Editorial

β-Blocker Treatment for Chronic Heart Failure
The Frog Prince
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β-Blocking Agents Are Introduced:
The Promise of the Frog

In 1975, Waagstein and colleagues1 published several case reports of patients with heart failure and tachycardia who clinically improved after long-term administration of β-adrenergic antagonists. These initial reports were met with substantial skepticism, since β-blocking agents are negatively inotropic and chronotropic. Their use for treatment of heart failure is counterintuitive and demands considerable clinical acumen and patience to safely institute therapy.2 Thus, on the surface, this therapy is “ugly,” much like the frog from the fable of the Frog Prince.

Since Waagstein’s initial report, the Göteborg collaborators have published several studies on larger patient groups that confirmed their early findings with favorable effects of metoprolol on cardiac function, exercise capacity, and tolerance.3-5 It was reported that institution of long-term β-blockade improved cardiac function and functional class, withdrawal caused deterioration, and reinstitution resulted in improvement.3,5 This group also suggested that chronic β-blockade in patients with idiopathic dilated cardiomyopathy may prolong survival.6 Although this was a small prospective study, a historical control group with matched patients was used, and this was a significant limitation.

Twenty-two randomized trials involving 1679 patients have been performed to examine changes in ventricular function, functional status, morbidity, and mortality when β-adrenergic blockade is given to patients with congestive heart failure.2,7-28 In addition, ongoing but as yet unanalyzed studies with carvedilol have involved more than 700 patients. Thus, β-blockers have been administered safely to more than 2300 patients with heart failure. Although some of these trials are small, there is remarkable consistency between trials.

Effects on Ventricular Function:
The Frog Keeps His Promise

Two facts are clear from examination of the literature: (1) Judicious use of β-blockade under controlled conditions and with careful up-titration is safe and well tolerated (with tolerability in excess of 90% for most studies), and (2) treatment of heart failure with β-blockade produces improvement in left ventricular systolic function and reduction in ventricular size. No β-blocker trial of >1 month’s duration has shown a reduction or worsening in ventricular function.2 Indeed, a consistent improvement in ejection fraction is seen in studies of ≥3 months’ duration. Studies by both Eichhorn et al14,29 and Wisenbaugh et al17 suggested that β-antagonists improve contractility, reduce systolic wall stress and end-diastolic pressure, and increase myocardial work without increasing myocardial oxygen consumption. This suggests that β-blockade improves myocardial efficiency. These effects appear to occur whether a selective14,17 or a nonselective29 β-antagonist is used. Although the mechanism of these findings has yet to be elucidated, neurohormonal antagonism with a β-blocking agent appears to be mechanically and energetically favorable. More recent studies have suggested that changes in substrate utilization produced by neurohormonal antagonism14 and upregulation of calcium uptake proteins30 may play a role in these favorable changes.

Changes in Functional Status

In contrast to the changes in left ventricular function, the changes in functional capacity produced by β-blockade in heart failure patients have been somewhat inconsistent. Although every study of >1 month’s duration has shown improvement in functional classification,5 it has been difficult to demonstrate improved exercise capacity. Since β-antagonists block maximal heart rate increases, maximal workload will not be achieved in the presence of these agents. This appears to be especially cogent in the face of nonselective β-blockade. Since β1-receptors are down-regulated in response to norepinephrine exposure, the β2-receptor may play a more prominent role in the failing heart.31,32 Several trials of exercise tolerance using the β1-selective agent metoprolol demonstrated improvement in maximal exercise tolerance.5,15 By contrast, β-adrenergic blockade with the nonselective antagonist bucindolol repeatedly failed to improve either exercise tolerance and/or peak VO2.11,16 These data suggest that the maximal exercise and left ventricular responses to β-blocking agents are not equivalent (ie, the improvement in left ventricular function is not uniformly translated into improved maximal
exercise). More recent trials have focused on submaximal exercise to show functional improvement. Although submaximal exercise is more representative of performance of daily activities than maximal exercise, the results of these studies are pending. Because exercise tolerance has been difficult to demonstrate with β-blockers, approval of these agents by the Food and Drug Administration for use in heart failure may rely on demonstration of a survival benefit.

**Differing Effects on Neurohormonal Activation**

β-Blockers result in antagonism of the sympathetic nervous system at the receptor level. However, β-blocking agents have differing effects on plasma norepinephrine. Bucindolol, a nonselective α-antagonist, results in reduction in plasma norepinephrine, whereas metoprolol, an agent that reduces clearance of norepinephrine, results in no change or only mild reduction. In addition, metoprolol up-regulates β₁-receptors, whereas carvedilol and bucindolol (which have guanine nucleotide–modulatable binding) do not. Thus, bucindolol more completely inactivates the sympathetic drive to the heart, because it lowers plasma norepinephrine, blocks both receptors (β₁ and β₂), and does not increase receptor density. By contrast, metoprolol neither lowers plasma norepinephrine nor blocks the β₂-receptor. This may result in unblocked sympathetic drive to the heart mediated by the β₂-receptor. Since this receptor may play a more prominent role in the failing heart, this may account for the possible differences in exercise tolerance. As one exercises, sympathetic drive to the heart increases, and the unblocked β₂-receptor may allow more complete heart rate response and better exercise tolerance.

**Effect of β-Blockers on Survival**

It was first proposed by the Göteborg group that long-term β-blockade may reduce mortality in patients with idiopathic dilated cardiomyopathy. More recently, a larger study, the Metoprolol in Dilated Cardiomyopathy (MDC) trial, was published on effects of β-blockers on a combined end point of death and need for cardiac transplantation. There were 34% fewer (95% confidence interval, −6 to +62%; P = .058) primary end points in the metoprolol than the placebo group. Fewer patients in the metoprolol group (2 versus 19) deteriorated to the point of needing transplantation, and a nearly equal number of patients (23 versus 19) died.

Several trials have examined the secondary prevention effect of β-blockers on survival after myocardial infarction. From pooled data of a total of more than 25,000 patients in 24 trials, a significant reduction in total mortality and sudden death has been shown. Although no differences between β₁-selective and nonselective agents have been detected from pooled results with regard to their effect on overall mortality and sudden death, results from the two largest late-entry (>48 hours after infarction) trials of nonselective β-blockade, the β-Blocker Heart Attack Trial (3837 patients) and the Norwegian Multicenter trial (1884 patients), revealed 26% and 45% reductions in sudden death, respectively. By contrast, the largest study of late-entry β₁-selective blockade, the Lopressor Intervention Trial (2395 patients), failed to show any reduction in sudden death. In addition, the ISIS-1 trial, an early-entry trial of atenolol in more than 16,000 patients suffering a myocardial infarction, failed to show an in-hospital reduction in sudden death. Conversely, pooled data of all metoprolol long-term postinfarction studies, including the Lopressor Intervention Trial (5474 patients, 2195 early entry and 3279 late entry), showed a 40% reduction in sudden death. Thus, the question whether differences in sudden death exist between selective and nonselective β-blockers in patients with left ventricular dysfunction or injury is still unresolved. If such differences in sudden death do exist, one might postulate that incomplete deactivation of the sympathetic nervous system (an unblocked β₁-receptor), while beneficial to achieve a more appropriate exercise response in patients with heart failure, may be less beneficial with regard to survival. However, such differences have yet to be conclusively demonstrated.

Whether other properties of β-blockers may impact favorably on survival is not known. It has been proposed that lipophilicity with penetration to the central nervous system may be of importance, since only β-blockers with a higher degree of lipophilicity have shown significant effects on post–myocardial infarction survival.

In addition, it is more complete heart rate response and better exercise tolerance.

**The CIBIS Trial**

In this issue of *Circulation*, Lechat and associates present the primary outcome data from the Cardiac Insufficiency Bisoprolol Study (CIBIS). This study is the largest prospective heart failure mortality study of β-blockade published to date. The authors of this study randomized 641 patients with heart failure of various causes to bisoprolol, a highly selective β₁-antagonist, or placebo. Patients had an ejection fraction <40% and were in New York Heart Association functional class III (95%) or IV (5%) at randomization. Participants received background therapy with diuretics and vasodilators (primarily angiotensin-converting enzyme inhibitors) and were followed for 1.9 years. The authors demonstrated the safety and tolerability of β-blockade, even in very functionally impaired patients. The authors found no difference in overall mortality for β-blockade versus placebo (relative risk, 0.80 [95% confidence interval, 0.56 to 1.15], P = .22). In addition, as with the MDC trial, no differences in sudden death were seen. However, subgroup analysis demonstrated a survival benefit of bisoprolol in those patients without a history of myocardial infarction or with a diagnosis of primary dilated cardiomyopathy. This finding is consistent with the more favorable hemodynamic effects of β-blockade seen in patients with dilated versus ischemic cardiomyopathy. Functional status of the patients on bisoprolol was improved, with less heart failure decompensation and hospitalization, a finding similar to that seen in the Metoprolol and Dilated Cardiomyopathy Trial. Unfortunately, the CIBIS trial was underpowered, thus leaving unanswered the question of a survival benefit of β-blockers in subjects with heart failure. The trial was underpowered because (1) the assumption of a 33% mortality reduction in the face of background angiotensin-converting enzyme inhibitor
therapy was overly optimistic; (2) although a 2-year 36% to 38% placebo mortality is reasonable for a balanced group of patients with class III and IV heart failure, the investigators randomized almost exclusively class III patients, a group with a lower mortality. If the β-blocker paradigm acts in a fashion similar to that of ACE inhibitors, the more symptomatically advanced patients may derive the most survival benefit from therapy; (3) since previous studies have shown a more favorable hemodynamic response in patients with dilated as opposed to ischemic cardiomyopathy and since the CIBIS study suggests a more favorable survival benefit for nonischemic origin, the disproportionate randomization of patients with previous myocardial infarction to the bisoprolol arm of this study may have reduced the investigators' chances of detecting a survival benefit; and (4) only 53% of the patients randomized to bisoprolol received ≥3.75 mg of the drug. Since a previous dose-ranging bucindolol study has shown a more favorable ejection fraction response to higher doses of β-blockade, it is possible that higher doses of β-blockade may provide more survival benefit, although this has not been tested. Because bisoprolol (a β-selective agent) did not reduce sudden death, to show a survival benefit it had to win solely on ventricular function (ie, reduce death from pump failure). This increases the importance of increasing dosage to target so as to maximally improve ventricular function. Thus, it is possible that the bisoprolol group may have been undertreated.

**Future Studies of β-Blockers on Survival:**

Will the Frog Turn Into a Prince?

Despite these limitations, the CIBIS and MDC investigators have given us a glimpse of a very promising therapy. In the MDC trial, metoprolol therapy reduced the need for cardiac transplantation. In the CIBIS trial, survival tended to be better in the bisoprolol group, and within the subgroup of patients with no history of myocardial infarction, there was a survival benefit. One must be cautious, though, with a retrospective subgroup analysis. However, judging by the rationale that these drugs are well tolerated, improve myocardial efficiency and energetics, reduce hospitalization and functional deterioration, and may have a beneficial effect on survival, β-blockers may still be a very promising therapy for heart failure. However, the frog remains an amphibian. The Clinical Trials Division of the National Heart, Lung, and Blood Institute and the Cooperative Studies Program of the Veterans Administration will initiate a multicenter trial of β-blockade later this year. This study, the β-Blocker Evaluation of Survival Trial (BEST), will randomize 2800 patients with ejection fractions ≤0.35 and New York Heart Association class III or IV heart failure to bucindolol (a nonselective β-antagonist that lowers adrenergic activity) or placebo. Patients with and without coronary artery disease will be randomized, and follow-up will be a minimum of 18 months. Similar studies are planned in Europe on carvedilol and metoprolol. It is hoped that these studies will have enough power to finally determine whether the frog is in fact a prince.

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