Both experimental and clinical observation suggest that activation of the sympathetic nervous system exerts an important deleterious effect in patients with chronic heart failure. The precise mechanisms responsible for this effect have not been defined, but prolonged exposure to norepinephrine is associated with a variety of adverse physiologic and biochemical/molecular actions. Identification of these deleterious pathways has helped to explain why drugs that block the cardiac effects of norepinephrine (ie, β-blockers) retard remodeling and prolong life in experimental models of heart failure.

β-Blockers have been shown to reduce the mortality of patients after an acute myocardial infarction; this effect appears to be particularly marked in patients with postinfarction heart failure. Results of several trials suggest that long-term treatment with β-blockers can improve symptoms and reduce the frequency of hospitalizations for heart failure. Most recently, carvedilol has been shown to reduce the risk of all-cause mortality by 65% in patients with either an ischemic or nonischemic cardiomyopathy.

These findings, taken together, suggest that pharmacologic interference with the sympathetic nervous system can produce important clinical benefits in patients with left ventricular systolic dysfunction. Am J Hypertens 1998;11:23S–37S © 1998 American Journal of Hypertension, Ltd.

KEY WORDS: β-Blockers, carvedilol, heart failure, norepinephrine.

When β-adrenergic-blocking agents were first introduced into the practice of medicine more than 30 years ago, physicians were advised that the use of these drugs was contraindicated in patients with heart failure. This recommendation was based on the belief that the sympathetic nervous system provided important support for the failing heart; this belief was consistent with reports that clinical deterioration could occur following short-term treatment with a β-blocker in patients with impaired ventricular function.1 During the past 20 years, however, several observations have led to the concept that β-blockade might have beneficial effects in patients with heart failure:

• Prolonged activation of the sympathetic nervous system has been shown to exert deleterious effects in heart failure, in vitro, in experimental models of heart failure, and in the clinical setting.
• β-Blocking agents have been reported to reduce the mortality of survivors of an acute myocardial infarction, particularly in patients with left ventricular dysfunction.
• Controlled clinical trials have demonstrated improvement in symptoms, functional capacity, ventricular function, and morbidity and mortality following long-term β-blockade in patients with heart failure.

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Address correspondence and reprint requests to: Milton Packer, MD, Division of Circulatory Physiology, Columbia-Presbyterian Medical Center, Milstein Building, 5th Floor, Room 435, 177 Fort Washington Avenue, New York, NY, 10032.
This paper reviews the scientific and clinical findings, including the results of recent clinical trials, that provide insight into the potential role of β-blockade in heart failure.

**THE SYMPATHETIC NERVOUS SYSTEM IN HEART FAILURE**

The Adrenergic Pathways in Heart Failure Heart failure is accompanied by early and progressive increases in the circulating level of norepinephrine. Plasma levels of norepinephrine are increased in proportion to the severity of the disease and patients with the highest level of this neurotransmitter have the most unfavorable long-term prognosis.

In response to the activation of the sympathetic nervous system, the cellular pathways that respond to and mediate the effects of catecholamines are altered in heart failure. Normally, catecholamines stimulate both β₁ and β₂-receptors on cardiac myocytes to modulate regulatory proteins that, in turn, alter the activity of adenyl cyclase and the intracellular concentration of cyclic AMP. In the nonfailing heart, about 80% of myocardial β-receptors are of the β₁-subtype and 20% are of the β₂-subtype. In contrast, in the failing heart, β₁-receptors are markedly reduced in number and density as a consequence of the process of down-regulation but the number and density of β₂-receptors are unchanged. Consequently, in the failing heart, the proportion of β₂-receptors increases to 40%. Furthermore, although the number of β₂-receptors may be unchanged, their function is altered because these receptors become partially uncoupled from adenyl cyclase, perhaps as a result of the change in the concentration of G-proteins that occurs in heart failure.

In addition to their effects on β-adrenergic receptors, catecholamines mediate many of their circulatory effects by acting on α-adrenergic receptors. Peripheral α₁-receptors mediate the constriction of peripheral blood vessels, whereas peripheral α₂-receptors mediate the reuptake of norepinephrine released into the synaptic cleft. Unlike β-adrenergic receptors, however, the α-adrenergic pathway in the periphery does not appear to be downregulated in heart failure, and experimental evidence suggests that its responsiveness may be enhanced. It should be noted that α-receptors (almost exclusively α₁-receptors) also exist within the heart, where their stimulation leads to hydrolysis of phosphatidyl inositol lipids, resulting in the generation of inositol trisphosphate and the release of calcium ions from intracellular stores. Although α₁-receptors comprise only a small proportion of the total adrenergic-receptor population in the human heart under normal conditions, the proportion of α₁-receptors increases in heart failure. This shift may be important because α₁-receptors may mediate both cardiac hypertrophy and increases in cardiac excitability, these two pathophysiologic actions may play an important role in the progression of heart failure.

**Adverse Effects of Sympathetic Activation in Heart Failure** Prolonged activation of the sympathetic nervous system may cause important adverse effects on the circulation.

- Norepinephrine can cause dysfunction and death of cardiac myocytes. By increasing cyclic AMP, norepinephrine can increase the concentration of intracellular calcium, which, if prolonged, may lead to a state of calcium overload and cell necrosis. In addition, norepinephrine can stimulate growth and provoke oxidative stress in terminally differentiated cardiac cells. These two factors can trigger the process of programmed cell death, known as apoptosis. Interestingly, both α₁- and β₁-adrenergic receptors may play a role in mediating the abnormal growth response in the failing heart and thus, both may be important in triggering cell death.

- Activation of the sympathetic nervous system can provoke myocardial ischemia in the failing heart, regardless of the state of the coronary circulation. The neurotransmitter can increase ventricular size and pressures, both of which act to increase myocardial oxygen demand. At the same time, norepinephrine can induce cardiac hypertrophy but restrict the ability of the coronary arteries to supply blood to the thickened ventricular wall.

- Norepinephrine can provoke arrhythmias in the failing heart through its ability to alter the structure (causing hypertrophy and fibrosis) and function of the heart. By increasing myocardial cyclic AMP via an agonist effect on β₁-receptors, norepinephrine can increase the automaticity of cardiac myocytes. Furthermore, by acting on β₂-receptors, catecholamines increase the transport of potassium from the extracellular to intracellular compartment; the resulting hypokalemia may provoke ventricular arrhythmias. Furthermore, stimulation of α₁-receptors by norepinephrine may increase delayed afterdepolarizations and triggered activity in the heart, especially in the presence of myocardial ischemia.

- Activation of the sympathetic nervous system can increase heart rate, which has several deleterious effects. Tachycardia not only exerts adverse effects on the relationship between myocardial supply and demand, but, more importantly, tachycardia may exacerbate the abnormal force-frequency relation that is known to exist in the failing heart. Whereas in normal hearts contractile force is enhanced as heart rate increases, contractile force decreases in the failing heart as its pacing frequency increases. Through this mechanism, tachycardia can directly...
impaired cardiac performance independent of its actions on ischemia and arrhythmias.

Drugs that interfere with the actions of the sympathetic nervous system by acting on α- or β-receptors might be expected to antagonize these deleterious effects. β-Receptor blockers can exert important peripheral and coronary vasodilator effects as well as favorable effects on myocardial hypertrophy and arrhythmias. α-Receptor blockers can prevent many of the toxic effects of catecholamines and have been shown to prevent and reverse the structural changes that occur during the progression of heart failure and prolong life in experimental models of the disease.

PHARMACOLOGY OF β-ADRENERGIC-BLOCKING AGENTS

β-Adrenergic-blocking drugs differ in their pharmacologic properties, and these differences may be important in determining their utility in the management of various cardiovascular disorders. Hence, it is important to characterize available β-blockers with respect to the following actions: 1) selectivity for β1-receptors versus β2-receptors; 2) intrinsic sympathomimetic activity (ISA); 3) action on other adrenergic receptors or vasodilator mechanisms; and 4) ancillary pharmacologic properties. Table 1 summarizes the profiles of the most frequently used β-blocking agents.

Receptor Subtype Selectivity To the extent that both β1- and β2-receptors mediate the toxic effects of catecholamines on the myocardium, pharmacologic agents that block both receptors may be more effective in producing long-term effects in heart failure than those that selectively block only β1-receptors. In addition, β2-receptors act to regulate the release of norepinephrine to the heart; this may explain why agents that block both β1- and β2-receptors (e.g., carvedilol) lower cardiac adrenergic drive in heart failure, whereas β1-selective agents (e.g., metoprolol) increase cardiac norepinephrine. Nonselectivity may be a particularly important characteristic of a β-blocker for heart failure, since β2-receptors comprise a much larger proportion of the β-receptor population in the failing heart than in the normal myocardium. However, β2-receptor blockade may be disadvantageous during initiation of treatment with a β-blocker in heart failure because β2-receptors may act to support the failing ventricle when β1-receptors are blocked, either because they may mediate positive inotropic effects in the heart or because they may mediate vasodilatory effects in the peripheral circulation.

If these differences in pharmacology were to be translated to the clinical setting, we would expect drugs such as propranolol, carvedilol, and bucindolol to be more effective in the long-term, but more difficult to use in the short-term, than metoprolol or bisoprolol. Fortunately, in the case of carvedilol and bucindolol, their additional vasodilatory actions appear to enhance their early tolerability. Theoretically, an agent such as celiprolol (which blocks β1-receptors but stimulates β2-receptors) might be particularly well tolerated during initiation of therapy, but may be particularly disappointing in producing clinical benefits during long-term therapy. Direct comparative studies to support these conceptual advantages and disadvantages have not yet been conducted.

Table 1. Pharmacologic Characteristics of β-Blockers Used in Heart Failure

<table>
<thead>
<tr>
<th>Agent</th>
<th>β1- Blockade</th>
<th>β2- Blockade</th>
<th>ISA</th>
<th>β- Upregulation</th>
<th>α- Blockade</th>
<th>Vasodilation</th>
<th>Antioxidant Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bucindolol</td>
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<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
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<tr>
<td>Labetalol</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nebivolol</td>
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<td>+</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Pindolol</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

0 = no effect; ± = minimal activity; + = mild to moderate activity; ++ = marked activity. ISA = intrinsic sympathomimetic activity.
in stimulation of the β-adrenergic pathway to varying degrees. Such agents reduce the activity of adenylate cyclase when endogenous sympathetic activity is high, but may increase the generation of cyclic AMP when endogenous sympathetic activity is low. These drugs are considered to have ISA and produce less complete sympathetic antagonism than do β-blockers without this property. β-Blockers with ISA (pindolol, celiprolol, and xamoterol) produce fewer pronounced negative inotropic and chronotropic effects than do β-blockers without ISA (ie, propranolol, metoprolol, and bisoprolol), but β-blockers with ISA may be associated with fewer clinical benefits. For example, β-blocking agents without ISA significantly reduce the mortality of survivors of myocardial infarction, whereas drugs with ISA appear to have no favorable effect in this setting. Similarly, whereas β-blockers without ISA have improved the long-term outcome of patients with heart failure, the β-blocker with the most marked ISA (ie, xamoterol) has been associated with an increase in mortality in patients with advanced left ventricular dysfunction. These observations have led to the conclusion that β-blocking agents with ISA should not be used in patients with heart failure; consequently, clinical trials with β-blockers in this setting have focused on β-blocking agents without ISA.

Although β-blocking agents without ISA would appear to have several advantages, such agents generally lead to an increase in the number and density of β-adrenergic receptors following short-term and long-term use. The significance of such upregulation is unknown. Although early studies suggested that upregulation helped to mediate the benefits of β-blockers in heart failure, recent observations suggest that upregulation may be disadvantageous, because an increase in receptor density may limit the degree of sympathetic antagonism. Furthermore, β-receptor upregulation is believed to be responsible for the rebound phenomena that have been reported following the abrupt withdrawal of β-blockers in patients with ischemic heart disease. β-Blockers with ISA do not cause upregulation and thus do not have these disadvantages, but as noted above, they may produce undesired sympathetic stimulation and an inadequate therapeutic response. Interestingly, two β-blockers (carvedilol and bucindolol) possess unique binding properties with the β-receptor (known as guanine nucleotide modulatable binding). This property allows these β-blockers to produce complete sympathetic antagonism without ISA, but in a manner that is not associated with β-receptor upregulation.

Adrenergic and Nonadrenergic Vasodilatory Mechanisms Many β-blocking agents exert important dilatory effects on peripheral blood vessels that may be of benefit to patients with heart failure. Carvedilol and labetalol dilate blood vessels by blocking β1-adrenergic receptors; celiprolol exerts a similar action by an agonist effect on peripheral β2-receptors; and nebivolol and bucindolol are believed to exert vasodilatory actions by a direct effect on blood vessels. During initiation of therapy, these vasodilating effects could serve to unload the heart and thereby counteract the cardiodepressant actions of β-blockers. Such an action could improve the early tolerability of β-blockers in heart failure. Furthermore, during long-term therapy, these vasodilating effects could produce hemodynamic effects (on both peripheral and coronary blood vessels) that may add to the benefits that might be expected to follow long-term β-blockade. However, β-blockers that exert additional vasodilatory actions may produce symptomatic hypotension. This adverse reaction may be particularly common in patients with heart failure, many of whom are already receiving treatment with an angiotensin converting enzyme (ACE) inhibitor.

Given these advantages and disadvantages, it is possible that β-blockers that produce their vasodilatory actions as a result of α1-adrenergic blockade may be particularly useful in heart failure. Such agents would be expected to produce early vasodilation when it was needed most—during initiation of β-blockade. Yet, because the circulation develops tolerance to the hypotensive effects of α-blockers during long-term therapy, such vasodilatory effects might not persist and thus would be unlikely to precipitate hypotension. This adverse reaction may be particularly common in patients with heart failure, many of whom are already receiving treatment with an angiotensin converting enzyme inhibitor.

Experimental observations suggest that patients with heart failure are under considerable oxidative stress, and that such stress (as evidenced by the enhanced formation of oxygen free radicals) may cause myocardial cells to undergo programmed cell death or apoptosis, a process that has been implicated in the progression of heart failure. Interestingly, carvedilol appears to be more effective than other β-blockers in attenuating the process of apoptosis (Feuerstein GZ, personal communication, 1995). This action appears to be related to a direct antioxidant action of carvedilol and not to the adrenergic-receptor–blocking effects of the drug. In in vitro experiments, carvedilol inhibits oxygen free radical-mediated lipid peroxidation more effectively than propranolol, celiprolol, or labetalol. Moreover, carvedilol, but not propranolol, can scav-
enge oxygen free radicals. These observations may explain why carvedilol reduces infarct size to a greater extent than propranolol in experimentally induced myocardial injury.

In addition to its antioxidant actions, carvedilol exerts antiproliferative effects that are also independent of its actions as a β-blocker. Carvedilol, but not celiprolol, sotalol, or labetalol, inhibits the proliferation of rat aortic vascular smooth muscle cells under basal conditions and in response to endothelin-1. Carvedilol suppresses the intimal proliferation that occurs in the rat carotid artery after balloon angioplasty and inhibits the proliferation of human vascular smooth muscle cells in vitro. These antiproliferative effects may be important in preventing the progression of vascular remodeling that may contribute to the hemodynamic abnormalities in heart failure.

**PHYSIOLOGIC EFFECTS OF β-BLOCKADE IN HEART FAILURE**

**Hemodynamic Effects**  
*Short-Term Effects* When treatment with a β-blocker is initiated in patients with heart failure, the drug produces changes in ventricular function that are the expected consequences of its pharmacologic actions. Blockade of β₁-receptors leads to negative inotropic and chronotropic effects, whereas blockade of β₂-receptors can interfere with the peripheral vasodilator actions mediated by these receptors and causes peripheral vasoconstriction. Both of these pharmacologic effects, acting in concert, can cause a decline in ventricular performance, particularly in patients with heart failure whose ventricular function is already compromised.

Available evidence suggests that these early adverse hemodynamic effects may be minimized by β-blockers with additional vasodilator properties. Di Lenarda and colleagues compared the acute hemodynamic effects of metoprolol with those of carvedilol in patients with dilated cardiomyopathy. Both drugs significantly reduced heart rate, but carvedilol also reduced intracardiac filling pressures and systemic vascular resistance. These additional hemodynamic effects may act to enhance the tolerability of β-blockade during initiation of therapy.

*Long-Term Effects* Although β-blockers can depress left ventricular function during short-term therapy, these drugs are associated with an improvement in cardiac performance during long-term therapy. In controlled and uncontrolled studies, treatment with a β-blocker for 3 to 6 months produces an increase in stroke volume and stroke work associated with a decrease in pulmonary wedge pressure, right atrial pressure, heart rate and systemic vascular resistance. Cardiac output, initially decreased by short-term treatment, is restored or even increased during long-term treatment. These effects are apparent during both rest and exercise.

The most consistent hemodynamic response observed following long-term β-blockade in patients with heart failure has been an increase in left ventricular ejection fraction. Interestingly, the increase in ejection fraction following β-blockade is generally larger than that seen following other therapeutic interventions for heart failure. This improvement is frequently (but not uniformly) associated with a reduction in left ventricular systolic and diastolic dimensions.

Most hemodynamic studies with β-blockers in heart failure have been carried out with metoprolol, bucindolol, and carvedilol, but single reports using nebivolol and labetalol have also been performed. In the case of carvedilol, these hemodynamic benefits have been observed in patients with mild and moderate symptoms of heart failure as well as in those with the most advanced heart failure before initiation of therapy.

The difference between the short-term and long-term effects of β-blockers can be explained by the difference between the short-term and long-term effects of catecholamines on the heart. During short-term treatment, β-blockers interfere with the positive inotropic actions of endogenous catecholamines, and cardiac function declines. However, during long-term treatment, β-blockers interfere with the toxic effects of endogenous catecholamines. This action leads to an improvement in cardiac performance, because the recovery of myocardial function is sufficient to overwhelm the short-term cardiodepressant effects of these drugs. This point is illustrated by the work of Eichhorn and colleagues, who showed that cardiac contractility improves during long-term β-blockade, even though these drugs do not exert any direct positive inotropic effects.

Similarly, the short-term pharmacologic action of β-blockers is to cause peripheral vasoconstriction, reflected by an increase in systemic vascular resistance. This hemodynamic response has been seen during initiation of therapy with metoprolol (but not carvedilol). Yet systemic vascular resistance may decline during long-term therapy as cardiac function improves, even with the use of β-blockers that do not exert any direct vasodilatory effects.

Although some reports have suggested that the hemodynamic effects of β-adrenergic blockers may be more marked in patients with dilated cardiomyopathy, recent evidence indicates that patients with and without coronary artery disease respond similarly to these drugs.

**Neuroendocrine Effects** Since β-blockers interfere with the actions of an endogenous neuroendocrine system at a cellular level, the hormonal benefits of
these drugs might not be apparent from the measurement of circulating levels of norepinephrine or renin. Plasma levels of norepinephrine remain unchanged or may decline during long-term $\beta$-blockade\textsuperscript{49,53–55,63}; the latter is believed to reflect a decrease in neurohormonal activity resulting from an overall improvement in heart failure. Nevertheless, the biologic significance of any change in circulating norepinephrine remains uncertain, because the cardiac actions of endogenous catecholamines are blocked in patients receiving a $\beta$-receptor antagonist. Similarly, although $\beta$-blockers lower plasma renin activity in patients with heart failure,\textsuperscript{64} this effect has been seen in patients receiving treatment with an ACE inhibitor, in whom the biologic effects of renin are already attenuated.

However, it is likely that $\beta$-blockers exert favorable effects on neurohormonal systems other than the sympathetic nervous system and the renin-angiotensin system. In patients with heart failure, the activity of the parasympathetic nervous system is attenuated but the activity of the vascular endothelin system is enhanced.\textsuperscript{65,66} The former may contribute to the high risk of sudden death in these patients, and the latter is known to exert a variety of adverse hemodynamic and biologic effects. Interestingly, carvedilol has been shown to enhance parasympathetic activity and reduce circulating levels of endothelin in patients with heart failure.\textsuperscript{67,68} The biologic significance of these observations remains unknown.

**Antiarrhythmic and Antiischemic Effects** $\beta$-Blockers have established effects on cardiac arrhythmias and myocardial ischemia, both of which may play an important role in patients with heart failure.

**Antiarrhythmic Effects** Ventricular arrhythmias are extremely common in patients with heart failure; 50% to 70% of these patients have nonsustained ventricular tachycardia on ambulatory monitoring, and 35% to 50% die suddenly. $\beta$-Blockers have known antiarrhythmic and antifibrillatory effects in ischemic heart disease, both in the experimental and clinical setting.\textsuperscript{69} Some $\beta$-blockers (eg, carvedilol) have also been shown to reduce the frequency and complexity of ventricular arrhythmias in patients with heart failure. These benefits are believed to be related to the ability of $\beta$-blockers to block $\beta_1$-receptors and thereby reduce cardiac levels of cyclic AMP, an important factor in the provocation of sudden death.\textsuperscript{27} In addition, because activation of $\beta_2$-receptors can increase the transport of potassium into cells and provoke hypokalemia, agents that block $\beta_2$-receptors can attenuate this arrhythmogenic mechanism. This may explain why nonselective $\beta$-blockers may be more effective than $\beta_1$-selective agents in reducing the risk of sudden death in survivors of an acute myocardial infarction.\textsuperscript{70,71} Finally, because $\alpha$-receptors may act to enhance afterdepolarizations and triggered activity in injured hearts, drugs that block $\alpha_1$-receptors may exert important antiarrhythmic and antifibrillatory actions in patients with heart failure.\textsuperscript{19}

**Antiischemic Effects** Nearly two-thirds of patients with heart failure have underlying coronary artery disease as the cause of heart failure. Many have active myocardial ischemia (including angina), whereas others are at high risk of having a new myocardial infarction—commonly a fatal event in patients with compromised cardiac function. Myocardial ischemia may also play a role in patients with heart failure due to a dilated cardiomyopathy. These patients frequently have abnormalities of coronary vascular reserve and show metabolic evidence of myocardial ischemia during stress.\textsuperscript{51,72}

$\beta$-Blockers have known antiischemic effects and can prevent the occurrence of a new myocardial infarction in patients with previous myocardial injury.\textsuperscript{73,74} These benefits may be related to the ability of these drugs to reduce heart rate and myocardial oxygen demand (the basis of their antiischemic effect) or decrease the risk of plaque rupture (the basis of their antiinfarction effect). Interestingly, in patients with heart failure, $\beta$-blockade reduces myocardial oxygen consumption, even when the heart rate is maintained at a high constant rate by atrial pacing.\textsuperscript{50} In patients with dilated cardiomyopathy, long-term $\beta$-blockade converts the failing heart from a state of lactate production to a state of lactate extraction.\textsuperscript{49,71} Finally, some $\beta$-blockers may protect against myocardial ischemic injury by mechanisms other than $\beta$-blockade. As noted above, carvedilol exerts antioxidant effects (independent of its actions as an adrenoceptor blocker), which may protect the heart from ischemic or reperfusion damage.\textsuperscript{75}

**CLINICAL TRIALS OF $\beta$-BLOCKING DRUGS IN HEART FAILURE**

**Early Observations** The possibility that $\beta$-adrenergic-blocking drugs might exert favorable effects in heart failure was first raised by investigators from Göteborg, Sweden more than 20 years ago.\textsuperscript{76} In a series of reports, these physicians described hemodynamic and clinical benefits following long-term use of $\beta$-blockers in patients with a dilated cardiomyopathy; these benefits disappeared following withdrawal of treatment.\textsuperscript{77} The survival of patients treated with $\beta$-blockers was superior to that seen in historical controls.\textsuperscript{78} These observations, although intriguing, were difficult to interpret because these early reports did not evaluate the utility of $\beta$-blockers in the context of a controlled clinical trial.

During the following 5 years, two small, controlled trials evaluated the effects of $\beta$-blocking drugs admin-
istered for 1 month to patients with heart failure. Both studies failed to observe any clinical benefit of therapy, but the investigators found β-blockade to be surprisingly well tolerated in patients in whom it was previously believed to be contraindicated. The lack of benefit seen in these two studies has been attributed to their short duration. Drugs that interfere with neurohormonal systems (eg, ACE inhibitors and β-blockers) generally demonstrate improvement in heart failure over a period of 3 to 6 months; hence, trials of 1 month’s duration may not be adequate to evaluate a treatment effect.

**Effect of β-Blockers on the Clinical Status of Heart Failure in Controlled Clinical Trials**

The effects of β-blockade on the clinical status of patients with heart failure have been assessed in a number of single-center and multicenter placebo-controlled trials. Some trials have been too small (<40 patients), whereas others have been too brief (<2 to 3 months) to evaluate the effects of therapy. Nevertheless, several clinical trials have been adequately designed to evaluate the possibility of significant differences between the two treatment groups and are the primary focus of the present discussion.

In these studies, the effect of treatment on clinical status was assessed by direct measures (NYHA [New York Heart Association] class and symptom scores) and indirect measures (exercise tolerance and quality of life). The measurement of exercise tolerance has been particularly troublesome for the evaluation of β-blockers in heart failure because these drugs would be expected to attenuate any exercise-induced increases in heart rate, especially at peak effort. Consequently, many studies have used submaximal exercise testing to evaluate the efficacy of β-blockers. Unfortunately, the assessment of submaximal exercise capacity is not well standardized and the methods have varied from study to study.

**Metoprolol**

Controlled trials have shown that the addition of metoprolol to conventional therapy is associated with an improvement in NYHA class, quality of life, and exercise capacity in patients with heart failure. In single-center studies, metoprolol (in doses up to 200 mg daily for 3 to 6 months) produced an overall improvement in symptoms and exercise tolerance, both in patients with dilated cardiomyopathy and in those with ischemic heart disease. In the only multicenter study with metoprolol in heart failure—the Metoprolol in Dilated Cardiomyopathy (MDC) trial—treatment with the drug (mean dose 108 mg/day for 12 to 18 months) was associated with an improvement in NYHA class, quality of life, and exercise tolerance.

**Bisoprolol**

There are no single-center, placebo-controlled studies evaluating the effect of bisoprolol in patients with heart failure. In a large multicenter trial known as Cardiac Insufficiency Bisoprolol Study (CIBIS), the addition of bisoprolol to conventional therapy (up to 5 mg daily for 4 to 44 months) was associated with a significant improvement in NYHA class in patients with moderate to severe heart failure. This trial did not evaluate other measures of clinical status.

**Bucindolol**

Single-center studies with bucindolol have reported that treatment with the drug (up to 200 mg/day for 3 months) is associated with an improvement in NYHA class and symptoms in patients with dilated cardiomyopathy, but not in patients with ischemic heart disease. In contrast, in the only large multicenter study with bucindolol, treatment with the drug (up to 200 mg/day) had no effect on NYHA class, symptoms, quality of life, or exercise tolerance, regardless of the underlying cause of heart failure.

**Carvedilol**

The effects of carvedilol on the clinical status of patients with heart failure have been evaluated in three placebo-controlled, single-center studies and five multicenter, placebo-controlled trials. Hence, there is more experience in controlled clinical trials with carvedilol than with any other β-blocker used in the treatment of heart failure.

In the three single-center studies, treatment with carvedilol (in doses up to 50 to 100 mg daily for 3 to 4 months) was associated with an improvement in symptoms, NYHA class, quality of life (as assessed by the Minnesota Living with Heart Failure questionnaire), and submaximal exercise tolerance (as assessed by the distance traversed on a 6-min walk). In these studies, carvedilol was added to conventional therapy (which generally included ACE inhibitors); patients were enrolled with a wide range of severity of symptoms; and the effects were similar regardless of the etiology of heart failure.

In addition to the single-center studies, the effects of carvedilol have been evaluated in five multicenter studies, four conducted in the United States (U.S.) and one carried out in Australia and New Zealand (ANZ). In the ANZ study (which enrolled 415 patients with minimal or mild-to-moderate symptoms of heart failure), treatment with carvedilol was associated with no improvement (and a slight deterioration) in symptoms or exercise tolerance during a follow-up of 6 months. In contrast, in the four U.S. multicenter trials (which enrolled 1094 patients with mild, moderate, and severe heart failure), treatment with carvedilol was associated with an improvement in symptoms, NYHA class, and overall well-being, but had little effect on exercise tolerance. In all five trials, carvedilol was administered in doses up to 50 to 100 mg daily, which
was added to treatment with digitalis, diuretics, and an ACE inhibitor.

**Effect of β-Blockers on Morbidity and Mortality in Heart Failure in Controlled Clinical Trials**

Whereas the assessment of clinical status provides an accurate reflection of the benefits of a new drug in the near term, such data provides little information about the effects of treatment on the natural history of the disease. By its very nature, heart failure is a progressive disorder characterized by repeated hospitalization for clinical deterioration, and eventually death. The frequency of these two events over time provides objective endpoints for assessing the long-term efficacy of a new treatment.

Evidence from large multicenter trials in survivors of an acute myocardial infarction suggest that long-term β-blockade has favorable effects on the natural history of patients with ischemic heart disease. In these studies, prolonged therapy with many different β-blocking drugs was associated with a decrease in risk of death and recurrent infarction. Interestingly, these benefits appeared to be most marked in patients with heart failure at the time of enrollment into the studies. These observations suggested that β-blockers might favorably affect morbidity and mortality in patients with heart failure.

Although single-center studies have occasionally provided clues concerning the effects of β-blockade on morbidity and mortality, such trials are generally too small to allow adequate evaluation of the effect of these drugs on the natural history of heart failure. Thus, most of the information on the effect of β-blockers on morbidity and mortality is derived from multicenter studies of at least 6 months’ duration. Seven such studies have been conducted: one with metoprolol, one with bisoprolol, and five with carvedilol.

**Metoprolol**

In the MDC study, 383 patients with a nonischemic dilated cardiomyopathy and mild to moderate heart failure were randomized to placebo or metoprolol (up to 150 mg/day), which was added to conventional therapy for 12 to 18 months. The primary endpoint of the study was the combined risk of death and worsening heart failure sufficient to require placement of the patient on a heart transplant waiting list. Treatment with metoprolol was associated with a 34% reduction in the risk of death or clinical deterioration; this effect was nearly significant (P = .058) (Figure 1). The risk of death alone and the risk of cardiovascular hospitalizations alone were not favorably influenced by metoprolol.

**Bisoprolol**

In CIBIS, 641 patients with an ischemic and nonischemic cardiomyopathy and moderate to severe heart failure were randomized to placebo or bisoprolol (up to 5 mg/day), which was added to conventional therapy for 4 to 44 months (average 23 months). The primary endpoint of the study was all-cause mortality; an important secondary endpoint was hospitalization for worsening heart failure. Treatment with bisoprolol did not significantly reduce mortality (P = .22) (Figure 2), but bisoprolol did reduce the risk of hospitalization for heart failure by 34% (P < .01). A retrospective subgroup analysis suggested that bisoprolol reduced mortality in patients with a nonischemic dilated cardiomyopathy but had no effect in patients with heart failure due to underlying coronary artery disease.

**Carvedilol**

In the U.S. Carvedilol Heart Failure Trial program, 1,094 patients with mild, moderate, and severe heart failure were randomized to placebo or carvedilol (up to 50 to 100 mg/day), which was added to conventional therapy for 7 to 15 months. Patients were allocated to one of four component protocols.
based on the severity of symptoms and performance on an exercise test. Each of the protocols had specified primary and secondary endpoints, but an objective of the overall program was to evaluate the effect of carvedilol on survival; in this regard, the principal goal was to assess the safety of the drug while recognizing its potential to prolong life. An important prespecified secondary endpoint was hospitalization for cardiovascular causes. Treatment with carvedilol was associated with a 65% reduction in the risk of death, which was highly significant (Figure 3) \( P < .0001 \); this was reflected in a decrease in both death due to pump failure and sudden death. Two of the four component protocols observed a significant effect on mortality when analyzed on their own. In addition, carvedilol reduced the risk of hospitalization for cardiovascular causes by 27% \( P = .036 \) and the combined risk of all-cause mortality and cardiovascular hospitalization by 38% \( P < .001 \) (Figure 4).

The effects of carvedilol on mortality alone and the combined risk of morbidity and mortality were similar regardless of the cause or severity of heart failure. Carvedilol reduced the mortality rate both in patients with ischemic heart disease or nonischemic dilated cardiomyopathy as well as in those with mild to moderate or moderate to severe symptoms of heart failure. Carvedilol also reduced the combined risk of death and cardiovascular hospitalizations in patients with or without coronary artery disease; the reduction in risk was similar whether patients had class II or class III symptoms. Few patients in the U.S. Carvedilol Heart Failure Trial had class IV symptoms.

In the ANZ Heart Failure Trial, 415 patients with mild to moderate heart failure secondary to ischemic heart disease were randomized to placebo or carvedilol (up to 50 mg/day), which was added to conventional therapy for 18 to 24 months. The principal objective of the long-term phase of the study was to determine the combined risk of death and hospitalization for any reason. Treatment with carvedilol reduced the combined risk of morbidity and mortality by 26% \( P = .02 \) (Figure 5). The reduction in risk was similar when morbidity and mortality end points were analyzed separately. Treatment with carvedilol reduced mortality alone by 24%; this smaller effect may have been related to the lower dose of carvedilol achieved in the ANZ study than in the U.S. Carvedilol Heart Failure Trial. The effect of carvedilol on hospitalizations alone in the ANZ Heart Failure Trial was significant \( P = .05 \).

![FIGURE 3. Kaplan-Meier analysis of survival among 1,094 patients in U.S. Carvedilol Program (reproduced from Packer et al., with permission. © 1996 Massachusetts Medical Society. All rights reserved.).](image1)

![FIGURE 4. Kaplan-Meier analysis of survival without hospitalization for a cardiovascular reason in U.S. Carvedilol Program \( P < .001 \) (reproduced from Packer et al., with permission. © 1996 Massachusetts Medical Society. All rights reserved.).](image2)

![FIGURE 5. Effect of carvedilol on death or hospital admission in the Australia-New Zealand Heart Failure Trial (reproduced from Australia-New Zealand Heart Failure Research Collaborative Group, with permission. © 1997 The Lancet, Ltd.).](image3)
CLINICAL USE OF β-BLOCKING DRUGS IN HEART FAILURE

Who Should Receive a β-Blocker? Analysis of data from randomized trials suggests that most patients with heart failure are potential candidates for long-term treatment with a β-blocking drug. Clinical benefits have been reported in patients with a wide range of demographic and clinical characteristics, including patients with mild, moderate, and severe symptoms as well as those with and without underlying coronary artery disease. No baseline measurement has been able to identify the patients most likely to respond or the least likely to show benefit. Nevertheless, patients who have general contraindications to the use of β-blockers (ie, claudication, bronchospasm, or advanced heart block) should not receive these drugs.

However, clinical trials carried out to date have provided little information regarding the efficacy or safety of β-blockers in patients with severe or unstable heart failure. Only 3% to 5% of patients enrolled in the large multicenter trials with metoprolol, bisoprolol, and carvedilol, had class IV symptoms at the time of entry into the study. Furthermore, all patients enrolled in clinical trials were required to meet specific stability criteria (with respect to clinical status and background medications) before randomization. As a result, until further data are available, β-blockers should not be administered to patients with class IV heart failure or to those who are hospitalized or receiving intravenous medications for heart failure. Such patients are unlikely to tolerate the short-term negative inotropic effects of β-blocking drugs and could experience serious cardiovascular side effects following initiation of therapy.61,96

Should β-blockers be used instead of conventional agents (eg, digitalis and ACE inhibitors) for the treatment of heart failure? Most of the experience with β-blockers in heart failure has been in clinical trials that enrolled patients who were already receiving digitalis, diuretics, and an ACE inhibitor; hence, in general, β-blockers should be used together with existing therapies for heart failure. Such an approach is reasonable not only from a clinical perspective, but also from a pathophysiologic point of view. Because the neurohormonal activation in heart failure involves both the sympathetic nervous system and the renin-angiotensin system, it is reasonable to use antagonists of both systems (β-blockers and ACE inhibitors) in the treatment of patients with this disorder. In patients with heart failure following an acute myocardial infarction, ACE inhibitors have been effective in those already receiving a β-blocker.97 Similarly, in patients with long-standing heart failure remote from the initiating injury, β-blockers have been effective in those already receiving an ACE inhibitor.98

How Should Treatment With a β-Blocker Be Administered? Initiation of therapy with a β-blocker in patients with heart failure may be associated with some circulatory instability during the first 2 to 6 weeks of treatment. The two major cardiovascular side effects that can occur include: (1) worsening heart failure (as a result of the negative inotropic effects of the drugs); and (2) symptomatic hypotension (as a result of the peripheral vasodilator effects of the drugs). Patients taking β-blockers with vasodilator properties may be less likely to experience the former, but may be more likely to experience the latter. Nevertheless, both types of adverse reactions can be seen with all available β-blockers that have been used in the treatment of heart failure. The frequency of these side effects varies according to the severity of the disease, occurring in as little as 10% to 20% of patients with mild heart failure to as high as 50% in patients with the most advanced symptoms.

Fortunately, both the negative inotropic and peripheral vasodilatory actions of β-blockers in heart failure generally subside over time. The cardiodepressant actions of these drugs are eventually overcome by the beneficial effects of treatment on left ventricular function, whereas tolerance frequently develops to the vasodilatory actions, particularly in the case of drugs with α-blocking properties. Consequently, most of the adverse effects of early therapy with β-blockers in heart failure are short-lived and, if therapy with the β-blocker is maintained, are inevitably superseded within weeks by a progressive improvement in the patient’s clinical status. Therefore, the challenge to the physician is to support the patient through the first 2 to 6 weeks of therapy. This challenge can be successfully met in most patients using the following plan:

- Initiate therapy with the β-blocker in very small doses, followed by a doubling of the dose no more frequently than every 1 to 2 weeks. A more cautious schedule may be required in patients at high risk. Increments in dose should be carried out only after review of the patient’s clinical status. This careful approach allows the circulation to adapt to the withdrawal of the short-term support provided by activation of the sympathetic nervous system in patients with heart failure.
- If either worsening heart failure or symptomatic hypotension occurs, modify the dose of the concomitantly administered diuretic or ACE inhibitor, or both. The doses of these medications should be increased in patients who experience worsening symptoms of heart failure, but decreased in patients who have symptomatic hypotension. Further increases in the dose of the β-blocker should be delayed until the side effect subsides.
• Reduce the dose or discontinue the \(\beta\)-blocker only if the side effect does not respond to changes in the dose of diuretic or ACE inhibitor. Although the physician may elect to change the dose of the \(\beta\)-blocker first (before adjusting the dose of concomitant medications), doing so may hinder the ability of patients to eventually attain the doses of the \(\beta\)-blocker needed to achieve a therapeutic effect.

• Increase the dose of the \(\beta\)-blocker until target doses are achieved or until adverse reactions occur that limit further increases in dose. Dose-limiting side effects that have been observed in various \(\beta\)-blocker studies include bradycardia, weakness and fatigue, and gastrointestinal symptoms.\(^{53,82,84,94,96}\)

In large-scale clinical trials with carvedilol that used an algorithm similar to the one described above, 85% to 90% of patients with heart failure were able to achieve and tolerate target doses of the drug. Furthermore, once target doses were attained, the withdrawal rates were similar to or even higher in the placebo group than in the group of patients treated with the \(\beta\)-blocker, primarily because patients treated with placebo had a higher frequency of serious cardiovascular events.

It should be noted that clinical improvement following initiation of treatment with a \(\beta\)-blocker is usually delayed. A reduction in signs and symptoms of heart failure is not usually seen until 6 to 12 weeks of continuous treatment. This delay is related to the time required for the \(\beta\)-blocker to exert its long-term effects (ie, reversal of the toxicity produced by endogenous catecholamines). The recovery of cardiac function may require weeks or months of treatment to be apparent, but once achieved, can be sustained for long periods. Similar delays can characterize the use of other neurohormonal antagonists (eg, ACE inhibitors) in heart failure.\(^{81}\)

**CONCLUSIONS**

During the past decade, information derived from studies performed in the laboratory and from clinical trials suggests that antagonism of the sympathetic nervous system may be useful in the management of patients with heart failure. This knowledge reflects a substantial shift in the manner in which physicians view heart failure and the drugs used to treat this disorder. Because \(\beta\)-blockers were known to depress cardiac function, the use of these agents was considered to be contraindicated in patients with compromised ventricular function only 10 years ago. However, it is now recognized that the hemodynamic effects of drugs do not reliably predict their clinical effects in patients with heart failure, and that the actions of agents on neurohormonal systems may be the most useful guide to understanding their actions in the management of this syndrome. This recognition has occurred at a time when scientists have identified specific mechanisms whereby prolonged activation of the sympathetic nervous system can exert deleterious effects on the heart, including the recent finding that catecholamines may undermine the viability of cardiac cells at a fundamental molecular level.

Several controlled clinical trials have evaluated the efficacy and safety of \(\beta\)-blockers in patients with heart failure. These trials have demonstrated that the addition of a \(\beta\)-blocker to conventional therapy produces favorable effects on cardiac performance and significant benefits on symptoms and functional capacity. These effects have been observed in numerous controlled studies that have evaluated the effects of \(\beta\)-blockers in heart failure, but most of this experience has been derived in clinical trials with carvedilol. Not surprisingly, \(\beta\)-blockade seems to have little effect on indirect measures of patient benefit such as exercise tolerance because these drugs would be expected to attenuate the increases in heart rate required to maintain or enhance exercise capacity.

In addition to these favorable effects on symptoms and functional capacity, the results of large-scale trials have indicated that \(\beta\)-blockers can favorably influence the natural history of heart failure. In multicenter studies, treatment with bisoprolol, carvedilol, and metoprolol has been associated with a reduction in the risk of clinical deterioration and a decrease in the frequency of worsening heart failure. In addition, treatment with carvedilol has been associated with a reduction in the mortality of patients with heart failure. This benefit was observed regardless of the cause of heart failure or the severity of the patient’s symptoms. Is such an effect on survival a general characteristic of \(\beta\)-blockers or a unique property of carvedilol? Carvedilol is the only \(\beta\)-blocker that blocks \(\beta_1\), \(\beta_2\), and \(\alpha_1\)-receptors without producing intrinsic sympathomimetic effects, increasing cardiac norepinephrine, or causing upregulation of \(\beta\)-receptors. Hence, the use of the drug is associated with more complete antagonism of the sympathetic nervous system than that produced by other \(\beta\)-blockers. Furthermore, the agent has important vasodilatory properties that may enhance both its efficacy and safety. Finally, in addition to its actions as an adrenoceptor blocker, carvedilol exerts antioxidant and antiproliferative effects. These actions may play an important role in preventing the progressive loss of myocardial cells that is characteristic of the failing heart.

Because of its demonstrated ability to improve symptoms and clinical status as well as reduce morbidity and mortality, carvedilol has recently been approved by the U.S. Food and Drug Administration for the treatment of heart failure. This regulatory decision marks the first official recognition of the clinical ben-
efits of long-term β-blockade in the management of patients with left ventricular dysfunction. Large-scale clinical trials have now provided extensive clinical experience with the use of β-blockers in patients with heart failure that is sufficient to allow the development of clinical algorithms to guide the initiation and long-term use of these drugs. These algorithms have helped physicians overcome the early (2- to 4-week) period of clinical instability that can follow the commencement of treatment with a β-blocker. By using these prescribing algorithms, 85% to 90% of patients with heart failure were able to achieve and tolerate target doses of a β-blocker in controlled clinical trials.

As a result of this new information, physicians are now entering a new era in the treatment of heart failure, an era in which neurohormonal antagonists (ACE inhibitors and β-blockers) may be combined to provide important therapeutic benefits for patients with this disabling syndrome.

REFERENCES


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