Are \( \beta \)-adrenergic–blocking drugs useful in the treatment of dilated cardiomyopathy?

JAMES ALDERMAN, M.D., AND WILLIAM GROSSMAN, M.D.

CONVENTIONAL treatment of patients with dilated cardiomyopathy has focused on the use of diuretic, inotropic, and vasodilator drugs. Despite the development of new vasodilators and inotropic agents, the bleak prognosis for these patients has changed little. An innovative and somewhat radical approach to the therapy of dilated cardiomyopathy was reported in 1975 by Waagstein et al.\(^1\) in Goteborg, Sweden. These investigators described seven patients with dilated cardiomyopathy who responded to \( \beta \)-adrenergic–blocking drugs with marked clinical improvement over a period of several months.

Since 1975 several groups of investigators have studied the effects of \( \beta \)-adrenergic blockers on the hemodynamics, clinical course, and survival of patients with dilated cardiomyopathy. Despite a widespread belief by the medical community that \( \beta \)-adrenergic blockers are harmful to patients with congestive heart failure, several studies have reported a salutary effect of these drugs in patients with idiopathic dilated cardiomyopathy. The results of published studies on this subject have been inconsistent, however.

The evidence in favor

In the initial study by Waagstein et al.,\(^1\) seven patients with advanced idiopathic dilated cardiomyopathy were treated with \( \beta \)-adrenergic blockade for 2 to 12 months. All patients had resting tachycardia, with a mean heart rate (98 ± 13 beats/min) that fell to 69 ± 16 beats/min at an average of 5.4 months of \( \beta \)-blockade. All patients experienced improvement in symptoms — four immediately and three gradually — after 1 month of therapy. Resolution of peripheral edema and ascites was also noted, and allowed reduction of doses of diuretics given to these patients. There was improvement in exercise capacity (seven of seven patients) and an increase in left ventricular ejection time and velocity of circumferential fiber shortening.

As a pilot study, this investigation was quite provocative. Contrary to the deterioration expected in these seven patients, functional class improved, physical working capacity was increased, and noninvasive parameters of myocardial function suggested improved ventricular performance.

In 1979 the same group of investigators\(^2\) reported that the survival of 24 patients with dilated cardiomyopathy treated with \( \beta \)-blocking drugs was prolonged compared with that of a control group selected retrospectively. Further describing their experience, the Swedish group reported in 1980 to 1983 on an expanding cohort of patients with dilated cardiomyopathy studied in a nonrandomized fashion.\(^3\) In one study\(^4\) they examined the effects of withdrawal of \( \beta \)-adrenergic blockers in 15 patients who had improved on therapy with metoprolol. After discontinuation of metoprolol, six patients developed exacerbation of left and right heart failure within 2 to 14 days. Thirteen patients exhibited a fall in left ventricular ejection fraction (determined echocardiographically), with an overall decrease of from 0.46 ± 0.03 to 0.35 ± 0.03 (p < .01). All but one patient showed an increase in heart rate after withdrawal of metoprolol. By 1983, the Swedish group had entered 46 patients into their study, and the average follow-up time had been increased to 34 months (22 days to 110 months).\(^5\) Eighteen of the subjects that entered the study more recently underwent cardiac catheterization and endomyocardial biopsy before treatment with \( \beta \)-blockers and were given 15 mg iv metoprolol over a short term. All but one patient tolerated this dose. The findings from short- and long-term studies\(^6\) in these patients are summarized in figure 1. Cardiac index fell acutely with the initiation of \( \beta \)-blockade (2.2 ± 0.5 to 1.9 ± 0.5 liters/min/m\(^2\)), but six patients in whom cardiac index was measured during long-term therapy showed an increase in cardiac index (1.8 ± 0.7 to 2.5 ± 0.6 liters/min/m\(^2\)). Similarly, there were minimal changes in left ventricular filling pressures over the short term (left ventricular end-
diastolic pressure fell from 22 ± 8 to 20 ± 7 mm Hg), but in 11 patients in whom measurements were made during long-term therapy, substantial improvement was noted (pulmonary arterial end-diastolic pressure fell from 25 ± 8 to 10 ± 3 mm Hg). Echocardiographic left ventricular ejection fraction improved from 0.34 ± 0.11 to 0.50 ± 0.14 in the 32 patients examined after 6 months of oral metoprolol therapy (p < .001). Most impressively, the survival rate was 65% at 2 years and 50% at 5 years, which is far superior to the reported natural history of disease in patients with dilated cardiomyopathy presenting with NYHA functional class III or IV heart failure.

Thus, since 1975 this group of Swedish investigators has followed prospectively a growing cohort of patients with idiopathic dilated cardiomyopathy treated with β-adrenergic blockade. As the number of patients has grown, trends toward functional and hemodynamic improvement have persisted. On an individual basis, the response of some patients to β-blockade has been dramatic, with functional improvement from NYHA class IV to class I, increase in left ventricular ejection fraction from 0.25 to 0.70, and discontinuation of therapy with digoxin and diuretics. Approximately 25% of the patients have returned to work.

However, as these investigators themselves have emphasized, the studies cited above have lacked a simultaneous randomized control group, and not all patients have been assessed, treated, and followed in a similar fashion. Also, although there has been variability in response to β-blocking drugs in these patients, it has not been possible to identify specific subgroups of patients more or less likely to benefit from β-adrenergic blockade.

Recently, other groups have reported beneficial effects of β-blockade in patients with dilated cardiomyopathy.6–9 Englemeier et al.7 studied 25 patients in a randomized crossover trial in which 82% experienced improvement in symptoms and exercise tolerance and 30% have shown sustained improvement in left ventricular ejection fraction and left ventricular end-diastolic dimension while on metoprolol. Anderson et al.8 studied 50 patients with dilated cardiomyopathy in a prospective randomized trial of metoprolol vs placebo. Functional class improved substantially in patients actually treated with metoprolol (not significant by intention-to-treat analysis). At Stanford, Fowler et al.9 studied 15 patients referred for heart transplantation and treated with metoprolol. Of the 10 patients who tolerated therapy and were followed for longer than 2 months, nine showed clinical improvement and the mean peak exercise left ventricular ejection fraction for the group almost doubled while they were on metoprolol (0.15 ± 0.03 to 0.27 ± 0.07; p < .05). Four of these patients were removed from the transplant waiting list.

The evidence against

Despite these reports indicating a salutary effect of β-adrenergic–blocking drugs in the treatment of dilated cardiomyopathy, some investigators have obtained less encouraging results. In New Zealand, Ikram and Fitzpatrick10 have studied the clinical and hemodynamic response to acebutolol, a cardioselective β-adrenergic blocker with intrinsic sympathomimetic activity. They studied 17 patients with NYHA class II or III congestive heart failure and reported the results of a double-blind, randomized, crossover study of acebutolol vs placebo over a 1 month treatment period. No beneficial effect of acebutolol was detected. The investigators failed to find symptomatic improvement, increased exercise tolerance, or diminution of cardiac chamber size.

However, there are several important differences between the Swedish studies and those of the New Zealand group. These differences include better initial functional class of the patients in New Zealand, a treatment period that may have been too short to adequately assess long-term effects of β-adrenergic blockade, and the use of a β-adrenergic blocker with partial stimulatory effects.

An additional study with negative results has been reported by Currie et al.,11 who conducted a double-blind crossover trial to assess the effect of metoprolol in 10 patients with severe dilated cardiomyopathy (NYHA class III). Angiographic examination revealed coronary artery disease in four patients. After 4 weeks of therapy, metoprolol produced a significant reduc-
tion in heart rate at rest and during exercise, although no differences were noted in mean blood pressure or left ventricular filling pressure. Metoprolol failed to produce any change in symptoms or exercise tolerance.

Thus, the literature addressing the possible role of β-adrenergic–blocking drugs in the treatment of dilated cardiomyopathy is limited to studies by only a few groups. The patient populations, duration of therapy, and choice of drug used varied significantly among the investigations, and therefore the differing results are not necessarily contradictory. The dramatic clinical improvement observed by some investigators suggests that there may exist a subpopulation of patients with dilated cardiomyopathy in whom long-term β-adrenergic blockade will improve myocardial function and prolong life. However, the common denominator, if any, among responders to therapy remains to be elucidated.

Potential mechanisms of beneficial effect

If β-adrenergic blockers do benefit some patients with dilated cardiomyopathy, what are the potential mechanisms? A variety of mechanisms have been suggested, including the following: (1) increased myocardial energy available for synthetic and reparative processes, (2) improved diastolic relaxation, filling, and compliance, (3) inhibition of sympathetically mediated vasoconstriction via prostaglandins and renin release, (4) protection against catecholamine-induced myocardial damage and necrosis, and (5) up-regulation of β-adrenergic receptors, allowing restoration of catecholamine responsiveness. A mechanism that was proposed by Waagstein et al. in 1975 is a reduction in heart rate that results in a decrease in myocardial energy demand, “allowing more energy to be used for the contractile work.” This proposed mechanism may be playing some role, but major improvement in contractile function is not seen over the short term, despite an immediate reduction in heart rate. However, increased myocardial energy stores may renew a favorable balance between cellular reparative and synthetic processes on the one hand, and degenerative and catabolic processes on the other, thus permitting a gradual and progressive improvement in cellular structure and function. In this regard, a recent report described a reversible form of left ventricular dysfunction in patients with chronic, uncontrolled, symptomatic tachycardia. After tachyarrhythmias were stopped with a corrective procedure, patients experienced marked improvement in left ventricular ejection fraction, as determined by radionuclide ventriculography, from 0.19 ± 0.09 at baseline to 0.44 ± 0.14 at 11 to 51 months after surgery (p < .005). β-Adrenergic blockade may similarly improve left ventricular function in patients with cardiomyopathy and resting tachycardia.

Several investigators studying diastolic function have noted the deleterious physiologic effects of tachycardia in patients with dilated cardiomyopathy. Braunwald et al. found that “tachycardia above a rate critical for each heart elevated left ventricular end-diastolic pressure for any given end-diastolic circumference.” Mitchell et al. demonstrated that “abbreviation of diastole at high imposed heart rates . . . may leave an inadequate time for ventricular relaxation to take place and for inertial and viscous factors to be dissipated.” In a hemodynamic study of patients with congestive cardiomyopathy, Grossman et al. demonstrated impaired left ventricular relaxation (decreased peak negative dP/dt, depressed rate of early diastolic circumferential fiber lengthening) and decreased diastolic chamber distensibility. Indexes of left ventricular contractility and relaxation were depressed in patients at rest and failed to be augmented normally with pacing-induced tachycardia (figure 2). It was suggested in that study that the inability to increase the rates of left ventricular contraction and relaxation during tachycardia may be secondary to either alterations in wall viscoelasticity or to a biochemical effect such as defective calcium release and uptake.

Another possible mechanism of the beneficial effect of β-blockade in patients with dilated cardiomyopathy is the reduction in afterload yielded by inhibition of the sympathetically mediated increase in vasomotor tone

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\text{VCF}_L = \frac{\text{VCF}_F}{1 + \text{HEART RATE}}
\]

FIGURE 2. A comparison between normal subjects and those with cardiomyopathy with respect to the response of velocity of circumferential fiber shortening (VCF₉) and lengthening (VCF₉) to pacing-induced tachycardia. As heart rate was increased, velocity of shortening and lengthening failed to increase in the patients. (Reprinted with permission from Grossman et al.)
present in these patients (via stimulation of prostaglan-
dins or reduction of renin release).

Other speculation has focused on the protective ac-
tion of \(\beta\)-blockade against the possible deleterious ef-
fects of sympathetic activity on the myocardium. Flecken-
stein et al.\(^6\) demonstrated that high concen-
trations of isoproterenol led to excess calcium entry into
cells, causing overactivation of calcium-dependent in-
tracellular ATPases, resulting in energy depletion, mi-
 tochondrial damage, and cell necrosis. This effect was
prevented by \(\beta\)-blocking drugs. Bajusz et al.\(^7\) dem-
onstrated acceleration of the natural course of disease in
Syrian hamsters with hereditary cardiomyopathy by
the administration of catecholamines, an effect that
could be inhibited by \(\beta\)-blockers. In man, pheochrom-
ocyctoma may induce cardiomyopathy, and \(\beta\)-block-
ade has been used to protect the myocardium in pa-

Finally, there is evidence that \(\beta\)-adrenergic recep-
tors are down-regulated in patients with congestive
heart failure,\(^8\) and that myocardial catecholamine lev-
els are depleted even though serum levels are high. \(\beta\)-
Blockade may permit up-regulation of receptors,\(^9\)
allowing for restoration of cardiac norepinephrine and
improved myocardial function.

In conclusion, the treatment of patients with dilated
cardiomyopathy and congestive heart failure with \(\beta\)-
adrenergic blocking drugs remains controversial and
awaits ultimate support or discredit by a large, ran-
domized, double-blind controlled trial in which diag-
nostic entry criteria, type and dose of \(\beta\)-blocker used,
and follow-up regimen are standardized. However, it
appears likely that a subpopulation of patients with
dilated cardiomyopathy does respond dramatically to
this therapy with symptomatic and functional improve-
ment and prolonged life. The characteristics that de-

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J Alderman and W Grossman

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