EDITORIAL

β-Blockade — rational or irrational therapy for congestive heart failure?

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CLINICAL AND BASIC RESEARCH in the arena of congestive heart failure is intensive. Nevertheless, accepted treatment modalities for patients with this debilitating and fatal disease are limited to just three: digitalis, diuretics, and vasodilators, and only the latter has been demonstrated to improve survival in patients with congestive heart failure.1 Although cardiac transplantation markedly restores the patient’s functional capacity and reduces mortality in patients with symptomatic congestive heart failure, it is expensive, limited to selected patients, and commits the patient to the many risks of long-term immunosuppression.

Recent evidence now suggests that β-blockers may represent a new treatment modality that may not only improve symptoms of heart failure in some patients but reduce mortality and improve left ventricular function as well. Since the concept of administering β-blocking agents to patients with congestive heart failure runs contradictory to long-established teaching, I will review some of the evidence that they in fact do work and discuss some potential mechanisms of their action.

The early proponents of administering β-blocking agents to patients with congestive heart failure, specifically those with dilated cardiomyopathy, were those in the Swedish group from the University of Goteborg. These investigators reported their experience in 1975 after having administered β-blockers to seven patients with advanced cardiomyopathies who had resting tachycardias and symptoms refractory to conventional medical therapy.2 They were motivated to do this because of favorable results that they had observed in patients with acute myocardial infarctions complicated by tachycardia and heart failure. These patients with dilated cardiomyopathy noted improvements in their symptoms, their exercise capacity improved as measured by treadmill testing, and reductions in their heart size were documented by echocardiography and serial chest x-rays.

Since this initial favorable experience, these investigators have continued to publish encouraging data. This has included their continued favorable results in a larger group of 46 patients with dilated cardiomyopathy who were treated with long-term β-blockade.3 They have also shown that those treated with β-blockers appear to have improved survival as compared with a retrospective control population not treated with β-blockers but with similar degrees of left ventricular dysfunction and clinical characteristics.4 At 3 years of follow-up, the survival of patients treated with β-blockers was 52%, but was only 10% in matched controls. Finally, in a group of 15 patients who had particularly dramatic improvements with β-blocker therapy, all experienced either clinical deterioration or significant reductions in left ventricular function when β-blockade was withdrawn; one patient died 2 weeks after discontinuation of therapy.5

Despite these exciting results, the implications of these data have not been widely accepted because these studies were uncontrolled, unblinded, nonprospective, and could not be confirmed by other investigators in more controlled, although smaller and briefer, studies.6,7 More recent data, however, from other investigators now appear to substantiate the positive role of β-blockers in congestive cardiomyopathy.

The most compelling of these studies was performed at Loyola University by Engelmeier et al.8 In that study, eight patients were randomly assigned to receive either placebo or metoprolol in a double-blinded fashion and were followed for 12 months. In addition, 12 patients were followed for an average of 12 months after crossing over from placebo to open-label metoprolol. The metoprolol-treated patients experienced a significant improvement in exercise capacity and functional class, and in the double-blind study a significant improvement in the ejection fraction occurred as well. Particularly striking was the improvement that occurred in seven of the metoprolol-treated patients who had resolution of nearly all symptoms of congestive heart failure and a doubling of their exercise capacity, which correlated with a significant improvement in the ejection fraction and diminution of left ventricular size.

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Although encouraging, this study is still hampered by its small size, lack of differences in mortality between the treated and nontreated groups, and because not all patients were treated in a double-blind and randomized fashion.

Currently, a much larger trial is under way that by its design should give meaningful results as to the effects of metoprolol on cardiac function, hemodynamics, survival, and arrhythmias. This multicenter, international trial will blindly randomize over 300 patients to receive either metoprolol or placebo and will follow serially radionuclide ejection fraction, left ventricular size by echocardiography, 24 hr Holter monitors, exercise capacity as measured by treadmill testing, hemodynamics, and mortality for an 18 month period. The results of this study, if favorable for metoprolol, should have a strong impact on the treatment of patients with dilated cardiomyopathy, and regardless of the final outcome, will certainly further our understanding as to the role that chronic sympathetic stimulation plays in heart failure.

The mechanisms by which chronic /3-blockade could improve cardiac function in patients with dilated cardiomyopathy are unknown. Nevertheless, a variety of potential explanations are currently under investigation. Patients with congestive heart failure have chronically heightened sympathetic tone that exposes the myocardium to an excess of serum catecholamines.9 Early in the cycle of congestive heart failure this may be beneficial because of the positive inotropic and chronotropic effect that catecholamines exert on the myocardium.10 However, when the myocardium is exposed to continued and chronic excess catecholamine stimulation, the long-term effects on cardiac function may be detrimental. This could occur in a variety of ways.

Catecholamines are a cardiac toxin. Patients with pheochromocytoma, for example, have a high incidence of cardiomyopathy, and foci of necrosis and myocarditis can be demonstrated pathologically in such patients.11, 12 Similarly, a cardiomyopathy can be induced in a variety of animals given infusions of norepinephrine, and foci of necrosis have been demonstrated in the myocardium of patients with normal hearts who were given pharmacologic doses of catecholamines.13 /3-Blockade may thus be protective to the myocardium by blocking this direct toxic effect.

Besides this direct toxic effect, chronic sympathetic stimulation may lead to pathologic biochemical alterations within the myocardium. For catecholamines to exert their positive inotropic effect, they must first stimulate the /3-receptor that then leads to increased intracellular cyclic AMP. This allows more calcium to be available to the myocardial contractile elements and thus to enhanced cardiac contractility.14 However, chronic sympathetic stimulation leads to a reduction in the number of /3-blockers available for stimulation and a reduced responsiveness to catecholamine stimulation.15, 16 /3-Blockers are known to cause upregulation of /3-receptors and thus might restore the heart’s responsiveness to endogenous catecholamine stimulation, particularly when their levels rise during periods of exercise.17

A second biochemical alteration that occurs with chronic sympathetic stimulation is a reduced ability of the noradrenergic sympathetic nerves of the heart to synthesize norepinephrine. This has been demonstrated in animal preparations of cardiomyopathy with heightened sympathetic tone18 and in failing human hearts removed at the time of transplantation.19 Thus, a paradox develops. On the one hand, blood levels of catecholamines are elevated and potentially toxic to the myocardium, yet neuronal levels of norepinephrine, which are required for release to stimulate the myocardium during periods of enhanced cardiac sympathetic traffic, such as during exercise, may actually be reduced. Although /3-blockers have not been investigated as yet in this regard, ganglionic blockade in animals preparations has been shown to restore the ability of the noradrenergic sympathetic nerves to synthesize norepinephrine.18

Besides these direct myocardial effects, increased sympathetic tone plays an important role in enhancing a number of peripheral neuronendocrine mechanisms, all of which may lead to progressive heart failure.20 First, sympathetic stimulation leads to arterial and venoconstriction and thus increased preload and afterload. Second, sympathetic stimulation leads to increased production of renin and ultimately angiotensin II. Not only is angiotensin II a potent vasoconstrictor, which thus leads to further increases in cardiac afterload, but in addition it leads to the increased production of aldosterone and thereby enhances salt and water retention. Finally, sympathetic stimulation leads to the release of the hormone arginine vasopressin, a potent vasoconstrictor and stimulator of thirst, which also reduces the kidneys’ ability to excrete free water, thus leading to further worsening of congestive heart failure. Therefore, /3-blockade may improve cardiac performance by blocking the sympathetic enhancement of these neuroendocrine pathways.

Finally, some general actions of /3-blockers, including their anti-ischemic and antiarrhythmic effects,21 may contribute to the beneficial results seen with /3-
blocker administration, particularly with regard to mortality from sudden death, which occurs in approximately 50% of patients with congestive heart failure regardless of the cause.

Thus, ample mechanisms are available to explain why β-blockers might be effective therapy for patients with congestive heart failure, particularly those with dilated cardiomyopathy. These mechanisms give further support to the initial positive clinical experience that some investigators have reported.

β-Blockade must be used with extreme caution when given to patients with active congestive heart failure. These patients must first be stabilized on maximum medical therapy, including vasodilators, and begun on very small doses of β-blockers that are gradually titrated upward; this may take 1 to 2 months. Based on current knowledge, β-blocker therapy should not be considered part of the management of patients with congestive heart failure until the results of larger trials such as Metoprolol in Idiopathic Dilated Cardiomyopathy are available. Nevertheless, just as the concept of vasodilator therapy was initially met with great skepticism, yet is now universally embraced, so too may be the case for β-adrenergic blockade for the treatment of congestive heart failure in the years to come.

References
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