Beta blockers as cardioprotective agents: Part I—Insights into mechanisms of action

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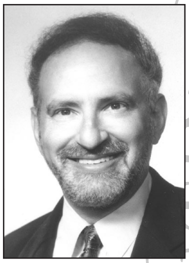

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Sympathetic nervous system activation, which is teleologically defined as an acute response system for the flight-or-fight reaction and other acute hemodynamic stresses, occurs early after the onset of left ventricular systolic dysfunction and continues throughout the history of heart failure.[1] Sustained activation of the sympathetic nervous system in the heart, kidneys, and peripheral vasculature can have adverse effects and appears to be at least partly responsible for the clinical progression of heart failure. Plasma levels of norepinephrine, the mediator of the sympathetic nervous system, are elevated in patients with chronic congestive heart failure (CHF), and outcomes tend to be poorest in patients with the highest plasma levels of norepinephrine.[2]

The direct biologic effects of norepinephrine include cardiac myocyte hypertrophy and death, accomplished through increases in cyclic AMP that lead to calcium overload and cell necrosis, and stimulation of growth and enhancement of oxidative stress in terminally differentiated cardiac cells.[1-4]

By elevating cardiac output, chronic sympathetic activation increases myocardial demand for oxygen, predisposing to myocardial ischemia and oxidative stress.[5] Neurohormonal activation is intensely vasoconstrictive. The peripheral and venous vasoconstriction caused by chronic sympathetic nervous system activation increases ventricular afterload and preload, adding burden to the failing heart. Increased impedance to left ventricular ejection impairs left ventricular performance.

Myocyte hypertrophy and death, along with the sustained mechanical stress caused by vasoconstriction, can cause cardiac remodeling, characterized by an increase in chamber size, resulting in a less contractile chamber and a decrease in ejection fraction.[6,7] Once remodeling occurs, further activation of neurohormonal systems is evident, creating a vicious circle that contributes to heart failure progression, worsening symptoms, need for hospitalization, and premature mortality (Figure 1).

The structural and functional alterations of the heart influenced by norepinephrine can provoke arrhythmias in patients with heart failure.[8] Beta receptors in the heart are mediators of ion transport and homeostasis and, with sustained stimulation, can cause adverse effects on the timing of myocardial muscle contraction. Beta$_1$ and beta$_2$ receptors also mediate the electrophysiologic effects of catecholamines. Through its action on the beta$_1$ and beta$_2$ receptors, sympathetic nervous system activation can increase heart rate and contractility, promoting the imbalance between myocardial supply and demand while exacerbating the abnormal force–frequency relation in heart failure.[9]

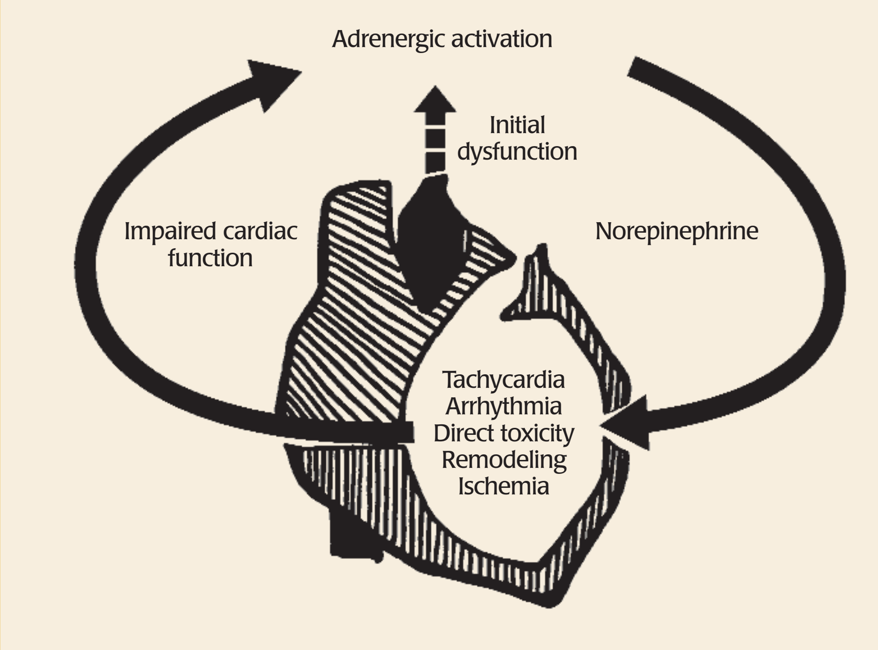
Mechanisms of beta blockers' effects

Interfering with the actions of the sympathetic nervous system can improve outcomes in patients with heart failure. Angiotensin-converting enzyme (ACE) inhibition is beneficial in heart failure and reduces levels of neurosympathetic hormones, but alone, it does not sufficiently limit sympathetic activation. The mechanisms responsible for the efficacy of beta blocking agents in prolonging life after myocardial infarction (MI) and in patients with heart failure are probably numerous, but chief among them is their antagonistic actions on the sympathetic nervous system (Table).[10,11]

Beta blockers favorably affect cardiac structure. Attenuation and reversal of cardiac remodeling has been demonstrated with beta blockade. In the Australia-New Zealand carvedilol trial, the risks of mortality and hospitalization and the requirement for ancillary heart failure medications were all reduced with carvedilol treatment in patients with ischemic left ventricular dysfunction.[12] These improvements correlated with a reduction in left ventricular volume on echocardiography. Because patients enrolled in trials of beta blockade for the treatment of heart failure were already receiving ACE inhibitors, the effect of beta

FIGURE 1

The role of chronic adrenergic activation in progressive systolic dysfunction*



*Shown is a simplified depiction of the vicious circle of impaired cardiac output, adrenergic stimulation, and changes in left ventricular structure and function that fuel the progression of heart failure.
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blockers on remodeling is additive to that of ACE inhibitors.

Long-term beta blockade has been associated with improvements in ejection fraction.[12] These agents also favorably alter the electrophysiologic properties of cardiac myocytes to reduce arrhythmic potential.[8] More recent evidence indicates that beta blockers may reduce oxidative stress by inhibiting the generation of oxygen-derived free radicals.

Beta blockers have a favorable impact on recurrent cardiac events in survivors of MI and patients with documented coronary artery disease (CAD). Because CAD plays a major role in the etiology of heart failure, the favorable effect of beta blockers on reinfarction risk may partly explain their benefits in heart failure. The protection against recurrent myocardial ischemia afforded by beta blockade is closely related to their protection against reinfarction. Beta blockers decrease myocardial oxygen consumption and improve left ventricular function at rest and during exercise. Cumulatively, these beneficial effects should protect against recurrent myocardial ischemia.

In the short term, beta blockade impairs ventricular performance by decreasing cardiac contractility, especially in patients whose cardiac function was already compromised. In the past, these short-term effects were cited as reasons to avoid beta blockade in heart failure; however, long-term treatment with beta blockade improves cardiac performance, producing increases in stroke volume and decreases in pulmonary wedge pressure, right atrial pressure, heart rate, and systemic vascular resistance. Cardiac output is also restored with long-term treatment. The increases in left ventricular ejection fraction observed with long-term beta blockade are associated with reductions in left ventricular systolic and diastolic dimensions.

The different hemodynamic effects between short-term and long-term beta blockade can be explained by the differing effects of catecholamines over the short and long term. Over the short term, beta blockers interfere with the positive inotropic actions of catecholamines to reduce cardiac function.[13,14] Over the long term, however, catecholamines have toxic effects on cardiac myocytes and can promote myocyte apoptosis.[15] In addition, catecholamines downregulate and desensitize beta receptors. Beta blockers may protect against the toxic catecholamine cascade that develops in patients with failing hearts.[11,16,17]

Clinical trials of long-term beta blockade show an initial reduction in left ventricular ejection fraction followed by improvement in ejection fraction. The improvement in contractile function with long-term beta blockade represents another mechanism by which these agents improve outcomes in heart failure and after MI.[15,18] Beta blockers may also favorably influence diastolic function. In patients with dilated cardiomyopathy, 6 months of metoprolol treatment reduced left ventricular end-diastolic pressure, which was associated with improvement in isovolumic relaxation and indices of myocardial stiffness.[19]

Beta blockers are highly effective in preventing sudden cardiac death in patients with MI, hypertension, or heart failure. The evidence is so strong that the reduction in total mortality with beta blockade in high-risk patients is primarily a result of a decrease in sudden cardiac death. A pooled analysis of five placebo-controlled trials of metoprolol treatment after MI demonstrated a 42% reduction in sudden death.[20] More recent trials in heart failure have also shown significant reductions in sudden cardiac death in patients with heart failure who were treated with beta blockers.[21-24] Whether the beneficial effect of beta blockers in reducing the incidence of sudden death can be attributed to a favorable effect on cardiac remodeling, an antiarrhythmic effect, or some other effect has not been established.

Sympathetic activation and atherosclerosis

The sympathetic nervous system may be involved in the chain of events leading to atherosclerosis, particularly at arterial bifurcations. Emotional stress is known to cause sympathetic nervous system arousal. Exposure to psychosocial stress has been shown to be atherogenic as a result of sympathetic activation, among other factors, which stimulates beta adrenoreceptor–mediated mechanisms.[25] Independent of hypertension, sympathetic nervous system arousal can be damaging to the endothelium. Rats exposed to stress-induced sympathetic arousal show endothelial injury even in the absence of an atherogenic diet.[26,27] With endothelial damage and resultant dysfunction, platelet-derived adhesive glycoproteins adhere to the surface of endothelial cells, attracting monocytes and T lymphocytes that migrate between the endothelial cells. Once they penetrate beneath the arterial surface, monocytes transform to macrophages and accumulate lipids to form foam cells. Accompanied by lymphocytes, the foam cells develop into the fatty streak, the precursor to the atherosclerotic lesion.

Other evidence indicates that hemodynamic factors related to sympathetic nervous system activation are atherogenic. In particular, the increased heart rate response to sympathetic nervous system arousal may be atherogenic at arterial sites subject to abrupt changes in blood flow, such as at arterial bifurcations. Additionally, rabbits exposed to sympathetic activation show increased platelet deposition at arterial bifurcations.[28]

The atherogenic effects of sympathetic activation can be inhibited by beta blockers, most likely through a complex interaction of hemodynamic and biochemical factors.[29] Sympathetic activation is decreased significantly by beta blockade, and beta blockade has been shown to prevent platelet deposition caused by increased sympathetic activation.[30] Furthermore, plasma noradrenaline levels are reduced by beta blockade, suggesting inhibition of sympathetic nerve discharge in the central nervous system.[31] Blocking beta receptors in the heart can also have a beneficial effect on hemodynamics through reductions in heart rate and contractility.[32] Beta blockade of biochemical systems may also reduce atherogenesis. In fact, less platelet

TABLE

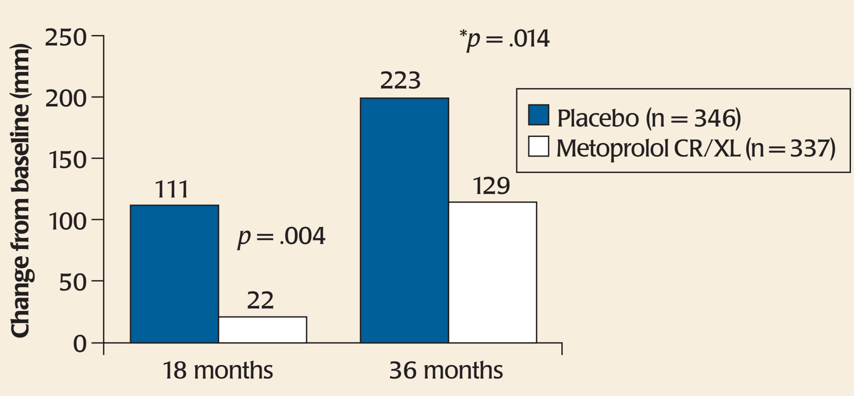
Possible mechanisms by which beta blocking agents improve ventricular function in chronic CHF
• Upregulation of beta receptors
• Direct myocardial protective action against catecholamine toxicity
• Improved ability of noradrenergic sympathetic nerves to synthesize norepinephrine
• Decreased release of norepinephrine from sympathetic nerve endings
• Decreased stimulation of other vasoconstrictive systems including renin-angiotensin, aldosterone, vasopressin, and endothelin
• Potentiation of kallikrein-kinin system and natural vasodilatation (increase in bradykinin)
• Antiarrhythmic effects raising ventricular fibrillation threshold
• Protection against catecholamine-induced hypokalemia
• Increase in coronary blood flow by reducing heart rate and improving diastolic perfusion time; possible coronary dilation with vasodilator-beta blocker
• Restoration of abnormal baroreflex function
• Prevention of ventricular muscle hypertrophy and vascular remodeling
• Antioxidant effects (carvedilol?)
• Shift from free fatty acid to carbohydrate metabolism (improved metabolic efficiency)
• Vasodilation (carvedilol)
• Anti-apoptosis effect allowing natural myocardial cell regeneration
• Improved left atrial contribution to left ventricular filling
• Modulation of post-receptor inhibitory G proteins
• Normalization of myocyte calcium-regulating proteins and improved calcium-handling
• Increasing natriuretic peptide production
• Attenuation of inflammatory cytokines

CHF = congestive heart failure.

aggregation in response to thrombin or arachidonic acid is observed in propranolol-treated patients compared with controls, as well as reduced production of thromboxane A_2 from platelets.

Figure 2

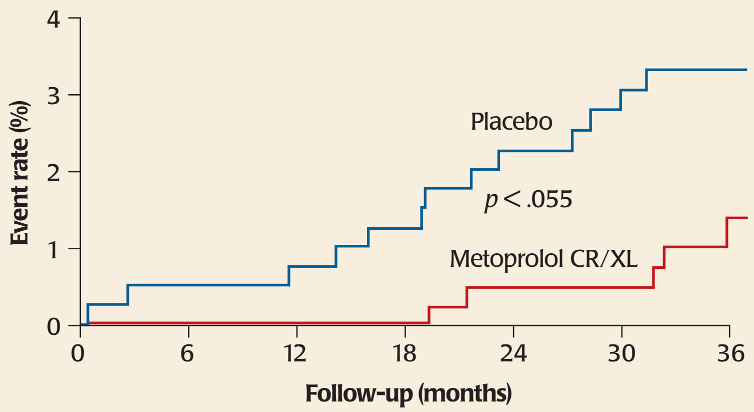
Net difference from baseline in maximal intima-media thickness of the carotid bulb



*p values refer to between group comparison.
Source: Hedblad B, et al.[33]

Figure 3

MI, stroke, and death from cardiovascular disease in patients taking metoprolol CR/XL or placebo



MI = myocardial infarction.
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Recent findings demonstrate that extended-release (ER) metoprolol succinate (metoprolol CR/XL) may have antiatherosclerotic effects. In the Beta Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS), 793 patients with carotid artery plaque but no symptoms were randomized to placebo, metoprolol CR/XL, 25 mg daily, fluvastatin, or the combination of metoprolol CR/XL and fluvastatin.[33] This discussion will focus solely on the effects of beta blockade compared with placebo on carotid intima-media thickness and clinical events.

At 18 and 36 months, metoprolol CR/XL significantly slowed the progression of maximal intima-media thickness in the carotid bulb compared with placebo (p = .004 and p = .014, respectively; Figure 2). It had no effect on atherosclerotic progression in the common carotid artery. The study was not powered to detect differences in clinical event rates. Nevertheless, there was a trend toward a lower cardiovascular event rate in patients taking metoprolol CR/XL compared with placebo (5 versus 13 events, p = .055; Figure 3). The combined end point of all-cause mortality and a cardiovascular event was significantly lower in the patients taking metoprolol CR/XL (p = .031).

These results indicate that the sympathetic nervous system is involved in the chain of events leading to atherosclerosis at arterial bifurcations. In a low, nonhypotensive dose, metoprolol CR/XL reduced the progression rate of maximum intima-media thickness in the carotid artery bulb and tended to decrease the cardiovascular event rate. ■

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