The Cellular and Physiologic Effects of Beta Blockers in Heart Failure

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Summary: Enhanced and sustained cardiac adrenergic drive occurs in heart failure (HF) and contributes, in part, to the progression of left ventricular (LV) dysfunction and remodeling that are characteristic of this disease state. Enhanced sympathetic drive in HF can lead to downregulation and desensitization of cardiac beta-adrenergic receptors with a consequent impairment of myocardial reserve and exercise tolerance. This sympathoadrenergic maladaptation can also lead to cellular abnormalities in the failing heart, manifested by defects in calcium handling of the sarcoplasmic reticulum, by defects in myocardial energetics, and by ongoing loss of cardiomyocytes through necrosis or apoptosis. Chronic treatment with beta blockers in patients with HF and in animals with experimentally induced HF has been shown to reverse, prevent, or, at the least, arrest many, if not all, of these adverse processes. Beta blockers improve function of the failing LV, prevent or reverse progressive LV dilation, chamber sphericity, and hypertrophy, and consequently have positive impact on cardiac remodeling. Beta blockers also reduce heart rate and LV wall stress, leading to reduced myocardial oxygen consumption, a clear benefit to the failing heart. Beta blockers can also improve the intrinsic contractile function of cardiomyocytes and have also been shown to improve myocardial energetics in HF, possibly through desirable changes in substrate utilization. Recent studies from our laboratories have also shown that beta blockers can attenuate cardiomyocyte apoptosis in HF. These benefits provide strong reinforcement to the clinical findings that beta blockers are highly beneficial for the management of patients with chronic HF and, when properly used, afford unequivocal reductions in mortality and morbidity in this patient population.

At present, there is general agreement that increased cardiac sympathetic drive occurs in HF and may potentially be an important contributor to the progression of LV dysfunction and chamber remodeling that is characteristic of this disease state. Experimental studies in animal models of HF as well as clinical studies in patients with HF have suggested that chronic therapy with beta blockade is effective in preventing the progression of LV dysfunction and remodeling. Results of recent multicenter clinical trials support these findings and have made it abundantly clear that long-term therapy with beta blockade inhibits clinical progression and has a major impact on mortality and morbidity in patients with HF that is at least as favorable, if not better, than that observed with angiotensin-converting enzyme (ACE) inhibitors. Beta blockers improve mortality and morbidity in HF and also improve LV ejection fraction (EF) and LV systolic function, thereby improving LV mechanical performance.

Key words: heart failure, beta blockade, mortality, morbidity

Abnormalities of the Beta-Adrenergic Receptor Pathway in Heart Failure

To appreciate the benefits derived from long-term beta blockade in HF fully, one should appreciate the adverse effects that a sustained increase of adrenergic drive can have on the failing heart. Over the years, several abnormalities of the cardiac beta-adrenoceptor pathway have been uncovered in the setting of HF and have previously been reviewed in detail. These abnormalities include downregulation of cardiac beta1-receptors, uncoupling of beta2-receptors, possibly mediated through an increase in the functional activity or amount of inhibitory guanine nucleotide binding protein (Gi protein), uncoupling of beta1-receptors observed only in patients with ischemic cardiomyopathy, upregulation of beta-adrenergic-receptor kinase (βARK) which can lead to beta1 and beta2 phosphorylation and contributes to receptor uncoupling, and downregulation in the function and possibly amount of adenyl cyclase observed primarily in HF secondary to pressure overload.
Consequences of Enhanced Beta-Adrenergic Drive in Heart Failure: Effects of Receptor Downregulation and Desensitization and Modulation by Beta Blockade

Abnormalities of enhanced and sustained sympathetic drive impact the failing heart in two major ways. First, it results in desensitization of beta-adrenergic signal transduction system evidenced by decreased responsiveness to beta-agonist stimulation. The marked attenuation in inotropic response is readily apparent during exogenous infusion of the beta-agonist dobutamine. This blunted inotropic response can contribute to a decline in myocardial reserve and to a reduction in exercise capacity. A close relationship between the decrease in total cardiac beta-adrenergic receptor density and impaired maximal exercise response has been shown in patients with idiopathic dilated cardiomyopathy. In the setting of HF, beta-receptor density was shown to be the only measurable parameter predictive of maximal exercise response. Long-term treatment with so-called second-generation beta-selective antagonists such as metoprolol CR/XL, but not third-generation mixed beta1 and beta2 antagonists such as carvedilol, have been shown to upregulate cardiac beta1-adrenergic receptors and increase cardiac responsiveness to exogenous catecholamines in patients with heart failure. Second-generation agents also have been shown to recouple uncoupled beta2 adrenoceptors. Consistent with these observations, several studies have shown that therapy with the beta1-selective receptor blocker metoprolol CR/XL is associated with improvements in exercise capacity in patients with congestive heart failure (CHF).

Consequences of Enhanced Beta-Adrenergic Drive in Heart Failure: Adverse Biologic Effects and Modulation by Beta Blockade

A second path by which a sustained increase of sympathetic drive impacts the failing heart is through a direct adverse effect on the functional cardiac unit itself: the cardiomyocytes. The adverse biologic effects are manifested through alterations in calcium handling at the level of the sarcoplasmic reticulum (SR). through cardiac myocyte cell death by necrosis or apoptosis, and by an effect on high-energy phosphate generation or metabolic substrate utilization. All of these abnormalities are subject, directly or indirectly, to sympathoadrenergic regulation, and all potentially play key roles in the progression of LV dysfunction and remodeling.

Abnormalities of Sarcoplasmic Reticulum Calcium Handling

Cardiac myocytes isolated from explanted failed human hearts as well as from hearts of animals with experimentally induced HF manifest diminished systolic shortening. The contractile response of isolated failed myocytes to increasing concentrations of calcium is also severely blunted compared with cardiac myocytes isolated from normal hearts. Studies from our laboratories and others also showed that contrary to normal myocytes, myocytes isolated from failing hearts exhibit altered shortening–frequency response, a finding consistent with the characteristic inverse force–frequency relation observed in the failing heart. Thus, instead of increasing force of contraction with increasing heart rates in the chronically failing myocardium, the contractile performance declines with increasing heart rates. Associated with these functional abnormalities are biochemical abnormalities of calcium mobilization in the SR of the failing heart. We and others have shown that the activity and expression of Ca2+-adenosine triphosphatase (ATPase) are reduced in HF, as is the rate of Ca2+ uptake into the SR. At the same time, the cardiac sarcolemmal Na+-Ca2+ exchanger is increased in both function and expression in end-stage human HF. In addition to their sympathoadrenergic inhibition, all beta blockers reduce heart rate. For any given patient with HF, a reduction of heart rate can cause a leftward shift along the intrinsic force–frequency relation curve, with resulting improvement in the force of contraction. A reduction in heart rate with the use of beta blockers can also prolong the diastolic period allowing a longer time for the depressed Ca2+ -ATPase pump to continue loading calcium into the SR, which, in turn, can be used for contraction during systole. Unfortunately, things are not as simple as they seem. Although reducing heart rate with beta blockers in patients with HF is important, a direct cause and effect relationship between reduction of heart rate and improvement of LV function remains difficult to establish.

Ongoing Cardiac Myocyte Death

It has been long recognized that high concentrations of catecholamines can produce myocardial necrosis. Studies in rats in which isoproterenol was administered subcutaneously at a dose of 1 mg/kg for several days showed considerable cardiomyocyte necrosis evidenced by in vivo labeling with antimyosin antibody. Studies by Mann et al. showed that norepinephrine can be cytotoxic to cultured cardiac myocytes at concentration (10–100 nM) present in the failing human heart. The observation that beta-adrenergic receptor desensitization can ameliorate catecholamine-induced cardiomyocyte toxicity provides further support to this concept of cardiac myocyte death in HF secondary to enhanced and sustained sympathoadrenergic drive. Based on these observations, one can safely assume that drugs that attenuate sympathetic drive such as beta blockers are likely to attenuate this form of cell death.

Loss of cardiac myocytes in HF can also occur as a result of programmed cell death or apoptosis. Whereas cell necrosis occurs in response to lethal injury, apoptosis is an active,
energy-requiring process that appears to be under genetic control. Apoptosis differs from necrosis in that cell death occurs in the absence of cell membrane rupture and inflammation and is characterized by nuclear DNA fragmentation. Although factors that trigger cardiocyte apoptosis in the failing heart are not fully understood, there is some evidence to suggest that certain pathophysiologic conditions common to the heart failure state may contribute to or play an important role in promoting cardiac myocyte apoptosis. Some of the triggers of cardiac myocyte apoptosis can be modulated by beta blockade and include increased cytosolic calcium concentration, exposure of cardiac myocytes to hypoxia, and excess levels of norepinephrine, all of which are common features of the failing heart. As eluded to earlier, beta blockers can limit calcium overload by positively altering the dynamics of calcium transport. Beta blockers can also have a positive impact on myocardial hypoxia, given their well-recognized capability to reduce myocardial oxygen consumption. In a recent study, Communal et al. showed that exposure of adult rat ventricular myocytes to norepinephrine leads to apoptosis. When cells were incubated with norepinephrine in the presence of the beta blocker, propranolol, the rate of myocyte apoptosis was substantially attenuated, leading, in part, to the conclusion that myocyte apoptosis resulting from exposure to norepinephrine was mediated through activation of the beta-adrenergic receptor pathway. Other studies have shown that enhanced activation of beta-adrenergic signaling by overexpression of Gs in hearts of transgenic mice also induces apoptosis of cardiac myocytes.

Limited oxygenation of the myocardium or localized hypoxia has received considerable interest in recent years. In dogs with chronic HF produced by intracoronary microembolizations, we have shown that accumulation of collagen in the cardiac interstitium or “reactive interstitial fibrosis” can lead to hypoxia of the collagen-encircled cardiomyocytes. This concept was based on evidence of decreased capillary density, increased oxygen diffusion distance, and increased myocyte lactate dehydrogenase activity in myocardial regions manifesting severe interstitial fibrosis compared with myocardial regions with little or no fibrosis. Furthermore, studies in our laboratories in both patients and dogs with HF showed that the highest incidence of cardiac myocyte apoptosis occurred in myocardial regions that bordered old infarcts, where interstitial fibrosis tends to be most severe. In a recent study in dogs with HF treated long-term with the beta, selective blocker metoprolol CR/XL, we showed significant attenuation of cardiomyocyte apoptosis. In this study, apoptosis was significantly reduced in myocardial regions bordering old infarcts as well as in regions remote from any infarcts. We also observed an upregulation in the expression of the Bcl-2 protein—an inhibitor of apoptosis—in dogs treated with metoprolol CR/XL compared with untreated dogs. The increase of Bcl-2 in metoprolol CR/XL-treated dogs occurred in the absence of any changes in Bax, a promoter of apoptosis. The increase in Bcl-2 in untreated dogs with HF may have limited the formation of Bax homodimers. These data suggest the possibility that metoprolol CR/XL induces expression of Bcl-2 independent of HF and that this independently confers protection. Furthermore, the observed increase in the Bcl-2 to Bax ratio, the so-called “death switch,” favors cell survival over cell death, a finding consistent with marked attenuation of cardiomyocyte apoptosis in dogs treated with metoprolol CR/XL. Another factor intimately involved in promoting apoptosis is the interleukin-converting enzyme (ICE) family of cysteine proteases also known as caspases. Bcl-2 expression has been shown to prevent activation of the ICE protease cascade.

**Abnormalities of Myocardial Energetics**

In chronic HF, a state of high myocardial metabolic load exists despite low mechanical output. The syndrome is often characterized by limited aerobic function of the myocardium and limited ATPase production by mitochondria that lead to a state of so-called energy depletion. Long-term treatment with beta blockers counteracts these abnormalities of myocardial energetics. Studies with metoprolol CR/XL in both patients and animals with HF have shown a reduction in myocardial oxygen consumption along with reductions of heart rate and LV wall stress, both of which are primary determinants of myocardial oxygen consumption. In a randomized trial of patients with dilated cardiomyopathy, Eichhorn et al. showed that metoprolol CR/XL, in fact, can improve myocardial efficiency of the failing heart. These benefits of beta blockade are difficult to justify as merely the consequences of reduced oxygen consumption. It has recently been suggested that beta blockade causes a shift in myosin isoform gene expression to alpha-myosin heavy chain with downregulation of the beta-myosin heavy chain. Downregulation of alpha-myosin heavy chain in the failing heart may be related to the depression of systolic performance characteristic of this disease state. Of interest, increased LV wall stress may play a key role in the regulation of alpha-myosin heavy chain.

Another possible explanation for the improvement in function and efficiency of the failing heart after long-term therapy with beta blockade may be related to alterations in energy substrate utilization. The hyperadrenergic state that exists in HF can lead to hypermetabolic state due to increased blood levels and utilization of fatty acids resulting from norepinephrine stimulation of lipolysis in both fat and other cells. This can lead to fatty acid-induced “ATPase wastage” and limit ATPase availability that, in turn, compromises myocardial performance. Metoprolol CR/XL has been shown to correct this hypermetabolic state by increasing dependency on carbohydrate utilization and away from fatty acid oxidation. In a recent study of dogs with HF, we observed a significant reduction in carnitine palmitoyl transferase I (CPT-I) activity in dogs treated long-term with metoprolol CR/XL compared with untreated dogs. Carnitine palmitoyl transferase-I is the enzyme that controls the rate of fatty acid transport into mitochondria. Studies by Rupp et al. showed that inhibition of CPT-I by etomoxir in spontaneously hypertensive rats (SHR) increases the rate of SR Ca$^{2+}$ uptake. Increase in SR Ca$^{2+}$ uptake can mediate improvements in both systolic and diastolic cardiac performance.
Conclusion

Available studies to date support the conclusion that, in the setting of HF, beta blockers elicit substantial physiologic and cellular benefits. Available data point to a multiplicity of mechanisms through which beta blockers elicit these beneficial effects. Each of the many possible mechanisms is plausible and all appear to be closely interrelated so that the emergence of a single predominant mechanism is becoming less likely. What is certain is the undeniable fact that beta blockers are highly beneficial in the management of patients with chronic HF and, when properly used, afford unequivocal reductions in mortality and morbidity in this patient population.

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