h (Holter), n</td>
<td>32.8±28.2</td>
<td>24.0±11.4</td>
<td>6.6±2.6</td>
<td>4.4±1.5</td>
</tr>
<tr>
<td>% Taking ACEIs</td>
<td>88</td>
<td>87</td>
<td>78</td>
<td>97</td>
</tr>
<tr>
<td>% Taking digoxin</td>
<td>76</td>
<td>66</td>
<td>81</td>
<td>91</td>
</tr>
<tr>
<td>% Taking diuretics</td>
<td>91</td>
<td>92</td>
<td>94</td>
<td>100</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; IDC, idiopathic dilated cardiomyopathy; ISCDC, ischemic cardiomyopathy; LVEF, left ventricular ejection fraction; LVDD, echocardiographically determined left ventricular internal diastolic dimension; ETT, exercise treadmill time; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; PVCs, premature ventricular contractions; VT, ventricular tachycardia; and ACEI, angiotensin-converting enzyme inhibitors.

P=NS for all by ANOVA or Fisher's exact test. Values are frequency or mean±SEM.

Fractional shortening were performed at baseline and at the end of study by standard techniques.

Radionuclide Ejection Fraction

Ejection fraction (EF) was determined by radionuclide techniques in the resting state by standard methods. The EF was calculated according to local institutional protocols without benefit of a central laboratory.

Holter Monitoring

Holter monitoring was performed using a 24-hour recording. Criteria evaluated included the number of premature ventricular contractions per hour and episodes of ventricular tachycardia (runs of three or more beats) per day.

Statistical Analysis

The sample size calculations were based on previous trials of bucindolol in which left ventricular function was shown to improve in 3-month studies with 20 to 25 subjects randomized to two groups. Based on the four-group design of the present study and an expected 10% attrition rate, the target enrollment was 35 subjects in each of the four groups. Analysis of results between groups was by intent to treat. One-way ANOVA was used to compare baseline characteristics in the four treatment groups. The ANOVA F test was used to compare changes from baseline among the four groups. When the overall F test was significant at the 5% level, Dunnett's multiple comparison procedure was used to determine whether a bucindolol-treated group differed from the placebo group. A paired t test was used to compare changes from baseline in each study group. A t test for two independent samples was used to compare changes in the combined bucindolol-treated groups with placebo. A dose-response multiple regression model was used to test for linear and quadratic relations with increasing bucindolol dose. Linear and polynomial regression was used to estimate the association among the most important outcomes. For data not distributed normally, the same analysis as described above was performed using normalized ranks instead of the raw data. Fisher's exact test was used to compare categorical responses among the four treatment groups. A value of P<.05 in a two-tailed distribution was taken as statistical significance, with P<.10 but ≥.05 taken as a statistically marginal result.

Results

Baseline Characteristics of Enrolled Subjects

The baseline characteristics of the four groups are given in Table 1. By ANOVA there were no differences among the four groups.

General Outcome of Randomized Subjects

Of 141 subjects who signed consent, 139 tolerated the challenge dose of bucindolol. The 2 subjects who did not tolerate challenge developed clinical evidence of hypoperfusion typical of myocardial depression. One of these subjects went on to transiently stabilize for a 6-week period, followed by deterioration to intravenous inotrope dependency and then a successful cardiac transplant. The other subject was lost to follow-up.
TABLE 2. Withdrawals (Deaths and Dropouts) Before End of Study

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>Bucindolol 12.5 mg/d</th>
<th>Bucindolol 50 mg/d</th>
<th>Bucindolol 200 mg/d</th>
<th>All Bucindolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number randomized</td>
<td>34</td>
<td>38</td>
<td>32</td>
<td>35</td>
<td>105</td>
</tr>
<tr>
<td>Number completing study</td>
<td>28 (82.4)</td>
<td>34 (89.5)</td>
<td>23 (71.9)</td>
<td>32 (91.4)</td>
<td>89 (84.8)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (5.9)</td>
<td>1 (2.6)</td>
<td>3 (9.4)</td>
<td>0 (0)</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Dropouts</td>
<td>4 (11.8)</td>
<td>3 (7.9)</td>
<td>6 (18.7)</td>
<td>3 (8.6)</td>
<td>12 (11.4)</td>
</tr>
<tr>
<td>Deaths+dropouts</td>
<td>6 (17.6)</td>
<td>4 (10.5)</td>
<td>9 (28.1)</td>
<td>3 (8.6)</td>
<td>16 (15.2)</td>
</tr>
</tbody>
</table>

Values are no. of patients (%).

The general outcome of subjects randomized to the four treatment groups is given in Table 2. It can be seen that the percent mortality over the 3-month study ranged from 0% in the highest bucin- dolol group to 9.4% in the medium-dose bucin- dolol group, with the placebo group having a 5.9% mortality. The dropout rate (excluding deaths) ranged from 7.9% in the low-dose bucin- dolol group to 18.7% in the medium-dose group, with the placebo group having an 11.8% dropout rate (Table 2). In terms of the percentage of subjects completing the study, the range was from 91.4% in the high-dose bucin- dolol group to 71.9% in the medium- dose bucin- dolol group, with 82.4% of the subjects in the placebo group completing the 3-month trial. In the bucin- dolol groups, none of the differences in mortality, dropout rate, or completion percentage were significantly different from placebo. By Fisher's exact test there were no significant differences (P = .34) in these parameters among the four groups. Respective mean dosages in the low-, medium-, and high-dose groups at the end of study or time of death or dropout were 12.5 ± 0.9, 44 ± 2.1, and 192 ± 6 mg/d. Respective mean doses in milligram per kilogram were 0.157 ± 0.005, 0.608 ± 0.038, and 2.47 ± 0.12 mg/kg (P = .0001 by ANOVA, all groups different from one another by Dunnett's t test).

The more detailed list of deaths and other events that led to premature discontinuation of study medication is given in Table 3. All six deaths in this study were classified by the investigators as sudden, defined as death within 24 hours of the onset of symptoms. Also given in Table 3 is the total daily dose at which a bucin- dolol-treated subject died or dropped out.

**Effect on LVEF**

Changes in LVEF over the course of the study are given in Fig 2. Placebo treatment resulted in a negligible change in ejection fraction of 1.7 ± 1.6 EF units (%) (P = NS versus baseline). All three bucin- dolol-treated groups exhibited a numerically greater increase that ranged from 3.9 ± 2.0% (P = .06 versus baseline) in the medium-dose group to 7.8 ± 1.6% (P = .001) versus baseline) in the high-dose group. By ANOVA, changes in the four groups were significantly different, with the 200-mg dose being different from placebo by Dunnett's t test. Since the EF data were not normally distributed, normalized ranks were used, which revealed that both the 12.5-mg bucin- dolol group and the 200-mg bucin-

TABLE 3. Assessment of Type of Death and Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>Bucindolol 12.5 mg/d</th>
<th>Bucindolol 50 mg/d</th>
<th>Bucindolol 200 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients randomized</td>
<td>34</td>
<td>38</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (0.4)</td>
<td>1 (12.5,3)</td>
<td>3 (50,8)</td>
<td>0</td>
</tr>
<tr>
<td>Dropouts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>0</td>
<td>1 (12.5,4)</td>
<td>3 (25,3)</td>
<td>1 (25,2)</td>
</tr>
<tr>
<td>Removal for transplantation</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drug ineffective</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (200,9)</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1 (12.5,5)</td>
<td>2 (50,4)</td>
<td>1 (100,3)</td>
</tr>
</tbody>
</table>

Values are no. of patients, dosages in milligrams per day, and week of study at time of death or dropout.
dolol group were different from placebo. When all three bucindolol-treated groups were compared with placebo, the change in EF was 6.3±0.9% versus 1.7±1.6% (P=.02). A significant linear upward trend was found on analysis by the dose-response model (P=.02).

The percentage of subjects exhibiting an increase or decrease in LVEF by ≥5 EF units (%) in the four groups is shown in Fig 3. As can be seen, in the placebo group, substantial percentages of subjects exhibited both an increase (36%) and a decrease (29%) in LVEF, and the distribution was altered in the bucindolol groups (P=.036 by Fisher’s exact test). Compared with placebo, all three bucindolol-treated groups demonstrated a reduction in the percentage of subjects with a decline in LVEF, with P values ranging from .02 in the 12.5- and 200-mg bucindolol groups to .075 in the 50-mg group. Conversely, the percentage of bucindolol-treated subjects exhibiting an increase in LVEF was significantly increased only in the high-dose bucindolol group (P=.0038 versus placebo).

Fig 4 gives the LVEF data stratified for IDC versus ISCDC. Relative to baseline values, LVEF improved significantly in the IDC bucindolol 12.5-mg, 200-mg, and the combined subgroups, with the 50-mg group nearly achieving statistical significance (P=.06 by paired t test). In the ISCDC bucindolol-treated subgroups, only in the 200-mg and combined subgroups did LVEF statistically improve relative to baseline, with the 12.5-mg subgroup reaching a value of P=.09. Placebo-treated subgroups behaved differently in the IDC and ISCDC subgroups, with IDC subjects exhibiting a significant increase and ISCDC subjects tending to have a decrease in LVEF (P=.055 by paired t test). As a result, the changes in LVEF in the placebo ISCDC and IDC subgroups were significantly different from one another (P=.016 by unpaired t test). Such a difference was not present in any of the bucindolol-treated IDC or ISCDC subgroups. Because of the degree of “spontaneous” improvement in the placebo-treated subgroup, the change in LVEF in the bucindolol-treated subgroups as well as in the combined bucindolol subgroups did not differ significantly from placebo. In the ISCDC subgroups, the 200-mg bucindolol subgroup and the combined subgroup demonstrated statistically significant improvement in LVEF relative to placebo.

Since ejection fraction data are not load independent and bucindolol has weak vasodilator properties, we measured cuff SBP and diastolic blood pressure (DBP) in two settings before the maximal exercise and 6-minute walk tests (Table 4). By ANOVA there were no significant changes among the four groups. Within groups the only significant changes were a reduction in SBP in the 12.5-mg group and a reduction in DBP in the 50-mg group recorded before the maximal exercise test. There were no changes in any group in either SBP or DBP when the measurements were taken before the 6-minute walk test, and no significant changes were noted in the 200-mg group for either premaximal exercise or pre–6-minute walk blood pressure recordings.

**Effect on Left Ventricular Size**

Fig 5 gives left ventricular internal dimension data in the four groups. As can be seen, both left ventricular end-diastolic and end-systolic dimensions measured echocardiographically exhibited only small tendencies for a reduction in the placebo and low-dose bucindolol groups and somewhat greater tendencies for a reduction in the medium- and high-dose groups. By ANOVA, none of these groups were different from placebo. There were statistically insignificant trends in favor of the combined bucindolol groups exhibiting a reduction in both systolic and diastolic dimensions. In the bucindolol groups there was a trend toward a dose-related reduction in left ventricular end-diastolic internal dimension, with a statistically marginal downward dose response (P=.06 by linear model).
Effects on Maximal Exercise

Table 5 gives the effect of each treatment on maximal exercise heart rate, which was unchanged by 3 months of placebo treatment and significantly reduced by all three doses of bucindolol. The degree of reduction was clearly dose related (P<.001 [linear term], \( P=.018 \) [quadratic term]). The change in maximum SBP is also given in Table 5. All doses of bucindolol significantly lowered SBP, and both linear (\( P=.011 \)) and quadratic (\( P=.024 \)) dose-response models were statistically significant.

Table 5 gives data for maximal exercise time in the two groups. All three bucindolol groups tended to have a reduced total maximal exercise time compared with placebo, but none of the differences were statistically significant by ANOVA. No significant trends were noted when randomized by dose-response model. However, when all bucindolol groups were combined, they exhibited a significantly lowered maximal exercise time (by 0.4±15 seconds in bucindolol groups versus 64±23 seconds in the placebo group; \( P=.036 \) by unpaired t test). To explore a potential relation between the degree of \( \beta \)-blockade and inhibition of maximal exercise time, change in maximal exercise heart rate and change in maximal exercise time were plotted for all groups (Fig 6A). As can be observed, there is a significant (\( r=.41, P=.001 \)) direct relation between reduction in maximum exercise heart rate and reduction in maximum exercise time. In contrast, change in exercise heart rate and change in LVEF were inversely related (\( r=.24, P=.015 \), as shown in Fig 6B.

Effects on Submaximal Exercise

Shown in Table 5 are the distances walked in the 6-minute walk test. By ANOVA, none of the bucindolol treated groups exhibited a significant change compared with the placebo group, although the medium and high groups tended toward greater exercise times. No significant trends were noted with the dose-response model. Unlike the maximal exercise time, there was no relation between reduction in maximal exercise heart rate and submaximal exercise distance walked (\( r=.03, P=.78 \).

Effect on NYHA Functional Class and Quality of Life

Shown in Table 6 are the NYHA functional class and MLHF questionnaire data. The Minnesota quality-of-life instrument is divided into "physical" or "emotional" dimensions that are related, respectively, to dyspnea and fatigue or cognitive symptoms, and a lower score means symptomatic improvement. By ANOVA there were no significant changes among the four groups in either NYHA class or quality of life, and no significant dose-response trends were noted.

Effects on Holter Monitoring Data

Shown in Table 7 are Holter monitoring data for the four groups. Baseline values and changes in the lowest, highest, and average heart rate per 24 hours are given in Table 7. The highest heart rate achieved in a 24-hour period was lowered by all three bucindolol doses, with a significant linear downward trend on evaluation of dose-response (\( P=.04 \)). In addition, the average heart rate achieved was lowered by all doses of bucindolol, with no significant dose-response relation. In contrast, the lowest heart rate achieved was not affected by any bucindolol dose (Table 7). The reduction in average heart rate noted on Holter monitoring was not correlated with change in LVEF (\( r=.03, P=.72 \), and in bucindolol-treated subjects, responders (defined as an LVEF increase of \( \geq 5 \) units) did not differ from nonresponders with regard to reduction in average heart rate (responders, \(-8.4±3.2\) beats per minute; nonresponders, \(-4.8±0.9\) beats per minute; \( P=.32 \) by unpaired \( t \) test), highest heart rate (responders, \(-21.0±6.4\); nonresponders, \(-16.1±4.2\); \( P=.54 \) by un-
paired $t$ test), or average baseline heart rate (44 responders, 86.9±1.9 beats per minute; 41 nonresponders, 86.3±1.7 beats per minute; $P=0.81$ by unpaired $t$ test).

The effect of placebo or bucindolol on arrhythmia parameters is given in Table 7. In the placebo group, no significant change from baseline was noted in pre-ventricular contractions per hour or runs of ventricular tachycardia per day. By ANOVA there were no significant differences among the four groups in these arrhythmia parameters.

**Discussion**

This heart failure investigation represents the first full-length report of a multicenter placebo-controlled clinical trial of $\beta$-blockade in subjects with multiple causes of heart muscle disease, the first report of the dose-response of $\beta$-blockade, and the first report to examine the effects of $\beta$-blocker treatment on progression and reversal of myocardial dysfunction. In an attempt to define a dose-response relation for $\beta$-blockade in subjects with heart failure from dilated cardiomyopathy of either idiopathic or ischemic cause, a broad (16-fold) range of $\beta$-blocker dose was examined to produce low, medium, and high degrees of $\beta$-blockade. As assessed by inhibition of exercise or average Holter monitor–measured heart rate, all three doses of the potent, nonselective, non–ISA $\beta$-blocker/vasodilator bucindolol\textsuperscript{28} produced $\beta$-blockade, with the 200-mg dose producing greater blockade than the 12.5- or 50-mg dose.

The effects of bucindolol on ventricular function were qualitatively similar to those previously reported in IDC.\textsuperscript{14} That is, in a subject population composed of patients with dilated cardiomyopathy from either primary or secondary (ischemic heart disease) causes, bucindolol produced an increase in LVEF measured by radionuclide techniques and tended to reduce left ventricular size measured echocardiographically. Despite producing a profound inhibition of exercise heart rate, high doses of bucindolol were extremely well tolerated, with fewer numbers of deaths and dropouts in the high-dose group than in the placebo group. Moreover, the initial and short-term tolerability of bucindolol (139 of 141 or 98.6% of subjects tolerated a challenge dose of 12.5 mg) was excellent. In comparison, short-term tolerability of the conventional $\beta$-blocker metoprolol has generally been reported to be 80% to 90% in heart failure trials.\textsuperscript{35}

The long-term tolerability of high-dose bucindolol was also quite good, since 91.4% of the subjects in the high-dose group completed the 3-month trial and all achieved titration to the target dose of 100 mg BID. This compares with respective completion and up-titration rates of 96.4% and 100% in a previously reported medium-sized, two-center trial with bucindolol.\textsuperscript{17} In fact, on the basis of initial tolerability and dropout rates, bucindolol was at least as well tolerated as are ACE inhibitors in placebo-controlled trials.\textsuperscript{35} Importantly, bucindolol did not reduce the lowest heart rate achieved
Table 6. NYHA Functional Class and Quality of Life as Assessed by MLHFQ

<table>
<thead>
<tr>
<th>Group</th>
<th>NYHA Class</th>
<th>MLHFQ Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Improving</td>
<td>% Worsening</td>
</tr>
<tr>
<td>Placebo</td>
<td>48.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Bucindolol 12.5 mg</td>
<td>40.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Bucindolol 50 mg</td>
<td>36.4</td>
<td>0</td>
</tr>
<tr>
<td>Bucindolol 200 mg</td>
<td>20.0</td>
<td>0</td>
</tr>
<tr>
<td>All bucindolol</td>
<td>31.6</td>
<td>3.8</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; MLHFQ, Minnesota Living with Heart Failure Questionnaire. Negative values indicate improving symptoms.

as assessed by 24-hour Holter monitoring, and there were no clinical adverse events that could be attributed to bradycardia.

It should be emphasized that high-dose bucindolol produces a much greater degree of β-blockade than the lower β-blocking dosages of metoprolol (80 to 120 mg/d) that are ordinarily used in heart failure trials. In the present study, 200 mg bucindolol reduced maximum exercise heart rate from 150 to 110 beats per minute, compared with 150 to 147 beats per minute in a previous placebo-controlled trial with metoprolol that reported an improved maximal exercise time. Compared with metoprolol, bucindolol is 5- to 10-fold more potent for blockade of β1-receptors, bucindolol blocks both β1- and β2-receptors, and the milligram dose of bucindolol in the high-dose group was greater than is ordinarily used for metoprolol. This is probably why maximum exercise time was not improved in bucindolol-treated subjects, in contrast to subjects treated with low to moderate doses of metoprolol. Maximal treadmill times tended to decrease on bucindolol because of β-blocker-related blunting of exercise heat rate, since subjects with heart failure are almost totally dependent on chronotropic response to increased cardiac output during maximal exercise. This explanation is supported by a significant relation between the degree of blunting of maximum exercise heart rate and decreasing maximal exercise time in subjects treated with bucindolol. Paradoxically, increasing blunting of maximal exercise heart rate by bucindolol was also associated with improvement in LVEF, which supports the idea that β-blockade is responsible for both the favorable (improving LVEF) and potentially unfavorable (reduced maximal exercise time) effects and that these effects are generally related to the degree of β-blockade. This observation illustrates the limitation of maximal exercise as a general tool for detecting improvement in cardiac function or clinical condition in heart failure subjects treated with β-blocking agents. Conversely, submaximal exercise, which more accurately simulates activities of daily living, exhibited a trend toward improvement at higher bucindolol doses, suggesting that this form of exercise may be useful in the evaluation of heart failure patients treated with β-blocking agents.

In this study some aspects of the effect of β-blockade were dose related and some were not. Improvement in ventricular function and reduction in left ventricular diastolic and systolic dimensions appeared to be dose related, with the highest dosage of bucindolol producing a more beneficial effect than lower dosages. Conversely, prevention of deterioration in left ventricular function as assessed by the percentage of subjects exhibiting a decline in LVEF of ≥0.05 appeared not to be dose related, since all three bucindolol doses were associated with prevention of LVEF decline. Thus, it is possible that β-blocker-related improvement in ventricular function may be the result of mechanisms that are distinct from those responsible for prevention of deterioration in function or that the two types of effects exhibit different sensitivities to β-blockade. At any rate, this study demonstrates that β-blocker therapy can both prevent progression of left ventricular dysfunction and reverse it in a subject population consisting of IDC or ISDC. This has not previously been demonstrated for any other form of medical heart failure therapy. Moreover, this improvement in and prevention of deterioration in left ventricular function was achieved in the presence of ACE inhibition, a treatment modality that has been shown to prevent deterioration in cardiac function.

Table 7. Holter Monitoring Data: Change From Baseline±SEM

<table>
<thead>
<tr>
<th>Group</th>
<th>Average HR, bpm</th>
<th>Lowest HR, bpm</th>
<th>Highest HR, bpm</th>
<th>VT Events/24 h</th>
<th>Average PVCs/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.2±2.6</td>
<td>0.0±1.7</td>
<td>7.0±7.2</td>
<td>-1.8±1.5</td>
<td>6±36</td>
</tr>
<tr>
<td>Bucindolol 12.5 mg</td>
<td>-6.0±1.2*</td>
<td>-5.0±1.2</td>
<td>-16.5±3.8*</td>
<td>-13.5±6.1</td>
<td>7±39</td>
</tr>
<tr>
<td>Bucindolol 50 mg</td>
<td>-5.0±1.4*</td>
<td>-2.0±1.8</td>
<td>-12.5±4.4*</td>
<td>1.5±2.8</td>
<td>4±31</td>
</tr>
<tr>
<td>Bucindolol 200 mg</td>
<td>-7.2±1.2*</td>
<td>-1.8±1.7</td>
<td>-23.4±7.3*</td>
<td>2.9±3.1</td>
<td>11±31</td>
</tr>
</tbody>
</table>

HR indicates heart rate; bpm, beats per minute; VT, ventricular tachycardia; and PVCs, preventricular contractions.

*P<.05 vs placebo, ANOVA/Dunnett’s t test.
General clinical outcome as assessed by the percentage of subjects completing the 3-month trial and submaximal exercise results also appeared to be dose related. However, these effects were more subtle than the effects on left ventricular function, and none of the changes were statistically significant compared with placebo.

In addition to the prevention of deterioration of left ventricular function, several measured variables appeared to have no relation to bucindolol dosage. These included effects on maximal exercise, which was unchanged in all bucindolol groups, and effects on ventricular arrhythmias, which also did not change in any bucindolol group.

In this study, bucindolol had no effect on NYHA functional class or quality of life as assessed by the MLHF questionnaire. In contrast, in a previous trial of bucindolol, quality of life was significantly improved according to a different quality-of-life instrument. Importantly, in the present trial, quality of life as assessed by the Minnesota method was not worsened by \( \beta \)-blockade. The failure to improve quality of life in this trial may relate to the short duration (12 weeks) of the trial, to the instrument used, or to an inherent inability of bucindolol to improve quality of life despite improving cardiac function. The latter possibility creates the potential for a heart failure therapy to improve quality of life (assuming the improved EF would translate into mortality reduction) without improving quality. However, the most likely reason why quality of life was not improved by bucindolol was the relatively brief duration of the trial (12 weeks), which is around the minimum time required to demonstrate a favorable effect of \( \beta \)-blockade on left ventricular function. In a previous study, Anderson et al. noted that LVEF and heart failure symptoms continued to improve over a 2-year period in IDC subjects treated with bucindolol.

Unlike a previous report, this study demonstrated that bucindolol improves LVEF in subjects with IDC. We had previously reported that bucindolol improves LVEF significantly and to a greater extent in IDC than in ISDC in a trial that had slightly greater numbers of subjects with each type of dilated cardiomyopathy treated with high-dose bucindolol. In the present study the ISDC subgroup exhibited a statistically significant increase in LVEF relative to the change in the placebo group both for the high-dose group and for all subjects treated with bucindolol. In contrast, change in LVEF in the IDC subgroup treated with high-dose bucindolol was not significantly different from the placebo-treated IDC subgroup. The main reason for this was that the placebo-treated IDC group exhibited a greater change in LVEF than the corresponding placebo-treated ISDC subgroup, such that when relative differences in change from baseline were examined between groups (bucindolol versus placebo), the relative change from baseline in the ISDC subgroup was superior. A greater “spontaneous” improvement in LVEF in IDC versus ISDC could be due to resolution of an occult inflammatory process or other factors more likely to affect the former type of cardiomyopathy. However, the high-dose bucindolol–treated ISDC subgroup also exhibited a tendency for a greater overall change in LVEF than the respective IDC subgroup, and the ISDC subgroup in the present trial had a greater degree of LVEF improvement (9.1±2.3% versus 2.3±1.1%) than the ISDC subjects in the study of Woodley et al. Although it is not clear why the bucindolol-treated ISDC subjects in this trial appeared to behave differently from subjects in the previous trial, it is possible that obscure differences in the subject population or random chance accounts for these differences. Nevertheless, the results of this study clearly demonstrate that subjects with heart failure from ISDC may also respond to \( \beta \)-blockade with an improved LVEF.

In this trial the medium dosage of bucindolol (50 mg/d) produced clinical results that appeared to be inferior to both the high- and low-dose groups. Although the reason for this “idiosyncratic” effect of medium-dose bucindolol is not clear, it is likely that the results in the medium-dose group were due to chance or to unrecognized baseline differences. However, another possibility is that withdrawal of adrenergic drive by the medium dose was just enough to precipitate acute myocardial depression but not enough to facilitate improved LV function, resulting in a worse clinical outcome than either low- or high-dose bucindolol. On the basis of this possibility and the clear demonstration of dose-related benefits of \( \beta \)-blockade on ventricular function, it would appear important to systematically assess the dose response of individual \( \beta \)-blocking agents in heart failure. Moreover, this dose response may vary by degree of \( \beta_1 \)-versus \( \beta_2 \)-receptor selectivity or the amount of ancillary vasodilation. Finally, although an upper dose limit of bucindolol that failed to produce further improvement of LVEF was not defined in this investigation, dosages of bucindolol >200 mg/d can be associated with an increased incidence of drug intolerance. It is therefore unlikely that a further augmentation of dosage would lead to a better therapeutic index. The mechanism of bucindolol’s benefit on left ventricular function was not addressed in this study. In previous studies left ventricular performance plots of stroke volume index versus pulmonary mean capillary wedge pressure were improved by bucindolol, suggesting improved contractile function. However, neither LVEF nor the plot of stroke volume index versus pulmonary wedge pressure is a load-independent measurement. The improvement in left ventricular function by bucindolol was subsequently shown to be load independent and a result of improvement in intrinsic contractile state rather than of vasodilation. In the present study only small and usually statistically insignificant changes in blood pressure were noted in the bucindolol-treated groups, and no significant changes were noted in the 200-mg group, which exhibited the greatest improvement in LVEF. Thus, it is likely that high-dose bucindolol directly improved intrinsic left ventricular function in this study by removing a reversible adverse myocardial process that was related to increased cardiac adrenergic drive.

In summary, the results of this investigation support the findings of recent small-scale placebo-controlled trials of \( \beta \)-blockade in heart failure from IDC and extend the results to the most common cause of heart failure in the United States, ISDC. Some aspects of \( \beta \)-blocker therapy in heart failure appear to be dose related, and other effects do not. The dose-related effects include improvement in left ventricular function and overall clinical response, whereas prevention of
deterioration of ventricular function appears to occur at all doses. Dose-effect considerations appear to be important in β-blocker therapy in heart failure, and these relations should be established for each type of β-blocker used.

We conclude that in heart failure from systolic dysfunction due to diverse causes, β-blocking agents can prevent functional deterioration and reverse cardiac dysfunction. Future larger trials should be able to ascertain whether the consistently observed favorable effects of β-blockers on left ventricular function translate into a positive effect on the natural history of heart failure.

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