Sympathetic Activation in Heart Failure and Its Treatment With β-Blockade

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Multiple models explaining the pathogenesis of heart failure have been put forth during the past 5 decades. These models were modified as clinical evidence supported or refuted their assumptions. During the past 2 decades, heart failure models emphasized the importance of neurohormonal systems in heart failure progression. The positive impact that angiotensin-converting enzyme inhibitors have had on mortality from heart failure has bolstered the neurohormonal theory. Attention recently has turned to the sympathetic nervous system and its potential deleterious effects on the cardiovascular system in heart failure. The sympathetic nervous system can negatively impact the cardiovascular system in heart failure in several ways, including down-regulating β₁-receptors, exerting direct toxic effects on the myocardium, and contributing to myocardial remodeling and life-threatening arrhythmias. β-Adrenergic blockers have shown promise for reducing morbidity and mortality in heart failure, but definitive reductions in mortality remain to be shown by future investigations.

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MODELS OF HEART FAILURE

A model of the pathophysiology of heart failure is required to develop and effectively evaluate new treatments of the disease. Three major evolutions of the heart failure model are listed in Table 1. Each model is based on an assumed principal abnormality that occurs as a result of cardiac dysfunction. Primary treatments in each model are aimed at countering the principal abnormality. The model was revised during the time frames listed as more was learned about the pathophysiology of heart failure.

Cardiorenal Model

The cardiorenal model explains the edema and volume expansion associated with heart failure occurring primarily from renal hypoperfusion caused by cardiac dysfunction. β-Adrenergic blockers were the primary treatments aimed at improving renal function, and they were effective for relieving symptoms of dyspnea and edema associated with heart failure. However, the continued poor prognosis for patients with other activated hormonal systems, and how β-blockade has become an effective treatment of heart failure.
heart failure receiving diuretics and digitalis led to the development of the hemodynamic model of heart failure.

**Hemodynamic Model**

According to the hemodynamic model of heart failure, chronically increased preload and afterload caused by cardiac dysfunction lead to progressive heart failure through structural remodeling of the myocardium. Hemodynamic improvement with peripheral vasodilators or positive inotropic agents, which both reduce wall stress, should reduce myocardial remodeling. The Veterans Affairs Heart Failure Trial evaluated the hemodynamic model by comparing the vasodilator prazosin hydrochloride with a combination of hydralazine hydrochloride and isosorbide dinitrate. Although the decrease in blood pressure was greater with prazosin, only hydralazine with isosorbide showed a significant reduction in mortality at 2 years ($P<.03$). Similarly, hemodynamic benefits from the positive inotropic agent milrinone do not favorably alter the natural course of heart failure. The Prospective Randomized Milrinone Survival Evaluation trial found a 28% increase in mortality from all causes and a 34% increase in the risk for cardiovascular death in patients treated with milrinone. Such lack of support for the hemodynamic model of heart failure led to development of the neurohormonal model.

**Neurohormonal Model**

The neurohormonal model explains progression of heart failure by activation of endogenous neurohormonal systems that create unfavorable hemodynamics and exert direct toxic effects on the myocardium. Table 2 shows the major neurohormonal systems activated in heart failure. They increase plasma levels of vasoconstricting and volume-expanding hormones as well as counterregulatory hormones. The net hemodynamic effects are vasoconstriction with increased blood volume, heart rate, and myocardial contractility. In the short term, these systems are compensatory and maintain perfusion of vital organs. Activated over the long term, however, they lead to decompensation with symptomatic heart failure and increased mortality. The sequence of activation of these systems is variable and dependent on the severity of the heart failure. The sympathetic nervous system is activated in mild congestive heart failure (CHF) after a small increase in left ventricular filling pressure, but the plasma renin-angiotensin system (RAS) is activated with severe CHF in symptomatic patients. Multiple complex interactions occur between the neurohormonal systems, and the importance of the sympathetic nervous system in chronic heart failure is evidenced by its direct or indirect interactions with the other systems shown in Figure 1. Although a complete discussion of the activated neurohormonal systems in heart failure is beyond the scope of this article, the systems listed in Table 2 and their interactions are described briefly.

**Renin-Angiotensin.** An early study in the 1960s supported activation of the RAS in heart failure by measuring increased levels of plasma renin and angiotensin in patients with edematous heart failure. The increased levels normalized after resolution of the edema by treatment with diuretics, digitalis, and sodium restriction. Another study showed that the RAS is related to the clinical state in CHF by comparing plasma renin activity and aldosterone level in patients who had severe decompensated CHF with those in patients who had chronic stable CHF. Plasma renin activity and plasma aldosterone level were increased in the patients with decompensated CHF, but they were normal in the patients with chronic stable CHF. These studies support the concept that the circulating RAS is activated only in decompensated heart failure. More recently, biochemical methods have shown that a localized tissue RAS exists in the heart, blood vessels, kidney, brain, and adrenal tissues that functions independently of the plasma RAS. Evidence suggests the tissue RAS is active in compensated heart failure when the plasma RAS is quiescent. The effects of the RAS are mediated primarily by interaction of the hormone angiotensin II with target tissue receptors, producing systemic vasoconstriction, adrenal aldosterone release, central vasopressin release, and renal sodium resorption. Angiotensin II also facilitates cardiac remodeling by inducing growth-related protooncogenes, and it has direct cardiotoxic effects. Indirect effects of angiotensin II occur through its interaction with other neurohormonal systems.

Angiotensin II augments adrenergic transmission presynaptically through a tyramineline action and an angiotensin II receptor–mediated mechanism. Postsynaptic adrenergic facilitation by angiotensin II also occurs by sensitization of $\alpha_1$- and $\alpha_2$-adrenergic receptors. The sympathetic nervous system augments the RAS by stimulating renin release through a $\beta_1$-receptor–mediated mechanism.

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**Table 1. Models of Heart Failure**

<table>
<thead>
<tr>
<th>Model</th>
<th>Time Frame</th>
<th>Principal Abnormality</th>
<th>Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiorenal</td>
<td>1940s-1960s</td>
<td>Renal hypoperfusion</td>
<td>Digitalis and diuretics</td>
</tr>
<tr>
<td>Hemodynamic</td>
<td>1960s-1980s</td>
<td>Increased ventricular wall stress</td>
<td>Vasodilators or positive inotropes</td>
</tr>
<tr>
<td>Neurohormonal</td>
<td>1980s-1990s</td>
<td>Neurohormonal activation</td>
<td>ACE inhibitors or $\beta$-blockers</td>
</tr>
</tbody>
</table>

*ACE indicates angiotensin-converting enzyme.

**Table 2. Neurohormonal Systems Affected in Heart Failure**

<table>
<thead>
<tr>
<th>Vasoconstricting or Volume Expanding</th>
<th>Vasodilating or Diuretic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine or epinephrine</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>Arginine vasopressin (antidiuretic)</td>
<td>Adrenomedullin</td>
</tr>
<tr>
<td>Endothelin 1</td>
<td></td>
</tr>
</tbody>
</table>
and β-receptors augment local angiotensin II release from mesenteric arteries.22 Evidence also shows that angiotensin II may stimulate secretion of arginine vasopressin (AVP) and atrial natriuretic peptide (ANP).23 The clinical importance of the RAS in heart failure is underscored by the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),24 Studies of Left Ventricular Dysfunction (SOLVD),25 and Veterans Affairs Heart Failure Trial26 trials, which all show reduced mortality in patients with heart failure treated with angiotensin-converting enzyme inhibitors.

Arginine Vasopressin. Arginine vasopressin is the antidiuretic hormone that promotes plasma osmoregulation and vasconstriction. Plasma levels of AVP are increased in some patients with heart failure who have loss of sodium or osmolality correlation.26,27 This increase implies a nonosmolar stimulus driving AVP in certain patients who have heart failure. A subset of patients with heart failure, however, have a normal plasma AVP level with normal plasma osmolality.24 The cause of the loss of osmolar stimulus to AVP in some patients is not clear, but angiotensin II may stimulate AVP secretion through a central-acting mechanism.28 Increased plasma AVP level may contribute to the increased peripheral vascular resistance, hyponatremia, and edema associated with heart failure.24,25

**Endothelin 1.** Endothelin 1 is an endothelium-derived peptide with potent long-acting venous and arterial vasoconstrictor properties, and it is cleaved from a larger precursor called “big endothelin 1” by an endo-thenin-converting enzyme.29 Plasma levels of big endothelin 1 and endothelin 1 are increased in heart failure.27,28 Endothelin 1 acts as a paracrine and autocrine local mediator; thus, plasma levels may reflect only a fraction of active endothelin 1. An increase in endothelin 1 level contributes to the maintenance of vascular tone in chronic heart failure through smooth muscle endothelin receptors,29 and its precursor, big endothelin 1, is strongly related to mortality in patients with heart failure.29 Big endothelin 1 appears to predict 1-year mortality in chronic heart failure better than hemodynamic variables and ANP.29 Endothelin 1 potentiates the actions of AVP and the RAS,27 and its synthesis is stimulated by various factors, including epinephrine and angiotensin II.30

**Atrial Natriuretic Peptide.** Atrial natriuretic peptide is a circulating peptide with natriuretic, diuretic, and vasorelaxing properties secreted from the atria in the heart.31 The primary stimulus for ANP secretion appears to be atrial stretch from increased atrial pressure.31 The level of ANP is increased in heart failure in proportion to atrial pressure,32 and plasma levels have been correlated with survival and New York Heart Association functional class.31 The SOLVD trial showed that ANP level was increased in association with asymptomatic left ventricular dysfunction without activation of the plasma RAS33; thus, it may have a key role in maintaining a compensated state in heart failure. Atrial natriuretic peptide appears to inhibit the RAS31 and reduce central sympathetich output, as measured by microneurographic techniques.34 However, circulating norepinephrine (NE) blunts the natriuretic effect of ANP,35 and angiotensin II facilitates the antinatriuretic effect of the renal sympathetic nerves.36

**Adrenomedullin.** Adrenomedullin is a potent vasorelaxing peptide that is synthesized in the adrenal medulla, heart, lung, aorta, vascular smooth muscle cells, and endothelial cells.36 There is a proportionate increase in plasma adrenomedullin levels in moderate to severe heart failure, and the increase is significantly correlated with plasma NE level (P < .001).37 Although the plasma level of adrenomedullin is increased, the vasodilatory effects are attenuated in heart failure.36 Adrenomedullin may have other indirect effects through interaction with the RAS and sympathetic nervous system. An in vitro study showed that adrenomedullin increases the release of adrenal epinephrine and NE in a concentration-dependent manner and that it inhibits angiotensin II–stimulated aldosterone secretion.38

**EVIDENCE OF SYMPATHETIC ACTIVATION IN CHF**

Sympathetic activation in CHF is evidenced by increased plasma NE levels, increased central sympathetic outflow, and NE spillover to the plasma from activated sympathetic nerve fibers.14,39

**Plasma NE**

Plasma NE was measured and compared in 54 normal controls, 151 asymptomatic patients with left ventricular dysfunction, and 81 symptomatic patients with heart failure in the SOLVD trial.33 The mean plasma NE level was 35% higher in the...
asymptomatic group than in controls, and it was 23% higher in the symptomatic group than in the asymptomatic group. However, plasma NE levels are not a reliable indicator of sympathetic activity in heart failure because of impaired clearance from reduced cardiac output. Sympathetic neurotransmitter release and clearance in heart failure were measured by means of tritiated NE in a study of 12 patients with heart failure and 15 normal controls. Plasma clearance of NE in the patients with heart failure was 67% of that in the control patients. Total NE spillover to plasma from sympathetic nerve terminals was 84% higher in the patients with heart failure than in controls. Cardiac and renal NE spillover accounted for 62% of the total spillover, with cardiac and renal spillover increasing 500% and 200%, respectively. Pulmonary spillover was similar in the 2 groups, however. That study confirms increased release of NE in heart failure, and the increased release of NE is organ specific.

Central Sympathetic Outflow

Increased central sympathetic outflow in heart failure has been demonstrated by directly recording muscle sympathetic nerve activity (mSNA) at the peroneal nerve with microneurography. Sympathetic activity in the peroneal nerve was identified by characteristic pulse-synchronous bursts and a conduction velocity of approximately 1 m/s, consistent with sympathetic C nerve fibers. Resting mean mSNA (in bursts per minute) was significantly higher in the patients with heart failure than in age-matched controls ($P < .01$). Because the mSNA is synchronized with pulse and the group with heart failure had higher mean heart rates than the control group, the mSNA also was expressed as bursts per 100 heartbeats. Bursts of mSNA per 100 heartbeats were also significantly higher in the heart failure group than in controls ($P < .05$). This increase in mSNA was correlated with plasma NE level, left ventricular filling pressures, and mean right atrial pressure. These correlations suggest that the sympathetic nervous system is activated in proportion to the degree of cardiac failure at rest.

Plasma Epinephrine

The plasma epinephrine level is increased in severe heart failure. In a study of 42 patients with severe CHF, radioligand methods showed a 49% increase in circulating epinephrine compared with controls. The epinephrine increase was primarily from decreased plasma clearance, with the whole-body release rate being normal or slightly reduced. There were, however, regional increases in epinephrine release from extra-adrenal tissues, including the heart, lung, and splanchnic beds, in the patients with heart failure. Clinical effects of epinephrine may occur in heart failure, because it can act as a neurotransmitter as a result of its increased plasma level. It participates in neuronal uptake and is incorporated into sympathetic vesicles with NE. Normally, epinephrine acts as a humoral agent and promotes postjunctional $\beta_2$-receptor-mediated vasodilation, but as a cotransmitter with NE it promotes vasoconstriction through prejunctional $\beta_2$-receptor–facilitated NE release. The plasma epinephrine level also was related to mortality in the CONSENSUS trial data. 

MECHANISM OF SYMPATHETIC ACTIVATION IN CHF

Studies show that multiple mechanisms may be responsible for activation of the sympathetic nervous system in heart failure. Loss of baroreflex sensitivity and increased sympathetic afferent activity increase total sympathetic nervous activity in heart failure.

Decreased Baroreflex Sensitivity

Cardiopulmonary and arterial baroreceptors modulate central sympathetic outflow with tonic inhibitory stimuli to the medullary cardiovascular center in the central nervous system. Reduced baroreceptor sensitivity was shown in 36 patients with heart failure by comparing changes in mSNA and heart rate with changes in mean arterial pressure after infusion of phenylephrine and nitroprusside. In patients with heart failure, there were significant reductions in the changes of mSNA and heart rate for those in New York Heart Association class III or IV ($P < .01$) and class I or II ($P < .05$) as mean arterial pressure changed.

The lost sensitivity is probably caused by multiple factors, which may include augmented Na-K adenosine triphosphatase activity, angiotensin II, and decreased arterial compliance. Administration of a cardiac glycoside to patients with heart failure causes reduced sympathetic nerve activity independent of changes in cardiac output. A study in dogs in which ouabain was used showed enhanced baroreceptor sensitivity in dogs with CHF and no change in sensitivity in normal dogs. These studies suggest that augmented Na-K adenosine triphosphatase activity depresses baroreceptor sensitivity in CHF. Aldosterone, which is increased in heart failure, augments Na-K pump activity in other tissues, and an infusion of aldosterone in dogs with CHF decreases baroreceptor sensitivity. This finding suggests that the increased aldosterone level in CHF may drive the reduction in baroreceptor sensitivity. Angiotensin II, which is also increased in heart failure, appears to decrease baroreceptor sensitivity through a centrally acting mechanism. Baroreceptor sensitivity is completely restored after heart transplantation, a finding that implies a functional rather than a structural impairment of baroreceptors in heart failure.

Sympathetic Afferents

Excitatory sympathetic afferents to the central nervous system are also activated in decompensated heart failure. The excitatory inputs develop from sensory endings that respond to products of metabolism and substances released during ischemia. Activation of the sensory receptors in CHF is probably related to increased receptor sensitivity analogous to the decreased receptor sensitivity of baroreceptors. The
increased receptor sensitivity is suggested by a study in dogs with CHF showing an augmented sympathetic activity in response to epicardial bradykinin and capsaicin, and this may provide a tonic level of excitatory sympathetic input to the central nervous system in CHF.44

**PROGNOSIS RELATED TO SYMPATHETIC ACTIVATION IN CHF**

The importance of the sympathetic nervous system in heart failure is underscored by studies showing that mortality is correlated with measurements of circulating catecholamines. In a study of 106 patients with moderate to severe heart failure, resting supine plasma NE levels were significant predictors of mortality ($P = .002$). Plasma NE levels were more sensitive than hemodynamic variables for predicting mortality, because NE levels were the only independent predictor of mortality on multivariate analysis. The CONSENSUS trial was a study of 253 patients with severe (New York Heart Association class IV) heart failure randomized to receive either placebo or enalapril. Survivors had lower baseline plasma levels of NE ($P < .001$) and epinephrine ($P < .005$) than nonsurvivors. In the placebo group, there was a positive relationship between NE ($P < .001$), epinephrine ($P = .001$), and 6-month mortality. The enalapril group had reduced plasma NE level at 6 weeks compared with baseline ($P < .05$) accompanied by significantly reduced mortality in patients with baseline NE ($P < .05$) and epinephrine ($P < .05$) levels above the median. In a study of patients with severe heart failure, cardiac NE spillover, measured by means of titrated NE, was a better predictor of mortality than plasma NE. The increased mortality is probably multifactorial and may be related to processes discussed below.

**MYOCARDIAL RESPONSE TO CATECHOLAMINES**

Catecholamines increase both myocardial contractility and heart rate, but $\beta_1$-receptor–mediated inotropic changes are the primary mechanism to increase myocardial performance. Figure 2 is a schematic representation of a cardiac myocyte and the interaction of the $\beta$-adrenergic receptors with the contractile apparatus. The myocardial $\beta_1$- and $\beta_2$-receptors respond to catecholamines by activating the $G_i$ protein. The $G_i$ protein activates adenylate cyclase, which increases cyclic adenosine monophosphate. Cyclic adenosine monophosphate activates protein kinase, which increases intracellular calcium and ultimately myocardial contractility. The relative effectiveness of each $\beta$-receptor type is determined by the number of each receptor, the degree of coupling to adenylate cyclase, and the receptors’ affinity for NE. The $\beta_2$-receptor is coupled to adenylate cyclase approximately 4 to 5 times more strongly than $\beta_1$-receptors. However, in the nonfailing ventricle, approximately 80% of the $\beta$-receptors are $\beta_1$, and NE affinity for $\beta_1$-receptors is 30 to 50 times greater than for $\beta_2$-receptors. Therefore, the $\beta_1$-receptor is the primary pathway for adrenergic drive increasing contractility in the nonfailing heart.

**EFFECTS OF SYMPATHETIC ACTIVATION IN CHF**

Various changes occur in the structure and function of the myocardium with chronic activation of the sympathetic nervous system. These changes lead to progressive myocardial dysfunction with decreased adrenergic sensitivity and increased frequency of arrhythmias.

**$\beta$-Receptor Down-regulation**

In the failing human heart, several mechanisms reduce the heart’s ability to respond to adrenergic stimulation. $\beta_1$-Receptor density is decreased 60% to 70% in heart failure. $\beta_2$-Receptor density remains constant, but its responsiveness to adrenergic stimulation is reduced approximately 30% through uncoupling from adenylate cyclase. The reduced $\beta_1$-receptor density increases the proportion of $\beta_2$- to $\beta_1$-receptors, which may increase the significance of the $\beta_2$-receptor in heart failure. There also is a 30% to 40% increase in $G_i$ protein activity, which inhibits adenylate cyclase in the failing heart. The cause of these changes is not completely understood. However, $\beta$-receptor density is inversely correlated with coronary sinus NE concentration, which implies that the increased circulating catecholamines may drive the change in $\beta$-receptor density. These changes reduce adrenergic sensitivity in the failing heart and may be responsible for decreased exercise tolerance in heart failure.

The changes noted above differ in magnitude based on the cause of the heart failure. Patients with ischemic dilated cardiomyopathy (ISDC) have less dramatic changes in $\beta$-receptor effector mechanisms than those with idiopathic dilated cardiomyopathy (IDC). Bristow et al showed that left ventricular $\beta_1$-receptor down-regulation is significantly less in ISDC than in IDC (30% vs 43%; $P < .05$).
Also, uncoupling of β-receptors from functional responses (positive inotropy and adenylate cyclase stimulation) is greater in ISCDC than in IDC. These differences may be responsible for the variable effects of β-blockade in ISCDC vs IDC.

A study in which bucindolol hydrochloride was used for heart failure compared responses to treatment in ISCDC and IDC groups.46 The IDC bucindolol-treated group showed significantly superior responses for increased left ventricular ejection fraction (8.7% ± 2.3% vs 2.3% ± 1.1%) and cardiac index (0.3 ± 0.1 vs −0.1 ± 0.2 L/min per meters squared) and decreased pulmonary artery pressure (−6.4 ± 2.4 vs −0.1 ± 2.0 mm Hg), pulmonary capillary wedge pressure (−7.2 ± 2.0 vs −1.2 ± 1.8 mm Hg), plasma NE level (−1478 ± 337 vs −136 ± 437 nmol/L [−250 ± 57 vs −23 ± 74 pg/mL]), and New York Heart Association functional class (−0.9 ± 0.1 vs −0.1 ± 0.1) compared with the ISCDC group (P<.05 for all).

**Myocardial Remodeling**

Norepinephrine, like angiotensin II, is a trophic factor in an anatomical adaptation to cardiac dysfunction known as myocardial remodeling.49 Remodeling involves myocardial hypertrophy, disruption of supporting structures by collagenase, cell slippage, synthesis of new collagen, and ultimately cardiac dilation.49 The trophic influences of NE and angiotensin II activate transcriptional regulation sequence-specific DNA-binding proteins known as transcription factor proteins. These proteins interact with DNA and ultimately lead to synthesis of new contractile proteins, resulting in myocardial hypertrophy. Initially this is adaptive, helping to maintain stroke volume with decreased contractility and increased preload and afterload, but continued remodeling results in excessive hypertrophy, fibrosis, and ultimately clinical CHF.

**Cardiotoxic Changes**

Chronic increase of NE level also exerts direct toxic effects on the myocardium.50 Norepinephrine causes a concentration- and time-dependent decrease in cell viability because of hypercontracture of cardiocytes. The hypercontracture is associated with increased levels of creatine kinase, implying irreversible damage. As myocytes are lost, the heart’s contractile ability declines, leading to progressive heart failure. These changes are caused by intracellular calcium overload and are attenuated in vitro with β-blockade. For the remaining viable cells, cardiocyte dysfunction develops, as evidenced by decreased protein synthesis.

**Arrhythmias**

Cardiovascular causes of death in heart failure are usually classified as heart failure progression or sudden cardiac death.5 Sudden cardiac death is usually from arrhythmias, and studies suggest a relationship between ventricular arrhythmias and activation of the sympathetic nervous system.51 A study of patients surviving a spontaneous sustained episode of ventricular tachycardia or fibrillation compared with 3 age-matched reference groups.52 These findings in combination with the favorable effect of β-blockers on ventricular arrhythmias substantiate the role of the sympathetic nervous system in the genesis of malignant arrhythmias.52

**Immunologic Alterations**

There are also sympathetically induced changes in immunologic function that may contribute to progression of myocardial dysfunction in patients with heart failure.53 Increased sympathetic activity is associated with decreased function of T-suppressor/cytotoxic and natural killer cells. In addition, mitogen responsiveness is decreased, interleukin 2 function is decreased, and the incidence of heterophile antibodies against the heart is increased. A study comparing immunologic function before and after treatment with metoprolol tartrate in patients with heart failure showed increases in natural killer cells and T-suppressor/cytotoxic cells (P=.001). There was also a trend toward increased mitogen proliferation and interleukin 2 receptor number.

**β-BLOCKER THERAPY IN CHF**

Interrupting the activated neurohormonal systems is a promising approach to altering the natural course of heart failure. The CONSENSUS and SOLVD trials show decreased mortality and morbidity from interrupting the RAS with angiotensin-converting enzyme inhibitors.21,22 Interrupting the sympathetic nervous system with β-blockade also shows promise for treating heart failure, probably by counteracting the harmful effects noted above. Three generations of β-blockers are currently available for clinical use. First-generation β-blockers, such as propranolol hydrochloride, are nonselective agents blocking both β1- and β2-receptors. First-generation β-blockers are not used to treat heart failure because they are poorly tolerated in this population of patients.54 Second-generation β-blockers, such as metoprolol and bisoprolol fumarate, selectively block β1-receptor subtypes preferentially. Metoprolol and bisoprolol are relatively well tolerated in patients with heart failure.55 Third-generation β-blockers, including carvedilol and bucindolol, are nonselective β-blockers with additional properties. Carvedilol is a nonselective β-blocker with vasodilating properties through α1-blockade and antioxidant properties. Carvedilol also inhibits vascular smooth muscle cell proliferation.56 Bucindolol is a nonselective β-blocker with direct vasodilating actions that are independent of α-adrenergic receptors.56 The vasodilating actions of third-generation β-blockers may make them more tolerable when β-blocker therapy is initiated in heart failure.

Different results have been obtained with various β-blockers in heart failure trials. A trial comparing hemodynamic, left ventricular function, and antiadrenergic effects of treatment with metoprolol vs carvedilol showed significant differences.57 Mean levels of coronary sinus NE were significantly
reduced in the carvedilol group at the end of the study compared with baseline (3014 ± 2027 vs 3930 ± 2074 nmol/mg; P = .001), but the metoprolol group had no significant change. Metoprolol was associated with a significant increase in total β-receptor density compared with baseline (75.0 ± 40.5 vs 47.8 ± 21.4 mol/mg; P = .005), but carvedilol did not. Carvedilol significantly increased left ventricular ejection fraction compared with placebo (32.5 ± 11.6 vs 20.1 ± 10.4 ejection fraction units; P = .05), but metoprolol did not. Although this trial was relatively small (total of 60 patients), it points out the potential for varied results with β-blockers of different generations.

A small study by Waagstein et al in 1975 showed clinical and left ventricular improvement in 7 patients with heart failure after treatment with β-blockade, and clinical deterioration followed β-blocker withdrawal. Other small, noncontrolled studies followed, and they showed positive benefits of β-blocker treatment in heart failure. Heilbrunn et al in 1976 showed increased cardiac index, ejection fraction, and α-adrenergic receptor density in 10 patients with dilated cardiomyopathy treated with metoprolol. Fowler et al in 1980 showed improved peak exercise left ventricular ejection fraction in 9 of 10 patients with severe heart failure referred for cardiac transplantation, and 4 of the 10 patients no longer needed heart transplantation after 2 months of treatment.

These and other studies led to the design and implementation of large multicenter, randomized, double-blind, placebo-controlled trials.

TRIALS OF β-BLOCKERS

At least 18 randomized clinical trials with a duration of at least 3 months have compared β-blockers with placebo in heart failure. The 4 largest trials (Table 3) are summarized below. A more complete meta-analysis is beyond the scope of this article and has been published previously.61 The Metoprolol in Dilated Cardiomyopathy (MDC) trial used the second-generation β1-selective β-blocker metoprolol, and it had a combined primary end point of death or need for cardiac transplantation. The Cardiac Insufficiency Bisoprolol Study (CIBIS) used a second-generation β1-selective β-blocker, bisoprolol. It is the only large published trial in which mortality was a primary end point. The Australia/New Zealand (ANZ) and US Carvedilol studies used the third-generation nonselective β-blocker carvedilol, and death was a secondary end point in both studies. The results of these studies are summarized in Table 4.

### Table 3. Multicenter Trials of β-Adrenergic Blockers in Heart Failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Cause</th>
<th>β-Blocker</th>
<th>β-Blocker Activity</th>
<th>End Point</th>
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<tbody>
<tr>
<td>MDC</td>
<td>383</td>
<td>IDCM</td>
<td>Metoprolol tartrate</td>
<td>β1-Selective blockade</td>
<td>Death or need for transplantation</td>
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<tr>
<td>CIBIS</td>
<td>641</td>
<td>Mixed†</td>
<td>Bisoprolol fumarate</td>
<td>β1-Selective blockade</td>
<td>Cardiac function, exercise capacity, quality of life, hospitalizations</td>
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<td>ANZ</td>
<td>415</td>
<td>Ischemic</td>
<td>Carvedilol</td>
<td>β1-, β2-, α1-Blockade</td>
<td>Total mortality, β-Blocker tolerability</td>
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<td>US Carvedilol</td>
<td>1094</td>
<td>Ischemic or IDCM</td>
<td>Carvedilol</td>
<td>β1-, β2-, α1-Blockade</td>
<td>Safety, LV dimensions, submaximal exercise, symptoms, death or hospitalization</td>
</tr>
</tbody>
</table>

*MDC indicates Metoprolol in Dilated Cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; CIBIS, Cardiac Insufficiency Bisoprolol Study; ANZ, Australia/New Zealand Heart Failure Research Collaborative Group; LVEF, left ventricular ejection fraction; and LV, left ventricle.

†Mixed included ischemic, IDCM, hypertensive, and valvular disease.

### Table 4. Results of Multicenter Trials of β-Adrenergic Blockers

<table>
<thead>
<tr>
<th>Trial</th>
<th>LVEF</th>
<th>Exercise Capacity</th>
<th>Quality of Life</th>
<th>NYHA Class</th>
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*LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; ↑, increase; ↓, decrease; →, no change; MDC, Metoprolol in Dilated Cardiomyopathy; CIBIS, Cardiac Insufficiency Bisoprolol Study; NA, not available; and ANZ, Australia/New Zealand Heart Failure Research Collaborative Group.

†Combined death or need for transplantation was decreased in MDC. Combined death or hospitalization was decreased in ANZ. Death alone was not decreased in MDC or ANZ.

Hemodynamics

Two of the 4 studies showed hemodynamic improvement with increased left ventricular ejection fraction in the treatment groups when compared with placebo. Mean left ventricular ejection fraction increased from 28% to 34% (P < .001) in the MDC study and from 28.4% to 33.5% (P value not published) in the ANZ study. In the MDC study,3 mean pulmonary capillary wedge pressure was significantly lower in the treatment group than in the placebo group at 6 months (10.6 ± 7.5 vs 14.4 ± 10.3 mm Hg; P = .01) and at 12 months (10.7 ± 6.7 vs 13.1 ± 8.8 mm Hg; P = .06). The ANZ study7 found a significant reduction in end-systolic (3.2 mm; 2P = .001) and end-diastolic (1.7 mm; 2P = .06) myocardial dimensions in the treatment group.
Exercise Tolerance

Only the MDC study\(^7\) showed a significant increase in exercise duration at 12 months in the treatment group (β-blocker) compared with placebo (76 seconds vs 15 seconds; \(P=.05\)). The CIBIS and US Carvedilol studies did not report exercise data. Exercise capacity was measured with the modified Naughton treadmill protocol in the ANZ\(^7\) and North American MDC\(^5\) study centers, and a bicycle exercise protocol was used in the European MDC study centers.\(^3\) The MDC Naughton and bicycle exercise protocol data were pooled, and this combining may have contributed to the discrepancy between these data and the maximal exercise data from the ANZ group, which also used the Naughton protocol. However, metoprolol up-regulates \(\beta_1\)-receptors in the myocardium, whereas carvedilol does not.\(^7\) The up-regulation of \(\beta_1\)-receptors may facilitate increased contractility through sympathetic stimulation during exercise, thus improving maximal exercise tolerance.\(^3\)

Quality of Life

Patient evaluation of quality of life was assessed with various instruments, primarily inquiring about symptoms. The studies compared results between the treatment and placebo groups. The MDC study\(^3\) showed a significantly improved assessment of quality of life based on a graded 26-item questionnaire in the treatment group (\(P=.01\)). The ANZ study\(^7\) showed no significant difference in the treatment vs placebo groups for improved or worsening symptoms based on a health self-assessment.\(^5\)

Functional Class

The MDC\(^2\) and CIBIS\(^6\) trials showed improvement in New York Heart Association functional class in the treatment groups compared with placebo. A higher percentage of patients had improvement in functional class in the metoprolol group than in the placebo group in the MDC trial (graphical data; \(P=.01\)). The CIBIS trial showed a significant increase in the number of patients improving at least 1 functional class in the treatment group compared with placebo (68 vs 48; \(P<.03\)). The ANZ study showed no significant difference in the number of patients with improved or worsening functional class in the carvedilol group vs placebo at 12 months (2\(P>.10\)).\(^7\)

Morbidity

Morbidity was assessed in the MDC,\(^5\) ANZ,\(^7\) and US Carvedilol\(^8\) studies by evaluating hospital admissions. The MDC study showed a significant decrease in the mean number of readmissions per patient for heart failure or arrhythmias in the metoprolol group vs placebo (47 vs 67; \(P<.04\)). The ANZ study found a borderline significant 23% decrease in risk of all hospital admissions in the carvedilol group vs placebo (99 vs 120; 2\(P=.05\)). The US Carvedilol study reported a significant 27% decrease in risk for hospitalization for cardiovascular causes, with fewer patients with at least 1 hospitalization in the carvedilol group than in the placebo group (95% confidence interval, 3%-45%; \(P=.04\)). In the CIBIS trial, the bisoprolol group significantly fewer episodes of heart failure decompensation leading to hospitalization than the placebo group (61 vs 90; \(P<.01\)).\(^6\) The bisoprolol group also had significantly fewer episodes of nonlethal critical events than the placebo group (107 vs 154; \(P<.001\)).

Mortality

Mortality data were collected in all 4 trials, but only the CIBIS trial\(^6\) had total mortality as its primary end point. The MDC trial\(^7\) used the primary end points of death or need for cardiac transplantation. The ANZ\(^7\) and US Carvedilol\(^8\) trials used nonfatal events as primary end points, and death or death combined with hospital admission was a secondary end point. The MDC study showed a significant 34% decrease in the combined risk of death or need for transplantation (95% confidence interval, 6%-62%; \(P=.06\)), but there was no significant difference in the number of deaths in the metoprolol group vs placebo (19 vs 23; \(P=.69\)). The ANZ group showed a significant 26% decrease in the risk of reaching the combined end point of death or hospital admission (relative risk, 74%; 95% confidence interval, 57%-95%; 2\(P=.02\)), but there was no significant difference in the risk of death alone in the carvedilol group vs placebo (2\(P>.1\)). The US Carvedilol study showed a significant 65% reduction in the risk of death in the carvedilol group vs placebo (95% confidence interval, 39%-80%; \(P<.001\)), a finding that led to early termination of the study at 6 months. Significant reductions in mortality were not convincingly shown in these studies because of the combined end points in the MDC and ANZ trials, lack of mortality reduction in the CIBIS trial, and several elements of the US Carvedilol study design.

Several features of the US Carvedilol study design, previously discussed,\(^62\) are noteworthy when the mortality data are considered. The study was a combination of 4 separate studies of the efficacy and safety of carvedilol in patients with heart failure; mortality data were summarized from the 4 studies. The duration of the trial was less than 7 months, and there were only 53 deaths. The trial also used a run-in period to evaluate whether patients would tolerate the drug. Seven patients who died during the run-in period were not counted in the mortality data for the carvedilol group, and they would have composed 24% of the patients in the carvedilol group who died. Seventeen other patients were not randomized because they experienced worsening heart failure during the run-in period. These findings leave the true magnitude and duration of the effect of carvedilol on mortality unclear.

The Beta-Blocker Evaluation Survival Trial\(^63\) is a large multicenter, double-blind, placebo-controlled trial currently under way. Its primary objective is to determine whether β-blockade in heart failure reduces mortality. The Beta-Blocker Evaluation Survival Trial has
a goal of enrolling 2800 patients with ISDC or IDC heart failure who are in New York Heart Association functional class III or IV. The treatment group will receive the third-generation nonselective β-blocker bucindolol. The results of the Beta-Blocker Evaluation Survival Trial should definitely determine whether β-blocker therapy reduces mortality in heart failure.

Carvedilol is the only β-blocker currently approved for use in heart failure. It is indicated in patients with mild to moderate heart failure (New York Heart Association class II or III).64 In the carvedilol studies referenced here, patients with heart failure receiving a cardiac glycoside, diuretic, or an angiotensin-converting enzyme inhibitor were stable with respect to dosages of those medications before carvedilol therapy was initiated. Carvedilol treatment was started with a low dose, and the patients were closely monitored. The dose was slowly titrated up to the maximal tolerated dose. This may be beneficial because dose-related improvements have been shown.

A 6-month study with carvedilol showed dose-related improvements in left ventricular ejection fraction and dose-related reductions in mortality.65 Left ventricular ejection fraction improved by 5, 6, and 8 percentage points with 6.25 mg, 12.5 mg, and 25 mg, respectively, compared with 2 percentage points with placebo (P<.01 for all 3 groups). Crude mortality rates were 6.0%, 6.7%, and 1.1% with the previously stated doses, compared with 15.5% in the placebo group (P<.05, P=.07, and P<.001, respectively).

CONCLUSIONS

There are now several lines of evidence that the sympathetic nervous system has a major role in the pathophysiology of heart failure. The interaction of the sympathetic nervous system with multiple hormonal systems, its hemodynamic and arrhythmogenic effects, and the direct toxic effects of catecholamines on the myocardium make it a prime therapeutic target. Although clinical response varies with different β-blockers, there is clear evidence of benefit from β-blocker treatment in heart failure. Both second- and third-generation β-blockers show improved New York Heart Association functional class and decreased hospitalizations. Decreased mortality is also suggested in the US Carvedilol study,66 but the definitive answer to whether β-blockers improve survival is eagerly awaited.

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