

## Cardiodynamic Effects and Mechanisms of Action of $\beta$ -Blockers

Based on a presentation by Barry H. Greenberg, MD

### *Presentation Summary*

The long-term beneficial effects of  $\beta$ -blocker therapy in heart failure have been clearly established. However, the underlying mechanisms responsible for the improvement in the clinical course and natural history of heart failure remain unclear.  $\beta$ -blockade could work through any number of pathways to improve survival and decrease the risk of progressive heart

failure. The possibilities include favorable effects on cardiac structure and function, protection from sudden cardiac death, prevention of coronary events, and reduction in oxidative stress. In all likelihood, no single mechanism accounts for the clinical benefits of  $\beta$ -blockade, but further studies are needed to identify and clarify the roles of the different mechanisms that contribute to the clinical benefits.

The benefits of long-term  $\beta$ -blocker therapy in chronic heart failure have become well established. Large, well-designed clinical trials have consistently shown that  $\beta$ -blockade significantly reduces the risk of morbidity and mortality in heart failure patients.

However, the mechanisms that underlie the clinical benefits and account for the ability of  $\beta$ -blockers to alter the natural history of chronic heart failure are less clear than the benefits themselves. A biological and clinical laundry list of putative mechanisms exists.<sup>1</sup> Chief suspects among the possibilities include the favorable effects of  $\beta$ -blockers on cardiac structure and function, protection against sudden cardiac death, prevention of coro-

nary events, and reduction of oxidative stress.

In all likelihood, no single mechanism can explain the beneficial effects of  $\beta$ -blockade that are seen in numerous clinical trials involving heart failure patients. Instead, a variety of interrelated factors most likely account for the benefits and cannot be easily separated. From the perspective of daily medical practice, understanding the reasons for the effects of  $\beta$ -blockers in heart failure might have little significance for patient management and clinical decision making. However, better recognition of the factors underlying the clinical benefits might provide insights that could lead to improved application of  $\beta$ -blockers in the setting of heart failure.

One potential mechanism of benefit can be gleaned from looking at the effects of  $\beta$ -blockade on the prevention of recurrent events in survivors of myocardial infarction (MI), and patients with documented coronary artery disease (CAD).  $\beta$ -blockers clearly reduce the risk of reinfarction in the post-MI population.<sup>2</sup> The reduced risk of reinfarction can be seen in patients who have uncomplicated MI and in those whose condition is complicated by other clinical factors, such as diabetes. Given the major role that CAD plays in the etiology of heart failure, the favorable impact of  $\beta$ -blockers on reinfarction risk represents at least part of the explanation for the drugs' beneficial effects.

Closely related to the reinfarction issue is the ability of  $\beta$ -blockers to protect against myocardial ischemia. Treatment with  $\beta$ -blockers decreases myocardial oxygen consumption and improves left ventricular function at rest and during exercise.<sup>3</sup> The cumulative effect of these benefits should include protection against recurrent myocardial ischemia.

$\beta$ -blockers also protect against the catecholamine storm that can develop in patients with left ventricular systolic dysfunction. High catecholamine levels are directly toxic to cardiac myocytes and can also promote myocyte apoptosis or programmed cell death. Additionally, catecholamines can downregulate and desensitize  $\beta$ -adrenergic receptors, 2 phenomena that appear in some cases to be reversed by  $\beta$ -blockade.

Most placebo-controlled clinical trials that have continued  $\beta$ -blocker therapy for at least a month have shown significant improvement in left ventricular ejection fraction, which is associated with a reduced risk of clinical events.  $\beta$ -blockade initially may lead to a reduction in left ventricular ejection fraction, but with sustained therapy, ejection fraction improves in most patients and is associated with a better outcome. Conversely, sus-

tained deterioration in contractile function is associated with an increased risk.<sup>4</sup> The improvement in contractile function observed with  $\beta$ -blockade clearly represents another mechanism by which treatment can improve outcome.

Interestingly,  $\beta$ -blocker-induced improvement in ejection fraction may not account entirely for the enhanced myocardial contractility that occurs with treatment. In placebo-treated patients, improved cardiac function has been shown to have no overall correlation with an improved clinical course or risk.<sup>4</sup> The dissociation between cardiac function and clinical course in placebo patients suggests that factors other than improved contractility account for the link between improved functional performance and outcome (or reduced risk) observed in heart failure patients who are treated with  $\beta$ -blockers.

Recent evidence has suggested that  $\beta$ -blockers also have a favorable influence on diastolic function.<sup>5</sup> The data showed that 6 months of treatment with metoprolol reduced left ventricular end-diastolic pressure (LVEDP). More important, reduced LVEDP was associated with significant improvement in isovolumic relaxation and indices of myocardial stiffness. The findings suggested that the reduction in filling pressure was related to an intrinsic change in left ventricular diastolic properties. Similar findings with bucindolol have been reported in experimental models of heart failure.<sup>6</sup>

Sudden death is one of the most feared complications of heart failure. Sound data exist to show that treatment with a  $\beta$ -blocker substantially reduces the risk of sudden cardiac death in heart failure patients. For example, a meta-analysis of data from 5 studies of post-MI patients showed striking, highly significant reductions in the incidence of sudden death in patients treated with metoprolol, compared with placebo.<sup>2</sup>

More recently, findings from the Metoprolol Controlled Release/Extended Release (CR/XL) Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) showed a marked 41% reduction in the incidence of sudden cardiac death in patients treated with metoprolol versus placebo.<sup>7</sup> Closer inspection of the data provided some insights into the risks of sudden death in the heart failure population. In patients with New York Heart Association class II heart function, sudden death accounted for the majority of deaths in the trial. With worsening heart function, the role of sudden death in mortality declined, and in class IV patients, worsening heart failure accounted for about half the deaths, compared with two thirds of the deaths among class II patients.

Similar favorable effects on the risk of sudden death have been reported in trials of bisoprolol<sup>8</sup> and carvedilol.<sup>9</sup> Collectively, data from trials of  $\beta$ -blockade in heart failure leave little doubt that the drugs reduce the risk of sudden cardiac death. Whether the beneficial effect relates to a favorable impact of  $\beta$ -blockers on cardiac remodeling, to some intrinsic antiarrhythmic effect, or to some other factor has not been determined.

Cardiac remodeling has emerged as a key contributor to the progression of heart failure. After infarction, remodeling initially presents as a thinning and bulging in the area of the infarct zone. Over months or years the remodeling process continues and eventually involves previously spared segments of myocardium, which undergo eccentric hypertrophy. Left ventricular volume and total mass increase, accompanied by changes in the geometry of the chamber itself. The cumulative effect of the remodeling process is systolic and diastolic dysfunction.<sup>10</sup>

Neuroendocrine activation, particularly the sympathetic nervous system and the renin-angiotensin system, plays a major role in the initiation and progression of cardiac remodeling.

Neurohormonal activation promotes remodeling in 2 major ways: 1) increased load brought about by

*“Cardiac remodeling has emerged as a key contributor to the progression of heart failure. After infarction, remodeling initially presents as a thinning and bulging in the area of the infarct zone.”*

sodium and water retention and 2) peripheral vasoconstriction. Neurohormonal activation also has direct effects on cardiac myocytes, including growth stimulation and direct toxicity. Additionally, primary neuroendocrine activation unleashes a cascade of secondary neurohormonal substances, such as endothelin, which further promotes the remodeling process.<sup>10</sup>

Clinical studies of heart failure have provided evidence that certain interventions, notably angiotensin-converting enzyme (ACE) inhibitors and  $\beta$ -blockers, can attenuate or reverse the remodeling process. Data from the Studies of Left Ventricular Dysfunction trial clearly showed a beneficial effect of ACE inhibition on remodeling.<sup>11</sup> Over time patients who were randomized to placebo had continued expansion of left ventricular mass; in contrast, patients treated with an ACE inhibitor had attenuation of remodeling, and some patients experienced a reversal of the process, causing the heart to revert toward its normal size and geometry.

$\beta$ -blockade not only leads to attenuation but also reverses the remodeling process. For example, in the Australia-New Zealand carvedilol trial patients with ischemic left ventricular dysfunction had a significant reduction in the risk of mortality, hospitalization, and the need for ancillary heart failure medications.<sup>12</sup> The clini-

cal improvement correlated with a reduction in left ventricular volume, as determined by echocardiography. Similar associations were demonstrated in the US carvedilol trials.<sup>13</sup>

Heart failure patients in trials of  $\beta$ -blocker therapy were already receiving an ACE inhibitor, which has been shown to have a favorable effect on cardiac remodeling. The effect of  $\beta$ -blockers on remodeling occurred in addition to the effect observed with ACE inhibitors.

The mechanisms discussed are very likely interrelated. The beneficial clinical effects of  $\beta$ -blockers cannot be traced to any single underlying mechanism. Further investigation of  $\beta$ -blockade in heart failure is needed to clarify the respective role of the individual mechanisms associated with clinical benefits and to provide further insight into available means of improving the clinical course of heart failure.

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... QUESTION-AND-ANSWER SESSION ...

After delivering his presentation, Dr. Greenberg answered questions from the audience.

*Question: What role does myocardial viability play in predicting response to  $\beta$ -blocker therapy?*

*Dr. Greenberg:* Myocardial viability might be an important factor in responsiveness to  $\beta$ -blockade in the ischemic population, but it's not the entire reason. If you look at non-ischemic patients, there is also significant improvement in the clinical course associated with  $\beta$ -blocker therapy. However, I'm not sure that improvement in the ischemic myocardium over time is the reason for improvement in the clinical course that is observed in patients who receive  $\beta$ -blockers.

*Question: Are there important differences between carvedilol and metoprolol in the treatment of heart failure?*

*Dr. Greenberg:* The 2 drugs are distinctly different molecules, and they have different pharmacologic properties, which might relate to different hemodynamic effects in patients. Right now, we don't know whether the additional properties of a molecule like carvedilol translate into additional clinical benefits compared with a drug like metoprolol. That issue is being evaluated in an ongoing head-to-head clinical comparison of the 2 drugs.

*Question: If a patient responds poorly to carvedilol or has problems with side effects, is it reasonable to try metoprolol?*

*Dr. Greenberg:* It has been my impression that if you have trouble with one  $\beta$ -blocker, you will have trouble with the others that are available. I'm not convinced that switching to another  $\beta$ -blocker will be helpful.

*Question: I'm having trouble getting metoprolol CRXL [controlled release/extended release] on the formulary. Can short-acting metoprolol be used instead? What about atenolol? Are there any data on the use of generic atenolol in heart failure?*

*Dr. Greenberg:* There are data to show that metoprolol CR/XL is associated with improved survival, and there are data on carvedilol to show marked improvement in the clinical course. There also are data on bisoprolol. Those are the only drugs I feel comfortable giving to heart failure patients, because they are the only ones for which clinical data are available.

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... REFERENCES ...

1. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart. A new era in the treatment of heart failure. *Circulation* 1996;94:2285-2296.

2. Kendall JM, Lynch KP, Hjalmarson A, Kjeksus J. Beta-blockers and sudden cardiac death. *Ann Intern Med* 1996;123:358-367.
3. Andersson B, Hamm C, Persson S, et al. Improved exercise hemodynamic status in dilated cardiomyopathy after beta-adrenergic blockade treatment. *J Am Coll Cardiol* 1994;23:1397-1404.
4. Lechat P, Escolano S, Golmard JL, et al. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1997;96:2197-2205.
5. Kim MH, Devlin WH, Das SK, et al. Effects of beta-adrenergic blocking therapy on left ventricular diastolic relaxation properties in patients with dilated cardiomyopathy. *Circulation* 1999;100:729-735.
6. Eichhorn EJ, Bedotto JB, Malloy CR, et al. Effect of beta-adrenergic blockade on myocardial function and energetics in congestive heart failure. Improvements in hemodynamic, contractile, and diastolic performance with bucindolol. *Circulation* 1990;82:473-483.
7. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure. *Lancet* 1999;353:2001-2007.
8. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. *Lancet* 1999;353:9-13.
9. Packer M, Bristow MR, Cohn JR, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;334:1349-1355.
10. Packer M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol* 1992;20:248-254.
11. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. *Circulation* 1995;91:2573-2581.
12. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet* 1997;349:375-380.
13. Colucci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. *Circulation* 1996;94:2800-2806.