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The Role of Third-Generation Beta-Blocking Agents in Chronic Heart Failure

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Summary: Third-generation beta-blocking agents developed for the hypertension market are proving useful in the treatment of chronic heart failure (HF). These compounds share the ancillary property of vasodilation, which improves acute tolerability by unloading the failing left ventricle at a time when beta-adrenergic withdrawal produces myocardial depression. In the case of carvedilol and bucindolol, this allows for the administration of nonselective beta blockade. Because of blockade of both β_1 and β_2 adrenergic receptors as well as other properties, these compounds possess a more comprehensive antiadrenergic profile than second-generation, β_1-selective compounds. For this and potentially other reasons, third-generation beta-blocking agents have theoretical efficacy advantages that have yet to be demonstrated in large-scale trials. Ongoing trials with either second- or third-generation compounds and one trial directly comparing a compound from each class will provide the answer as to whether third-generation compounds have an advantage in the treatment of chronic HF.

Key words: adrenergic nervous system, heart failure, beta-blocking agents, third-generation beta-blocking agents

Introduction

Recent research in chronic heart failure (HF) has resulted in a paradigm shift in the concept of how best to treat this syndrome. For many years, heart failure was viewed as an illness of hemodynamic inadequacy resulting in reflex vasoconstriction, thereby producing increased afterload, resulting in further deterioration in hemodynamics. Based on this notion, the most effective treatment of heart failure was thought to be amelioration of excessive load with vasodilators or improvement in contractility with positive inotropic agents, thereby normalizing hemodynamics. However, when evaluated in long-term clinical trials, these strategies generally failed, in part because progressive hemodynamic deterioration is not so much a result of excessive load per se as it is the consequence of abnormal phenotypic changes in the failing heart which may be made worse by these treatment strategies.

It has been recently postulated that chronic HF is a progressive illness of declining ventricular function due to (1) progressive myocyte dysfunction (caused by changes in gene expression), (2) cell loss (due to cell necrosis and apoptosis), and cell and chamber remodeling occurring in response to (1) and (2).[1] This series of events appears to be mediated at least in part by compensatory neurohormonal and autocrine/paracrine activation of a variety of growth promoting pathways. The remodeling process results in ventricular dilatation, elevated wall stress, relative myocardial ischemia, energy depletion, progressive interstitial fibrosis, and further activation of the adrenergic and renin-angiotensin systems.[1] Continued activation of these and other neurohormonal or autocrine/paracrine systems results in a vicious cycle which perpetuates further remodeling and neurohormonal activation.

With the exception of one early trial,[2] pure vasodilators have failed to have a positive impact on the natural history of heart failure. One potential explanation for this is that these agents have no effect on or reflexively activate neurohormones. The positive inotropic agents that have been evaluated in chronic HF work primarily by increasing intracellular cyclic adenosine monophosphate (cAMP), either as beta agonists or phosphodiesterase inhibitors. At least with the relatively high doses of positive inotropic agents that have been used in clinical trials conducted to date,[3–5] chronic elevations in cAMP may be toxic to cardiac myocytes and thus may accentuate the cycle of progressive ventricular dysfunction and neurohormonal activation. In addition, agents that raise cAMP increase intracellular Ca^{2+} and may lower the threshold for arrhythmias.[6]

Newer strategies for the treatment of chronic HF have focused on favorably changing the biology of the myocardium rather than directly improving hemodynamics. This newer

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strategy forgoes short-term hemodynamic improvement and may even transiently worsen hemodynamics. However, by slowly withdrawing adrenergic support to the failing heart, antiadrenergic agents can be administered with good or even excellent tolerability.[7] Use of beta-receptor blocking agents in combination with angiotensin-converting enzyme (ACE) inhibitors has resulted in inhibition of at least two deleterious neurohormonal pathways: the adrenergic and renin-angiotensin systems. Over a period of 3 to 6 months, this strategy results in improvement in ventricular systolic function, reduction in ventricular size, and improvement in myocardial energetics.[1] By 12 to 18 months, there is also a reversal of pathologic left ventricular (LV) remodeling, including a reduction in LV mass and reversion of ventricular shape from a globular toward a more elliptical or normal conformation.[1]

Improvement in myocardial function and reverse remodeling appear to be class effects of beta-blocking agents.[1] However, beta blockers are not equally capable of inhibiting adrenergic drive,[7] and therefore they may produce quantitative differences in myocardial function or even reverse remodeling. As a result, their salutary effects on the natural history of heart failure could be different, and this hypothesis is currently being directly tested in a survival study comparing the third-generation beta blocker carvedilol with the second-generation compound metoprolol (the COMET trial). What is clearly different about beta-blocking agents is their tolerability. First-generation agents are poorly tolerated, whereas second- and third-generation compounds are tolerated well enough—for different reasons—to be useful in treating chronic HF. This paper reviews the pharmacology and clinical experience with bucindolol, a third-generation beta-blocking agent currently undergoing Phase III testing for use in chronic HF.

Classification of Beta-Blocking Agents

As shown in Table I, there are currently three generations of beta-blocking agents. First-generation agents are defined as compounds that are nonselective for β_1 versus β_2 receptors, with no important ancillary properties; examples are propranolol and timolol. First-generation compounds are still widely used in the treatment of cardiovascular disease: primarily hypertension and coronary artery disease. First-generation compounds are considered to be contraindicated in the treatment of heart failure because of their myocardial depressant and afterload-enhancing effects.[8] Second-generation agents such as metoprolol, atenolol, and bisoprolol, are defined as β_1-receptor selective blockers with no ancillary properties. These compounds are also widely used in the treatment of cardiovascular disease, and they were developed as "cardioselective" agents to exploit the false premise[9] that beta receptors in the heart are confined to the β_1 subtype. The second-generation compounds can be tolerated by subjects with heart failure,[8] and two of these (metoprolol and bisoprolol) have had extensive evaluation in the treatment of chronic HF.

Third-generation beta-blocking agents are defined as nonselective or selective beta-receptor antagonists which have important ancillary properties such as vasodilation. The vasodilator beta blockers were initially developed for the hypertension market, and several have undergone or are undergoing extensive evaluation in the treatment of chronic HF. Thus, the first three generations of beta-blocking agents were developed for cardiovascular conditions other than heart failure, and there has not yet been a systematic development program to produce a compound for this indication. As more information emerges on the ideal pharmacologic profile for a beta-blocking agent used to treat heart failure, it is hoped that such "fourth-generation" compounds will be developed.

TABLE I Classification of beta-adrenergic blocking agents

Type	Definition
First generation	Nonselective for β_1, β_2 blockade; no ancillary properties (e.g., propranolol, timolol)
Second generation	Selective for β_1 or β_2 blockade, no ancillary properties (metoprolol, atenolol, bisoprolol)
Third generation	Selective or nonselective, has potentially important ancillary property (carvedilol, bucindolol, nebivolol)
Fourth generation	Nonselective; several "designer" efficacy-enhancing or adverse event-lowering ancillary properties

Pharmacology of Third-Generation Beta-Blocking Agents

The structures of representative first-, second-, and third-generation beta-blocking agents are shown in Figure 1, and their binding affinities for β_1-, β_2-, and α_1-adrenergic receptors are shown in Table II. At the final target doses used clinically, the third-generation compounds bucindolol, labetalol, and carvedilol are all nonselective agents, whereas nebivolol[10] and celiprolol are β_1-selective. Carvedilol is seven-to-eight-fold selective for β_1 versus β_2 receptors,[11] and as a result at low doses ($\leq$6.25 mg twice a day) carvedilol is mildly β_1 selective. Carvedilol and labetalol[12] are α_1-receptor antagonists and are vasodilators based on this property. Bucindolol has mild vasodilatory properties[13] that are mediated through an as yet undetermined mechanism, with the possibilities including weak α_1-receptor blockade,[13,14] a cyclic guanosine monophosphate (cGMP)-dependent mechanism, and β_3-receptor agonism.[15] The vasodilator properties of nebivolol are related to nitric oxide production,[16] and celiprolol is a vasodilator by virtue of β_2-receptor-mediated intrinsic sympathomimetic activity (ISA).[17–19] The addition of vasodilation to the pharmacologic profile of a beta blocker improves drug tolerability during initiation of therapy and uptitration by afterload reduction-related attenuation of the drop in cardiac output, which is associated with removal of beta-adrenergic support of heart rate and contractility.[8] It is unclear whether the vasodilator properties of third-generation beta-blockers contribute to

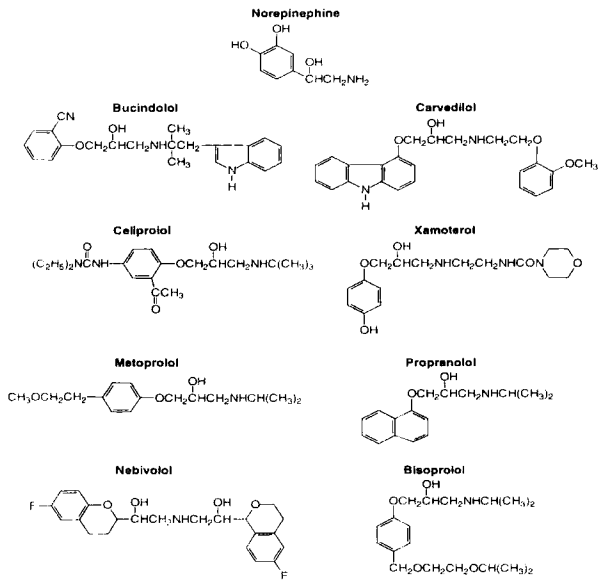


FIG. 1 Structures of norepinephrine and various beta-adrenergic blocking agents.

TABLE II Relative (to β_1-receptors) affinities of various beta-blocking agents for β_1-, β_2- and α_1-adrenergic receptors

Compound	β_1/β_2 selectivity, human[a] or model systems	β_1/α_1 selectivity, human[a] or model systems	Mechanism of vasodilation
Propranolol	2.1[a]	—	—
Metoprolol	79[a]	—	—
Bisoprolol	103[a]	—	—
Carvedilol	7.3[a]	2.4	α_1-blockade
Bucindolol	1.4[a]	73	?
Nebivolol	293	—	NO potentiation
Labetalol	1.5	1.0	α_1-blockade
Celiprolol	72	—	β_2 ISA
Xamoterol	69[a]	—	—

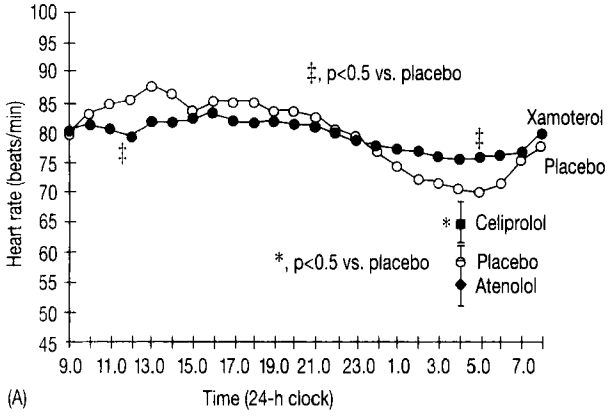
Abbreviations: NO = nitric oxide, ISA = intrinsic sympathomimetic activity.

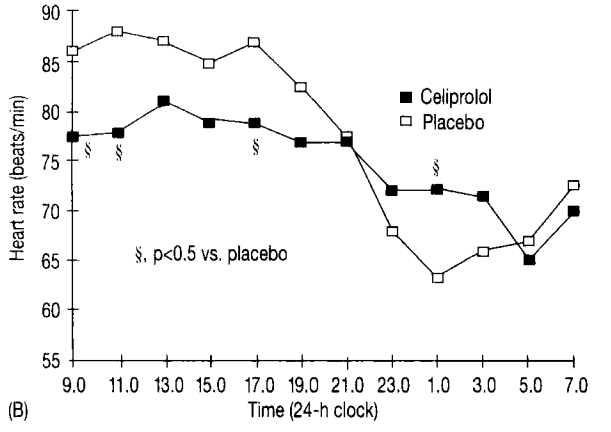
long-term efficacy, as compared with placebo[20] or second-generation compounds,[21] a reduction in systematic vascular resistance (SVR) may not be observed after chronic treatment.

Several third-generation compounds have additional ancillary properties which may be clinically important. Carvedilol and one of its metabolites have significant antioxidant properties,[22] although in human subjects it is not clear whether blood levels are sufficient to manifest any effects. If these antioxidant properties are in fact active in subjects with heart failure, they would be expected to produce an antiproliferative/growth-inhibiting effect. The nitric oxide-potentiating activity of nebivolol might also produce an antiproliferative effect. Carvedilol and bucindolol have unique "atypical" pharmacologic properties which include guanosine triphosphate (GTP)-dependent binding,[11, 14, 23] downregulation of beta-adrenergic receptors in cultured cells,[11] and prevention of receptor upregulation in the failing human heart.[21] The latter property gives both compounds an additional antiadrenergic action, but it may also contribute to the inability of either to improve maximal exercise responses.[20, 21, 24]

An important issue regarding beta-blocking agents is whether they contain ISA. In all model systems[17, 18] and in the human heart,[19] celiprolol and by definition the high-affinity partial agonist (which is only semantically different from an ISA-containing beta blocker) xamoterol possess this property. In some model systems,[25, 26] bucindolol has ISA, but not in the human heart.[14, 23] This is presumably due to differences in receptor-G protein coupling between human myocardium and animal models as the degree of agonist activity for the partial agonists xamoterol[27] and dobutamine[28] is much less in the human heart than in most animal systems. The issue of whether a beta blocker possesses ISA is important in view of the increase in mortality observed with xamoterol,[29] which, as can be observed in the reduction of daytime heart rate in Figure 2A, also functions as a beta-blocking agent. The agonist properties of xamoterol can be observed in Figure 2A as an increase in nighttime heart rate. This is because sympathetic drive is low during sleep, allowing partial agonist effects to be observed. As shown in Figure 2A and B, celiprolol has a similar effect on nighttime Holter-monitored heart rates,[30, 31] which is the most sensitive method of detecting ISA in the human heart. However, atenolol reduces nighttime heart rate (Fig. 2A).[30] In contrast to the effects of xamoterol or celiprolol in subjects with heart failure, as shown in Figure 2C, bucindolol does not increase nighttime heart rate, but, rather decreases it slightly. This is because bucindolol, unlike xamoterol and celiprolol, does not have ISA in the human heart.

According to recent modifications of receptor theory, most beta-blocking agents have "inverse agonist" activity: defined as the ability to inactivate active-state receptors.[32, 33] Active-state receptors, which can signal the effector enzyme(s) in adrenergic signal transduction pathways in the absence of agonist occupancy, exist in the myocardium as a minority (10–30%) of the total beta-receptor pathway. The interesting clinical aspect of this is that antagonists have different abilities to inactivate active-state receptors or different degrees of inverse agonist activity. Two third-generation compounds, labetalol[32] and bucindolol,[11, 34] have very low levels of inverse agonist activity for the human β_2 receptor compared with metoprolol,[11, 34] propranolol,[11, 34] timolol,[32] and carvedilol.[11, 34] As can be observed in Figure 2B, their relative inverse agonist properties of bucindolol and carvedilol are directly correlated with their effects on nighttime or lowest 24-h monitored heart rate.[34] This is likely the reason why symptomatic bradycardia is so infrequent with bucindolol[24] compared with carvedilol.[35, 36] In addition, in view of data in transgenic mice,[37] it is likely that inactivation of active state receptors produces a negative inotropic effect, and a low inverse agonist profile would translate into improved tolerability by subjects with heart failure because of less myocardial depression.





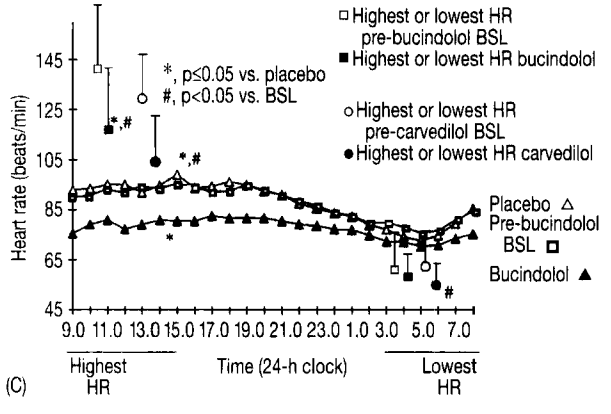


FIG. 2 (A) Average 24-h heart rates for subjects with heart failure treated with xamoterol or placebo in the Xamoterol in Severe Heart Failure Study. Reproduced from Ref. No. 29 with permission. Data for celiprolol and atenolol are for mean ± standard deviation (SD) lowest heart rates achieved over 24 h. Data reproduced from Ref. No. 30 with permission. (B) Average 24-h heart rates for subjects with hypertension treated with celiprolol or placebo. Reproduced from Ref. No. 31 with permission.(C) Average 24-h heart rates for subjects with heart failure treated with bucindolol or placebo in the Bucindolol Multicenter Trial.[24] Data for carvedilol or metoprolol and their respective placebo controls are for mean ± SD lowest and highest heart rates achieved on 24-h Holter monitoring in heart failure populations.[21] HR = heart rate, BSL = baseline.

Effect of Third-Generation Beta Blockers on Myocardial Function

With beta-blocking agents, it is important to distinguish between acute pharmacologic effects and long-term, time-dependent biologic effects of treatment.[1] The acute effects are generally adverse, and the idea is to minimize them through ancillary pharmacologic properties of the beta blocker or by administering other supportive medication. The time-dependent, long-term biologic effects of antiadrenergic therapy are the ones that produce the desired favorable effects on myocardial phenotype and the natural history of heart failure, and therefore in chronic HF the therapeutic strategy with beta-blocking agents is to minimize the consequences of the acute pharmacologic effects and to maximize the long-term responses.

Acute Effects

As might be expected from their pharmacologic profiles in the setting of heart failure, first-, second- and third-generation compounds differ in their acute hemodynamic effects (Fig. 3). Because the failing heart is dependent on beta-adrenergic support of heart rate and contractility to maintain cardiac performance, the acute pharmacologic effects of any antiadrenergic compound include myocardial depression. As shown in Figure 3, the first-generation compound propranolol produces a decrease in intrinsic systolic function (end-systolic elastance or Ees, a load-independent measure of systolic function), a reduction in cardiac index, and a trend toward an increase in SVR, with no effect on pulmonary wedge pressure.[38] Because of these profound myocardial depression and vasoconstrictor

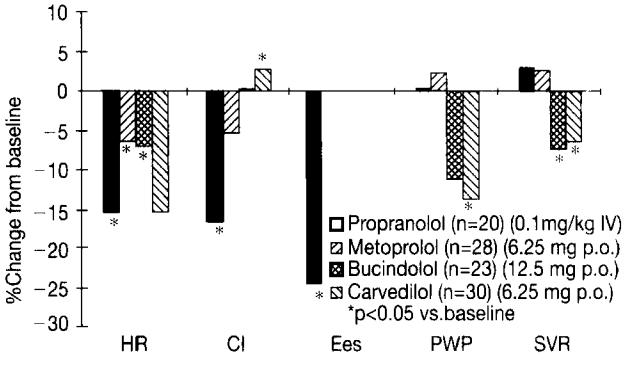


FIG. 3 Comparative acute hemodynamic effects of first-, second-, and third-generation beta blockers. HR= heart rate, CI = cardiac index; Ees = end-systolic elastance, a measure of load-independent systolic function (no data generated for orally administered beta blockers); PWP = mean pulmonary artery wedge pressure; SVR = systemic vascular resistance. Data for intravenous beta blockers are from Ref. No. 38 and from M. Feldman personal communication (SVR data). Data for p. o. metoprolol and carvedilol are from Gilbert EM and Bristow MR, unpublished data, and the bucindolol data are from Ref. No. 44. The response to p.o. beta blockers was taken from either the peak effect at 2 or 4 h (metoprolol and carvedilol) or 4 h after administration (bucindolol[44]). Figure is reproduced from Ref. No. 8 with permission.

TABLE III Properties of beta-blocking agents that contribute to good tolerability

Property	Compounds exhibiting minor profile	Compounds exhibiting major profile
Low inverse agonism	Carvedilol, propranolol	Bucindolol, labetalol
Vasodilation	Bucindolol, nebivolol	Carvedilol, labetalol
β_1 selectivity	Carvedilol	Metoprolol, bisoprolol, nebivolol

TABLE IV Tolerability rates of beta-blocking agents in chronic heart failure and pharmacologic properties contributing to tolerability

Compound	Tolerability rate[a]	Factors improving tolerability
Bucindolol	96–98%[24,44,66]	Low inverse agonism, mild vasodilation
Carvedilol	88–95%[20,35,57,60–62,72,73]	Slight β_1 selectivity at low doses, moderate vasodilation,
Nebivolol	94%[74]	Highly β_1 selective, mild vasodilation
Labetalol	?	Low inverse agonism, moderate vasodilation
Metoprolol	79–96%[36,75,76]	β_1 selective
Bisoprolol	?	β_1 selective
Propranolol	79%[39]	None

[a] Ability to tolerate initial open label challenge or 6 weeks of therapy.

effects, propranolol[39] and likely other first-generation compounds cannot be given to the majority of subjects with chronic HF. As shown in Figure 3, the second-generation compound metoprolol produces less reduction in cardiac index and less vasoconstriction because it does not antagonize β_2-receptor-mediated vasodilation, and cardiac β_2 receptors are not blocked. In contrast to propranolol and metoprolol, the third-generation compounds bucindolol and carvedilol do not on the average lower cardiac index acutely because myocardial depression is offset by vasodilation and a reduction in SVR (Fig. 3). Thus, despite the fact that at target doses both carvedilol and bucindolol are nonselective agents, they are relatively well tolerated in the setting of chronic HF because of their vasodilator properties. Note in Figure 3 the more powerful vasodilator effects of carvedilol, which can cause symptomatic hypotension in subjects with low filling pressures and/or borderline low baseline blood pressure.

Thus, the acute hemodynamic properties of beta blockers differ depending on the generation/class, and these differences impact tolerability on initial administration and during uptitration. Other properties that may affect tolerability are the degree of inverse agonism and β_1-selectivity. Table III summarizes how selected beta blockers rank in these categories, and Table IV summarizes the actual tolerability of first-, second-, and third-generation compounds in clinical trials.

Effects of Long-Term Treatment

Reversal of intrinsic myocardial dysfunction: Despite the negative inotropic-myocardial depressant effects of beta blockers when administered acutely to subjects with heart failure, the long-term (≥3 months) effects of treatment are quite different. As shown in Figure 4, long-term treatment with bucindolol produces a positive inotropic effect as deduced from another load-independent measurement of systolic function, the relation of dP/dT to end-diastolic volume.[40] Similar long-term improvement in intrinsic systolic function has been observed for nebivolol[41] and metoprolol,[42] and it is this property that leads to the increase in ejection fraction that is the signature effect of beta-blocking agents in primary and secondary dilated cardiomyopathies. An improvement in LV function by beta-blocking agents in chronic HF was first observed over 20 years ago,[43] but it was not until 1990 that this type of therapy was shown to be superior to placebo in improving LV ejection fraction (LVEF) and other indices of LV performance.[44] Since that time, more than 2,000 patients with chronic HF from systolic dysfunction have been treated with beta-blocking agents in placebo-controlled trials in which LV function was measured. Without exception, in every study carried out for > 1 month, LVEF increased with beta-blocker therapy compared with its effects in the placebo group.[1] Moreover, both right and LV function improve on beta-blocker therapy.[45] Finally, the favorable effects of beta blockade on LVEF continue and are progressive for up to at least 18 months,[46,47] and they may be lost on beta-blocker withdrawal.[48]

In view of the more comprehensive antiadrenergic effects produced by several third-generation beta-blocking agents, it is reasonable to hypothesize that the effects on improving LV function would be greater for these compounds than for second-generation agents. There is some support for this idea in the form of comparative data from concurrently conducted trials with multiple beta-blocking agents.[21,49,50] As shown in Figures 5 and 6, comparative LV functional measurements

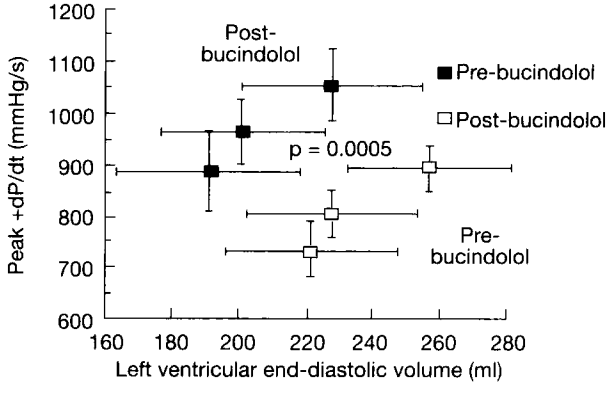


FIG. 4 Bucindolol dP/dT versus vol (EE). Reproduced from Ref. No. 40 with permission.

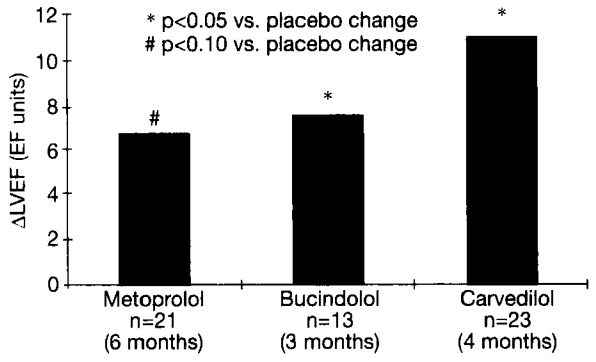


FIG. 5 Changes in left ventricular ejection fraction (LVEF): Comparison of metoprolol, bucindolol, and carvedilol (drug minus placebo effect). Reproduced from Ref. No. 50 with permission.

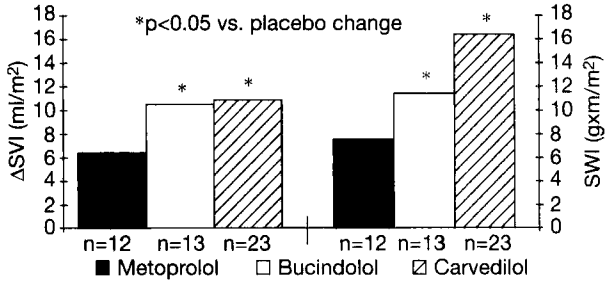


FIG. 6 Changes in stroke volume index (SVI) and stroke work index (SWI): Comparison of metoprolol, bucindolol, and carvedilol (drug minus placebo effect). Reproduced from Ref. No. 50 with permission.

from one center indicate that the third-generation agents bucindolol and carvedilol produce somewhat greater improvements in LVEF and stroke volume or stroke work index than the second-generation compound metoprolol.[50] The potential differences are even more impressive when one considers that the data are biased for metoprolol and against bucindolol because the respective lengths of treatment were 6 months and 3 months, with 4 months for carvedilol.[50] However, the data displayed in Figures 5 and 6 were not direct comparisons from a single trial; the number of subjects was limited and only subjects with idiopathic dilated cardiomyopathy were studied. The ongoing COMET trial compares the LV functional and mortality effects of carvedilol and placebo.

Reversal of remodeling: Remodeling is the word used to describe the increase in end-systolic and end-diastolic volumes, increase in muscle mass (hypertrophy), and change in chamber geometry to a more spherical, less elongated shape. Another aspect of remodeling is progressive mitral regurgitation secondary to chamber dilatation, alterations in geometry, and rising left atrial pressure. Recent data indicate that all these effects are reversed by chronic treatment with beta blockade,[51-55] with different kinetics for each effect. To summarize the studies that have examined this issue in placebo-controlled trials, the reversal of LV diastolic volume as measured by echocardiographic dimensions[24, 52-55] or radionuclide techniques[51] follows a time course of no detectable change[53] or is just beginning to decrease at 3 months,[24] becoming statistically significantly different from placebo-treated patients but not from baseline values after 4 months of treatment,[51, 54] and being statistically significant from baseline values and/or placebo-treated subjects after ≥ 6 months of treatment.[52-55] A detectable reduction in LV mass measurements occurs somewhat later than the decrease in diastolic volume, after 8–12 to 18 months of treatment compared with baseline.[41, 53-55] The change in sphericity is also a later-appearing phenomenon, detectable at 8–12 to 18 months.[53, 54] Finally, a reduction in mitral regurgitation has been detected in two studies.[54, 55] This effect was statistically significantly different from placebo at 4 months in one study[54] and significantly reduced in both[54, 55] compared with baseline at 8–12 months. Figure 7 illustrates the apparent time course[56] of these changes compared with the above-described initial myocardial depression/decrease in ejection fraction[53] and then the improvement in ejection fraction that is detectable at 3–4 months. To summarize, as illustrated in Figure 7, these changes appear to follow a time course of (1) decreased systolic function, (2) increased systolic function, (3) reduction in ventricular volumes, (4) regression of hypertrophy, and (5) normalization of chamber shape.

The limited number of published studies on remodeling reversal includes two clinical trials with the second-generation compound metoprolol,[53, 55] two with the third-generation agent carvedilol communicated in four separate reports,[51, 52, 54, 57] and one with the third-generation agent bucindolol.[24] Moreover, different time points were analyzed in each trial. This limited number of studies employing a variety of designs plus the lack of a study directly comparing second- to third-generation agents precludes drawing conclusions about the efficacy of one type of beta-blocking agent versus another in effecting reversal of remodeling. By way of speculation, there is perhaps a tendency for third-generation agents to reduce volume somewhat sooner than metoprolol: at 3–4

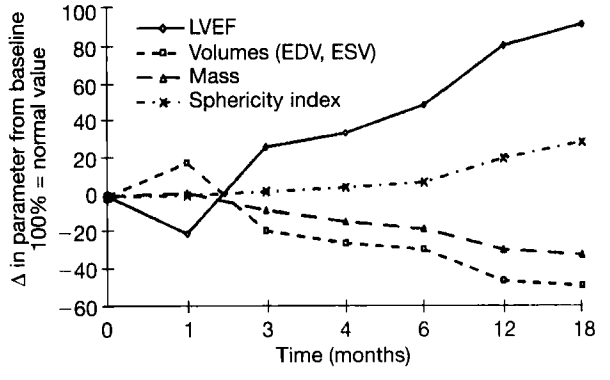


FIG. 7 Time course of change in ventricular function (LVEF), volume, mass, and sphericity index with beta-blocker treatment. EDV = end-diastolic volume, ESV = end-systolic volume. Reproduced from Ref. No. 56 with permission.

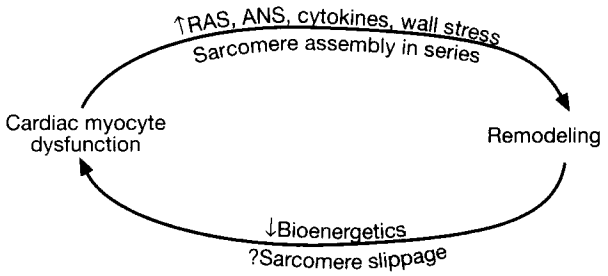


FIG. 8 Relationship between progressive myocardial dysfunction and remodeling. RAS = renin-angiotensin system, ANS = adrenergic nervous system. Reproduced from Ref. No. 8 with permission.

months with bucindolol[24] and carvedilol[51, 54] compared with no apparent change at 3 months with metoprolol.[53] The same quicker time course can be noted for carvedilol reducing mass and sphericity index (8–12 months[54] versus 18 months for metoprolol[53]), but in the metoprolol study[53], time points between 3 and 18 months were not investigated. The two studies in which mitral regurgitation was measured[54, 55] also suggest a faster response to carvedilol. However, more work needs to be done in this area before any conclusions can be drawn about relative efficacy of third- versus second-generation agents.

Regardless of whether beta-blocking agents have differences in the degree to or speed with which they improve myocardial function or reverse remodeling, all beta-blocking agents that can be given to subjects with chronic HF appear to possess these properties. In other words, reversal of myocardial systolic dysfunction and remodeling is a class effect of beta-blocking agents, by definition due to the direct or indirect effects of β_1-receptor blockade. Within this construct, the more comprehensive antiadrenergic effects of the third-generation agents potentially provide additional quantitative or time-related effects. An important point to emphasize is that the time-dependent "biologic" effects of improving myocardial function and reversing remodeling are unique to beta-blocker therapy and are not observed with other classes of heart failure treatment.[1] The only other type of treatment to have been shown to produce favorable biologic effects on function and structure is ACE inhibition, but, in this case, the effect is to attenuate the progression of myocardial dysfunction and remodeling as opposed to reversing them.[58]

The relationship between the improvement in intrinsic myocardial function and reversal of remodeling associated with beta-blocker treatment of chronic heart failure is interesting, as it appears that the improvement in function precedes the antiremodeling effect. In other words, it is possible that intrinsic myocyte dysfunction precedes remodeling, which apparently occurs as an attempt to stabilize cardiac output by increasing stroke volume. It is as though a larger end-diastolic volume is no longer needed to maintain stroke volume when intrinsic myocardial function is improved and remodeling then adaptively reverses. However, there is an alternative interpretation of the relationship of systolic dysfunction and remodeling that places the remodeling in a primary position, with myocardial dysfunction being secondary.[59] The precise temporal relationships of these events clearly need more vigorous investigation in the failing heart, including the relationships during reversal by antiadrenergic therapy. For the present, the data support only a relationship between myocyte dysfunction and remodeling, such that the presence of one will exacerbate the other (Fig. 8).

Effect of Beta-Blocking Agents on the Natural History of Heart Failure

It would be expected that an improvement in the biologic properties of the failing heart, as outlined above, would be translated into favorable effects on the natural history of heart failure. What is the evidence for this, and are there any differences between second- and third-generation agents in this regard?

Symptoms

Once beta-blocker-treated subjects with mild to moderate heart failure emerge from the initial period of myocardial depression or other reversible side effects, such as orthostatic hypotension with carvedilol, they typically have fewer symptoms than subjects treated with placebo.[20, 44, 60, 61] However, improved symptomatology has not been demonstrated in all studies.[24, 35, 57]

The issue of the effect on symptoms has not been answered in more advanced populations with heart failure. The few completed studies are not conclusive in this regard, inasmuch as one had an unusually high number of subjects eliminated from further consideration by adverse effects occurring during an initial beta-blocker challenge,[61] and the other trial in advanced heart failure was not completed.[51] However, the one large trial in advanced heart failure that is nearing completion[62] and the others that are underway, should settle this issue.

With regard to any apparent differences between second- and third-generation agents on symptoms, the only comparative study that evaluated symptoms found no difference.[21] However, this study was not a direct comparison in the same trial. The COMET trial directly comparing carvedilol and metoprolol will yield the definitive answer as to whether there are differences between different beta-blocking agents with regard to effects on heart failure symptoms.

Morbidity

Beta-blocking agents have favorable effects on heart failure morbidity, best detected by a lowering of hospitalization rate. In the first conducted and reported multicenter trial with a beta-blocking agent, The Metoprolol in Dilated Cardiomyopathy (MDC) trial,[47] metoprolol lowered hospitalizations by 39%. In the combined analysis of the U.S. Carvedilol Trials Program, this third-generation agent reduced the risk of hospitalization by 27%.[36] In fact, the reduction in hospitalizations was the basis for FDA approval of carvedilol as the first beta

blocker with a heart failure indication. As for symptoms, the clinical trial data base is not yet large enough to discern any differences between second- and third-generation agents for effects on hospitalization.

Mortality

Despite qualitatively similar class effects on ventricular function produced by β_1 blockade, hypothetical differences in mortality reduction may exist between selective and nonselective beta-blocking agents. In the failing heart, the β_1 receptor is downregulated and the relative proportion of β_1:β_2 receptors is altered from 75–80:20–25 to 60–65:35–40.[9] Thus, the β_2 receptor may assume a more prominent role in the failing heart. As second-generation agents only block the β_1 receptor, they allow continued transmission of β_2 receptor-mediated-adrenergic activity to the cardiac myocyte. In the human heart, the β_2-adrenrgic receptor is more efficiently coupled to adenylyl cyclase than the β_1 receptor,[63,64] and the enhanced cAMP generation produced by this pathway may predispose subjects to sudden death in view of the proarrhythmic potential of this second messenger.[65] In contrast, nonselective third-generation agents at target doses block both β_1 and β_2 receptors and more completely inhibit adrenergic activity at the receptor level. In addition, as presynaptic β_2-adrenergic receptors facilitate norepinephrine release, both bucindolol and carvedilol lower adrenergic drive.[21,66] Also, because of unique effects on receptor regulation that, in effect, prevent restoration of the downregulated β_1 receptor population,[11,21] carvedilol and bucindolol are more powerful β_1-blocking agents.[8,67] Finally, the α_1-receptor blocking properties of some third-generation compounds could potentially favorably impact on mortality reduction by virtue of greater effects on reverse remodeling or even antiarrhythmic effects.[68]

These theoretical differences in antiadrenergic profile create the potential for quantitative or qualitative differences in mortality reduction between second- and third-generation compounds, a hypothesis which is being tested in the COMET trial. The currently available data relevant to this hypothesis are summarized in Table V. As can be observed, the data are limited by the small number of completed trials that have incorporated mortality into an end point or, in the case of the carvedilol U.S. trials program, by reported effects on mortality tracked for safety reasons. There have been three such completed trials using a second-generation compound: one with metoprolol (MDC)[47] and two with bisoprolol, the Cardiac Insufficiency Bisoprolol Study (CIBIS I[69] and CIBIS II). The CIBIS II trial was recently stopped 18 months early because of a reduction in mortality but has not been reported. There is only one completed trial (or in this case, a group of trials pooled to assess effects on mortality) with a third-generation beta-blocking agent: the U.S. Carvedilol Trials Program.[36] As can be observed in Table V, compared with the two second-generation compounds, the third-generation compound carvedilol appears to exert a greater effect on mortality and also reduces sudden death. However, because the carvedilol data are not derived from a mortality trial, they can be criticized at multiple levels. Only the completion of multiple, properly designed mortality trials with second-[70] and third-generation agents,[71] as well as direct comparison trials such as COMET, will answer the question about differences in mortality effects between types of beta-blocking agents. These ongoing trials are summarized in Table VI.

TABLE V Effect of various beta-blocking agents on total mortality and sudden death in placebo-controlled trials that have included mortality in primary or secondary efficacy or safety end points

Trial and agent	Effect on total mortality	Effect on sudden death
MDC (metoprolol)[47]	↔ (21% increase)	↔
Carvedilol US Trials[36]	↓by 65%	↓
CIBIS I (bisoprolol)[69]	↔ (20% decrease)	↔
CIBIS II (bisoprolol)	↓ by ? 25%	?

Abbreviations: MDC = Metoprolol in Dilated Cardiomyopathy, CIBIS = Cardiac Insufficience Bisoprolol Study.

Conclusion

Relative to second-generation β_1-selective compounds, third-generation beta-blocking agents that are approved or are in development for a chronic heart failure indication have theoretical advantages that are based on their pharmacologic properties. These potential advantages consist of producing a more comprehensive antiadrenergic effect (carvedilol, bucindolol), having improved tolerability (bucindolol and, perhaps, nebivolol), and having unique ancillary properties that may be antiproliferative (carvedilol, nebivolol). However, there are only limited data on whether these properties translate into improved efficacy and safety. The extensive information

TABLE VI Ongoing heart failure multicenter trials with second- and third-generation beta-blocking agents

Trial	Beta blocker	Primary end point	Status
BEST[76]	Bucindolol	Total mortality	Enrollment ends 1/99
MERIT-HF[75]	Metoprolol[a]	Total mortality	Enrollment ended 4/98
COMET	Carvedilol, metoprolol	Total mortality	Enrollment ended 8/98
COPERNICUS	Carvedilol	Total mortality	Enrolling
Nebivolol[b]	Nebivolol	Mortality + hospitalizations	To start 1/99

[a] Metoprolol succinate (Toprol XL™).

[b] Trial not yet named.

Abbreviations: BEST = Beta-Blocker Evaluation Survival Trial, MERIT-HF = Metoprolol Randomized Intervention Trial in Heart Failure.

which will be forthcoming from ongoing clinical trials will ultimately answer this question.

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