Long-Term (3-month) Effects of a New Beta-Blocker (Nebivolol) on Cardiac Performance in Dilated Cardiomyopathy

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Objectives. This study examined the long-term (3-month) effects of nebivolol, a new beta-adrenergic blocking drug, on cardiac performance in patients with dilated cardiomyopathy.

Background. Several beta-blocking drugs have been reported to have a beneficial hemodynamic effect in patients with dilated cardiomyopathy, but few data obtained in a placebo-controlled randomized study have addressed the mechanisms of improvement.

Methods. Twenty-four patients with dilated idiopathic (n = 22) or ischemic (n = 2) cardiomyopathy (ejection fraction 0.15 to 0.40) in stable New York Heart Association functional class II or III were entered into a double-blind randomized trial of nebivolol, a new, potent, selective beta-1-antagonist. Exercise time, invasive hemodynamic data (12- and 24-h monitoring) and variables of left ventricular function were examined at baseline and after 3 months of orally administered nebivolol (1 to 5 mg/day, n = 11) or placebo (n = 13).

Results. Heart rate decreased (group mean 85 to 71 beats/min vs. 87 to 73 beats/min with placebo) and stroke volume increased significantly (group mean 43 to 55 ml vs. 42 to 43 ml) with nebivolol; decreases in systemic resistance, systemic arterial pressure, wedge pressure and pulmonary artery pressure were not significantly different from those with placebo. Similar hemodynamic results were obtained in the catheterization laboratory. Analysis of high-fidelity measurements of left ventricular end-diastolic pressure showed a decrease in left ventricular end-diastolic pressure in the nebivolol group (mean 21 to 15 vs. 24 to 20 mm Hg with placebo) but no change in the maximal rate of pressure development or in two variables of left ventricular relaxation (maximal negative rate of change of left ventricular pressure [dP/dt max] and the time constant tau). Left ventricular mass decreased (p = 0.04). Despite a decrease in heart rate with nebivolol, there was a slight decrease in left ventricular end-diastolic volume (p = NS). End-systolic volume tended to decrease (p = 0.07) despite no reduction in end-systolic stress. The net result was a significant increase in ejection fraction (group mean 0.23 to 0.33 vs. 0.21 to 0.23 with placebo), presumably as a result of an increase in contractile performance. This effect was corroborated by an increase in a relatively load-independent variable of myocardial performance.

Conclusions. Nebivolol improved stroke volume, ejection fraction and left ventricular end-diastolic pressure, not through a measurable reduction in afterload or a lusitropic effect, but by improving systolic contractile performance.

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Several beta-adrenergic blocking drugs have been reported (1–7) to have beneficial effects in patients with dilated cardiomyopathy. In a recent double-blind comparison of the nonselective beta-blocking agent bucindolol with placebo, Gilbert et al. (6) observed a beneficial effect on hemodynamic variables and ejection fraction after 3 months of treatment. They demonstrated in a subsequent study (7) that the beneficial effect was maintained for 2 years. However, they could not determine the mechanism for improved performance (that is, whether it was due to the nonadrenergic-mediated vasodilating effects of the drug or a direct myocardial effect of long-term beta-blockade). In an elegant but uncontrolled study of bucinolol on myocardial performance, Eichborn et al. (5) concluded that after 3 months of therapy, improved performance was the result of an improvement in myocardial contractility without an increase in myocardial oxygen demand.

Taken together, these studies suggest that long-term treatment with a beta-blocking drug with vasodilating properties may improve cardiac performance through a paradoxical improvement in contractility. However, because of the reluctance of many practitioners to initiate a potentially deleterious form of treatment in patients with cardiomyopathy, we thought it worthwhile to combine the separate strengths of these two studies in a comprehensive investigation of the new beta-blocking agent (RSSS + SRRR)[minobis(methylene)bis[6-fluoro-3,4-2H-1-benzopyran-2-methanol]-HCl—nebivolol—in patients with cardiomyopathy. Nebivolol is a racemic mixture of two enantiomers: the D-isomer is a long-acting beta-1-adrenergic antagonist that, although more potent and more beta-1-selective in vitro, has...

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a hemodynamic profile qualitatively resembling that of atenolol (8); the nonbeta-blocking L-isomer, in contrast to both D-nebivolol and atenolol, decreases peripheral resistance after intravenous injection in dogs by an unexplained mechanism that does not appear to be mediated by any known receptor (9). Racemic nebivolol also reduces peripheral resistance in humans after oral administration and a noninvasive index of left ventricular performance is improved (10). Nebivolol has little if any alpha-adrenoceptor antagonistic effects (10) and is devoid of intrinsic sympathomimetic activity (11).

Our protocol was randomized, double-blind and included exercise testing, measurement of plasma biochemical variables, including catecholamines at baseline and after 3 months, 24-h invasive hemodynamic monitoring and invasive assessment of left ventricular wall stress and contractility in an attempt to separate the effects of load and contractility on performance.

Methods

Study design. The protocol was approved by the Ethics Committee of the University of Witwatersrand and Baragwanath Hospital. After an explanation of the protocol in his or her own language, each patient gave informed consent before study entry. The study was double-blind, randomized and placebo-controlled with two parallel arms. Randomization block size was four. The placebo run-in phase was 1 month and the randomized phase was 12 weeks. Twelve patients were initially randomized to each group. However, four patients randomized to nebivolol therapy failed to complete the protocol: one died, two were withdrawn because of newly diagnosed or worsening diabetes mellitus and one defaulted for social reasons. The latter three patients, who either were withdrawn or defaulted, were replaced by an additional three patients at the randomized treatment by the investigators. Thus, 11 patients in the nebivolol arm completed the protocol. One patient in the placebo group defaulted for social reasons. This patient was inadvertently replaced with two patients; thus, 13 patients completed the placebo arm of the study. Hemodynamic assessment performed at the end of the run-in phase included 12 h of hemodynamic monitoring with Swan-Ganz catheters before randomization and at 4 h after placebo administration, left heart catheterization with left ventricular cineangiography. The 24-h hemodynamic study and angiographic assessment were repeated at the end of the randomized phase. Two exercise tests (modified Naughton protocol) were performed during the run-in phase at weekly intervals, again weekly during the 3-week titration phase, at week 6 and finally at completion of the trial.

Patient selection. Eligibility criteria were 1) age >18 and ≤65 years, 2) stable New York Heart Association functional class II or III congestive heart failure on diuretic therapy (furosemide), 3) systolic left ventricular dysfunction (ejection fraction 0.15 to 0.40 by gated radionuclide angiography), 4) ability to perform treadmill exercise for ≥4 and ≤12 min using a modified Naughton protocol, and 5) reproducible exercise performance during a 1-month placebo run-in phase (that is, two successive exercise durations within 2 min performed at weekly intervals). Exclusion criteria were 1) chronic obstructive pulmonary disease, 2) significant valvular heart disease, 3) diastolic blood pressure >105 mm Hg, 4) myocardial infarction or stroke within the past 6 months, 5) insulin-dependent diabetes, 6) creatinine >2.2 mg/dL, 7) liver disease defined as enzymes more than twice the upper limit of normal, 8) women of child-bearing potential, 9) symptomatic arrhythmias or atrial fibrillation, 9) use of digoxin, angiotensin-converting inhibitors or other beta-blocking drugs, 8) weight >150% of ideal weight, and 9) alcohol abuse.

Characteristics of the patients enrolled are shown in Table 1. Coronary angiography revealed severe two- and three-vessel disease suggestive of an ischemic origin in two patients (nebivolol group) and minor (<50% narrowing) disease in four others (three in the nebivolol group and one in the placebo group). No other specific etiologies for heart failure were identified and, on the basis of the exclusion criteria, no patient was thought to have a predominantly hypertensive origin of heart failure. All patients were native Africans.

Drug titration. After the baseline hemodynamic study, patients were randomized to receive nebivolol (1 mg/day) or placebo. The drug dose was increased at weekly intervals over the next 2 weeks to 2.5 and 5 mg if well tolerated. All patients were maintained on furosemide plus potassium supplementation.

Hemodynamic and angiographic studies. Twelve-hour monitoring with Swan-Ganz catheters was performed hourly at the end of the run-in phase and for 24 h again (hourly for 12 h and then once every 3 h for 12 h) at the completion of the trial. To ensure stability, catheters were inserted through the subclavian or jugular vein on the evening before the
monitoring period began; patients fasted during this time. Pulmonary wedge pressure and cardiac output measurements were repeated until <10% variation was observed between two consecutive measurements before drugs were administered. During the baseline study, left heart catheterization with left ventricular cine- and coronary angiography were performed 4 h after hemodynamic monitoring was initiated and placebo was given because this is the time estimated to reach peak effect for nebivolol. During the final period of hemodynamic monitoring, left heart catheterization and left ventricular cineangiography were again performed at 4 h after drug (nebivolol or placebo) was given. The femoral approach with local anesthesia only was used. Left ventricular pressure was measured with an 8F micro-manometer pigtail catheter. Biplane left ventricular cineangiography was performed with 40 to 50 ml of sodium meglumine ioxaglate.

Methods used for analysis of the left ventricular pressure and simultaneous angiographic volume data, and estimation of contractile function using the preload-corrected ejection fraction (EFc)–end systolic stress (ESS) relations have been described in detail (12). The perpendicular distance of data for each individual patient from the previously published regression line of a normal control group (12) was computed as: ΔESS × sine[arctangent(regression slope)], where ΔESS is the horizontal distance from the preload-corrected ejection fraction–end-systolic stress coordinate to the regression line. This is a modification of the method of Lang et al. (13), who used the vertical distance at a common end-systolic stress. Diastolic pressure-volume data were not considered adequate for estimation of preload-corrected ejection fraction in one patient in the nebivolol group and in one patient in the placebo group at baseline study and another at 3 months. All angiographic analyses were performed in a blinded fashion before the drug codes were broken. Pressure-volume loops were constructed from digitized micromanometer left ventricular pressure (not smoothed) and from frame by frame angiographic (area-length) volume-time data smoothed with a 10th-order polynomial equation using a Marquardt curve-fitting program.

Biochemical studies. Plasma norepinephrine analysis was performed by using high performance liquid chromatography; blood samples were immediately put on ice after they were drawn. Routine biochemistry studies were performed with standard technique.

Statistics. Two-way analysis of variance was used to assess different responses between the nebivolol and placebo groups.

Results

Drug dosing and side effects. The maximal dose of drug was reached in 7 of 11 patients randomized to nebivolol and 11 of 13 randomized to placebo therapy. Medication compliance determined by pill count was >90% in all but two patients (85% compliance by each) in the nebivolol group and >90% in all but one patient (79% compliance) in the placebo group.

Two patients initially randomized to nebivolol were withdrawn before completion of the protocol because of new or worsening diabetes (see Methods). There was one sudden death in the nebivolol group. Of the 11 patients who completed the nebivolol arm of the protocol, one complained of mental depression but did not have to be withdrawn from the study. In the remaining patients, side effect profiles were low, with no admissions for worsening heart failure.

Exercise time. There was no significant change in exercise duration in either group, nor was there any difference between the groups at baseline (554 ± 70 s at baseline to 536 ± 83 s at 3 months for the nebivolol group and 492 ± 121 s to 570 ± 105 s for the placebo group). Peak systolic blood pressure in the nebivolol group was 150 ± 24 mm Hg at baseline and 145 ± 22 mm Hg at 3 months (p = NS); maximal heart rate was 140 ± 12 beats/min at baseline and decreased to 120 ± 22 beats/min at 3 months (p = 0.005). In the placebo group, the corresponding exercise variables were 160 ± 19 mm Hg versus 155 ± 25 mm Hg at 3 months and 143 ± 22 beats/min to 147 ± 21 beats/min (p = NS for both).

Hemodynamics (Table 2, Fig. 1). Twelve- and 24-h invasive monitoring showed that only heart rate and stroke volume were significantly altered by nebivolol; decreases in systemic resistance, systemic arterial pressure, wedge

Table 2. Effects of Nebivolol Versus Placebo on 12- and 24-Hour Swan-Ganz Measurement of Hemodynamic Variables

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nebivolol Before</th>
<th>Nebivolol After</th>
<th>Placebo Before</th>
<th>Placebo After</th>
<th>p Value for Effect of Drug</th>
<th>p Value for Effect of Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>85 ± 12</td>
<td>71 ± 12</td>
<td>87 ± 11</td>
<td>87 ± 7</td>
<td>0.01</td>
<td>NS</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>6 ± 5</td>
<td>7 ± 4</td>
<td>7 ± 4</td>
<td>8 ± 7</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>30 ± 10</td>
<td>25 ± 9</td>
<td>30 ± 11</td>
<td>33 ± 14</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>14 ± 7</td>
<td>11 ± 5</td>
<td>14 ± 7</td>
<td>15 ± 9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>3.5 ± 0.5</td>
<td>3.8 ± 0.8</td>
<td>3.6 ± 0.7</td>
<td>3.7 ± 0.9</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>43 ± 9</td>
<td>55 ± 14</td>
<td>42 ± 10</td>
<td>43 ± 11</td>
<td>0.003</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>97 ± 17</td>
<td>91 ± 14</td>
<td>95 ± 15</td>
<td>96 ± 12</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SVR (dyne·s·cm⁻⁵)</td>
<td>2,234 ± 427</td>
<td>1,945 ± 339</td>
<td>2,192 ± 520</td>
<td>2,202 ± 647</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean value ± SD. BP = blood pressure; CO = cardiac output (CO/HR); RAP = right atrial pressure; PCWP = pulmonary capillary wedge pressure; SV = stroke volume (CO/HR); SVR = systemic vascular resistance. Statistics by two-way analysis of variance (ANOVA).
Figure 1. Percent change from baseline in mean arterial pressure (MAP), systemic vascular resistance (SVR), heart rate (HR), pulmonary capillary wedge pressure (PCW) and thermoliation stroke volume (SV) after 3 months of nebivolol or placebo administration.

Table 3. Effects of Nebivolol Versus Placebo on Hemodynamic Measurements in the Catheterization Laboratory

<table>
<thead>
<tr>
<th>Drug</th>
<th>Group</th>
<th>p Value for Effect of Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebivolol</td>
<td>Placebo</td>
<td>Before</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>91 ± 12</td>
<td>74 ± 15</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>6 ± 7</td>
<td>5 ± 7</td>
</tr>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>34 ± 11</td>
<td>28 ± 9</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>12 ± 7</td>
<td>11 ± 9</td>
</tr>
<tr>
<td>CO (liters/min)</td>
<td>3.51 ± 0.61</td>
<td>3.88 ± 1.28</td>
</tr>
<tr>
<td>Mean AoP (mm Hg)</td>
<td>101 ± 11</td>
<td>97 ± 14</td>
</tr>
<tr>
<td>SVR (dynes-sec/cm^-5)</td>
<td>2,362 ± 366</td>
<td>2,171 ± 665</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>21 ± 11</td>
<td>15 ± 9</td>
</tr>
<tr>
<td>LVESESP (mm Hg)</td>
<td>130 ± 21</td>
<td>131 ± 27</td>
</tr>
<tr>
<td>+dP/dt_max (mm Hg/s)</td>
<td>973 ± 259</td>
<td>904 ± 271</td>
</tr>
<tr>
<td>-dP/dt_max (mm Hg/s)</td>
<td>1,195 ± 277</td>
<td>1,157 ± 328</td>
</tr>
<tr>
<td>Tau (ms)</td>
<td>39 ± 7</td>
<td>40 ± 5</td>
</tr>
</tbody>
</table>

Data are expressed as mean value ± SD. AoP = aortic pressure; LVEDP = left ventricular end-diastolic pressure; LVESESP = left ventricular end-systolic pressure; + and - dP/dt_max = maximal negative and maximal positive rate of pressure change; Tau = time constant of isovolumetric pressure decay; other abbreviations in Table 2. Statistics by two-way ANOVA.

Discussion

Comparison with previous studies. One previous study (5) has shown that long-term beta-blockade may improve hemodynamics (1–7) in cardiomyopathy through a long-term increase in myocardial contractility. This is an intriguing
Table 4. Effects of Nebivolol Versus Placebo on Left Ventricular Volume and Stress

<table>
<thead>
<tr>
<th></th>
<th>Nebivolol Before</th>
<th>Nebivolol After</th>
<th>Placebo Before</th>
<th>Placebo After</th>
<th>p Value for Effect of Drug</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV (ml)</td>
<td>277 ± 72</td>
<td>263 ± 74</td>
<td>289 ± 70</td>
<td>285 ± 75</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>217 ± 74</td>
<td>184 ± 87</td>
<td>228 ± 62</td>
<td>222 ± 75</td>
<td>0.07</td>
<td>NS</td>
</tr>
<tr>
<td>EF</td>
<td>0.23 ± 0.08</td>
<td>0.33 ± 0.12</td>
<td>0.21 ± 0.05</td>
<td>0.23 ± 0.09</td>
<td>0.002</td>
<td>NS</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>2.28 ± 0.64</td>
<td>1.99 ± 0.52</td>
<td>1.93 ± 0.61</td>
<td>1.86 ± 0.55</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>ESS (kdynes/cm²)</td>
<td>267 ± 69</td>
<td>261 ± 62</td>
<td>318 ± 97</td>
<td>317 ± 78</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>EDS (kdynes/cm²)</td>
<td>53 ± 28</td>
<td>38 ± 25</td>
<td>66 ± 22</td>
<td>59 ± 34</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>EFc</td>
<td>0.20 ± 0.14</td>
<td>0.32 ± 0.13</td>
<td>0.21 ± 0.10</td>
<td>0.21 ± 0.17</td>
<td>0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as mean value ± SD. EDS = end-diastolic wall stress; EF and EFc = ejection fraction and ejection fraction corrected for preload; ESS = end-systolic wall stress; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LVMI = left ventricular mass indexed to body surface area. Statistics by two-way ANOVA.

possibility because the short-term administration of beta-blockers produces a negative inotropic effect. Although that study included elegant measurement of ventricular performance (Emax), it was not placebo controlled. Because of our interest in confirming such a mechanism of action in a placebo-controlled study and because of the reluctance of many to use a potentially deleterious therapy in patients with heart failure, the present detailed investigation was performed. Our results confirm those of Eichhorn et al. (5), who showed that hemodynamic improvement occurs through an improvement in contractile performance and not simply because of a change in heart rate or loading conditions.

Several strengths in our study design lend credibility to this seemingly paradoxical conclusion that long-term treatment with a beta-blocker improves depressed contractility in cardiomyopathy. First, the addition of a placebo control group ensures that improvement in the treatment group was not spontaneous, as may occur with some types of cardiomyopathy (14). Hemodynamic status and left ventricular size and function were remarkably stable over the 3-month period of placebo administration in this group, with no significant change in diuretic dose. Second, the immediate measurements obtained in the catheterization laboratory were corroborated by 12-h (at baseline) and 24-h (at 3 months) monitoring. This observation is critical because Packer et al. (15) have shown that hemodynamic status can change dramatically during the early period of monitoring after catheter insertion. Third, our patients were all stabilized on diuretic therapy alone, whereas in the study of Eichhorn et al. (5), all medications—including, presumably, positive inotropic agents such as digoxin and vasodilators such as angiotensin-converting enzyme inhibitors—were allowed. These medications were also allowed in the important studies of Gilbert et al. (6) and Anderson et al. (7). Finally, both bucindolol and nebivolol are thought to have vasodilating properties and we considered it important to assess long-term drug effects on end-systolic stress to ensure that improvement in ejection fraction was not a result of reduced wall stress. The similarity of baseline and 3-month end-systolic stress in both treatment arms of our study strengthens this conclusion and corroborates our estimate of contractility (12), which is otherwise open to criticism.

Contractile and relaxation indices. It is noteworthy that in 19 of 22 patients with cardiomyopathy in the present study, the preload-corrected ejection fraction—end-systolic stress relation, our index of contractile function, was below the 95% prediction band defined by a previously studied (12) control group. This finding suggests that our index is indeed sensitive to chronically depressed contractile state, and it has previously been shown to be relatively load independent (12). Although we could not detect any increase in peak positive dP/dt, this index of contractility decreases with decreasing preload (16), and the decrease in preload observed in our patients may have been responsible for negating the expected increase in peak positive dP/dt.

In contrast to the study of bucindolol of Eichhorn et al. (5), we were not able to demonstrate any improvement in variables of myocardial relaxation (peak negative dP/dt and the time constant tau). Whether this difference between studies is due to a difference in drug properties or simply a methodologic difference is not apparent. Nevertheless,
nebivolol significantly reduced left ventricular end-diastolic pressure, presumably as a result of the improvement in systolic performance.

**Exercise tolerance.** Exercise tolerance did not improve with treatment, an effect that may in part be due to the 20-beat/min decrease in maximal heart rate with nebivolol. In the few previous studies of beta-blockade for cardiomyopathy, the effect on exercise tolerance has differed. Currie et al. (17) found no improvement in filling pressure or exercise tolerance and a decrease in maximal heart rate of 32 beats/min after 1 month of treatment with metoprolol. In a recent study of bucindolol by Gilbert et al. (6), exercise tolerance did not improve despite improvements in both hemodynamics and left ventricular function; maximal heart rate was also significantly decreased by treatment. In contrast, Engelmeier et al. (18) observed an improvement in exercise time with metoprolol and no significant reduction in maximal heart rate. Other factors contributing to impaired exercise tolerance in patients treated for cardiomyopathy include abnormalities in exercising skeletal muscle (19) and direct effects of beta-blockade on skeletal muscle performance (20).

Figure 3. A. Contractility estimated as preload-corrected ejection fraction (EFc) versus afterload (end-systolic stress [ESS]) before and after nebivolol. There is a marked shift toward the normal regression line by a mean of +0.12 unit (from −0.36 ± 0.13 to −0.24 ± 0.13 at 3 months) for the 10 patients in whom adequate data were available. B. No change in estimated contractility for the placebo group (that is, the mean perpendicular distance to the EFc, ESS regression line [−0.29 ± 0.14 to −0.29 ± 0.14 unit at 3 months]).

Figure 4. Pressure-volume loops before (Baseline) and after (Final) nebivolol administration, demonstrating a marked reduction of both end-diastolic and end-systolic volume without a decrease in pressure. Pt = patient.

Figure 5. Placebo group. Regression line relating angiographic left ventricular mass index (LVMI) at baseline (ordinate) and 3 months (abscissa) is near identity.
Mechanisms. The mechanism by which long-term beta-blockade improves myocardial contractility is unknown. The work of Eichhorn et al. (5) suggests that improved myocardial energetics may play a role. It is also possible that beta-blockade reduces the toxic effects (21) of high catecholamine levels (22) on the myocardium. Increased beta-receptor density has also been proposed (23), but it is unclear how this would improve contractility if the receptors are pharmacologically blocked.

Drug safety. Long-term treatment with phosphodiesterase inhibitors, which have a short-term positive inotropic effect, is poorly tolerated and increases the incidence of death (24). In contrast, beta-blockade given in gradually increasing doses has been well tolerated in patients with cardiomyopathy and, in the few previous studies that included a control group (6,7,18), no deaths were attributable to treatment. There was one death in the nebivolol arm of the present study. Ischemia or a malignant arrhythmia, or both, probably accounted for this sudden death and, in view of the results of the Beta-Blocker Heart Attack Trial (25), it is unlikely that treatment with nebivolol played a causal role. Larger studies are needed to confirm the role of beta-blockade in reducing malignant arrhythmias and mortality in patients with dilated cardiomyopathy (3).

Limitations of the study. First, the small size of this study probably prevented us from documenting more significant improvement in hemodynamic variables. Second, estimation of contractile performance is a limitation with the present or any other index of contractility. However, an increase in ejection fraction despite a reduction in preload (end-diastolic pressure and volume) and no change in afterload (end-systolic stress) is difficult to explain by any mechanism other than an increase in contractile performance.

Conclusions. Nebivolol is well tolerated with few side effects in patients with cardiomyopathy who are in stable condition and who are on high dose diuretic therapy. With long-term treatment, the drug has a negative chronotropic effect but paradoxically a positive inotropic effect, which results in a favorable hemodynamic response with an increase in stroke volume and a reduction in left ventricular filling pressure. Finally, despite hemodynamic improvement, exercise tolerance does not improve.

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References


