Selective or Nonselective β-Adrenergic Blockade in Patients with Congestive Heart Failure

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Introduction

Controlled clinical trials, performed in more than 13,000 patients, have consistently shown the beneficial effects of long-term β-blocker therapy in patients with chronic heart failure. However, it is not clear whether this is a class effect or if it is specific only for some agents. Beneficial effects on the prognosis of the patients with mild to moderate heart failure have been obtained with metoprolol, bisoprolol, and carvedilol. Metoprolol and bisoprolol are selective for β1-receptors and without ancillary properties, carvedilol, at doses of 25 mg twice daily, blocks β1-, β2-, and α1-adrenergic receptors, and has associated antiproliferative and antioxidant activities. These differences are important for the acute hemodynamic effects, but it is still controversial whether they may also influence the long-term effects of therapy. Differently from selective β-blockers, carvedilol blocks all adrenergic receptors, does not upregulate β1-receptors, decreases cardiac norepinephrine release, and has associated antioxidant effects. These differences may cause a larger increase in left ventricular function, which was significant in some, but not all of the direct comparisons of the two agents. The long-term effects of different β-blockers on prognosis are currently compared in the Carvedilol or Metoprolol European Trial, in which more than 3000 patients with chronic heart failure have been 1:1 randomized to metoprolol or carvedilol and are going to be followed for more than 2 years.

Controlled clinical trials, performed in more than 13,000 patients with chronic heart failure, have consistently shown that the long-term administration of β-blockers is associated with a significant improvement in left ventricular (LV) function, symptoms, and clinical course, with a lower incidence of hospitalizations and episodes of worsening heart failure, and an improved survival [1–4,5,6••,7••]. As a result, the long-term administration of β-blockers is now recommended to all patients with mild to moderate heart failure caused by LV systolic dysfunction who do not have specific contraindications and who are on standard therapy with angiotensin-converting enzyme (ACE) inhibitors, diuretics as needed to control fluid retention, and digoxin [8••,9••].

Some major features of β-blocker treatment remain, however, controversial [10•–12•]. Among them, one of the most important is the clinical relevance of their pharmacologic differences. Unlike ACE inhibitors, β-blockers are not a homogeneous group of agents. They are generally differentiated on the basis of their degree of lipid solubility, presence of intrinsic sympathomimetic activity, ancillary properties, and selectivity for the cardiac β1-adrenergic receptors. Among all of these differential features, the role of the last one is still unsettled whereas the significance of the other properties seems more definite.

Lipid solubility is associated with hepatic, rather than renal, elimination. It may also cause direct effects in the central nervous system, as lipid soluble β-blockers may cross the blood-brain barrier. β-blockers used in patients with chronic heart failure are all highly lipid soluble with extensive liver metabolism (metoprolol, carvedilol, bucindolol), with the exception of bisoprolol, which is less lipophilic and has a mixed hepatic/renal clearance [13•].

β-blockers with intrinsic sympathomimetic activity have been shown to have no effect on survival in postinfarction patients and have increased mortality in patients with advanced heart failure [14,15]. They are therefore not used in the patients with heart failure. These results also suggested that the extent of the antiadrenergic activity is directly related to the magnitude of the long-term beneficial effects of β-blocker therapy. With regard to the β-blockers with ancillary properties, nonselective agents with associated vasodilating activity are considered in the next section. Sotalol is a peculiar β-blocker with associated type III antiarrhythmic properties. However, the placebo controlled trial conducted with d-sotalol, which has only the type III antiarrhythmic activity, in patients with heart failure, was prematurely terminated because of an...
increased mortality with this agent. There are therefore no data to show that type III antiarrhythmic activity may offer any additional advantage over β-blockade and sotalol has no specific indication in patients with heart failure. In contrast with the previous properties, the significance of the β-receptor selectivity remains controversial.

Selective Versus Nonselective β-Blockers

β-Blockers used in the treatment of the patients with heart failure have been subdivided in three classes on the basis of their degree of selectivity for the β1-receptors and of the presence of associated properties [16]. First generation agents, like propranolol, are nonselective and without ancillary properties; second generation agents, like metoprolol and bisoprolol, are selective for β1-adrenergic receptors; third generation agents are nonselective (bucindolol) or mildly selective (carvedilol) for β1-receptors and with associated vasodilating activity.

These pharmacologic differences are important during initiation of β-blocker therapy in the patients with heart failure [17]. Different from a normal heart, the failing heart is stimulated by the sympathetic nervous system even at rest and, despite the impairment of the mechanisms of transduction of the adrenergic signal, this has a significant inotropic and chronotropic effect [18,19]. Therefore, blockade of the β-adrenergic receptors has a short-term negative inotropic effect in the failing heart which may be overcome by the favorable effects on the myocyte biology only on the long-term [20–23].

First generation nonselective β-blockers, like propranolol, are poorly tolerated in the patients with heart failure. In fact, the negative inotropic effect secondary to blockade of β1-receptors is attended by the concomitant rise in peripheral resistance secondary to blockade of vascular β2-receptors [16,22,23]. On the other hand, more than 90% of the patients with heart failure may tolerate the second generation agents, such as metoprolol and bisoprolol. These agents are selective for myocardial β1-receptors thus leaving unblocked the β2-receptors, which exert a positive inotropic effect both directly, through the postsynaptic receptors located on the myocardial cells [24•], and indirectly, through the stimulation ofnorepinephrine release mediated by the presynaptic β2-receptors [25]. In addition, selective agents do not directly increase peripheral vascular resistance as they do not block the vascular β2 receptors. However, because of the negative inotropic effect of β1-receptor blockade, the acute administration of selective agents to patients with chronic heart failure is associated with adverse hemodynamic effects with a decline in cardiac output and stroke volume with a tendency to a rise in LV filling pressures [16,26,27]. Thus, despite a greater than or equal to 90% tolerance rate, worsening heart failure and fluid retention are the most common side effects during the first weeks of therapy in the patients with chronic heart failure. They may also cause a significant increase in the early heart failure hospitalization rate compared with placebo, as in the recent Randomized Evaluation of Strategies for Left Ventricular Dysfunction Pilot Study (RESOLVD) [28••].

Third generation agents are nonselective or mildly selective and with ancillary properties. Carvedilol is mildly selective for β1-receptors with a β1/β2 selectivity ratio of 7.3 so that, however, at doses greater than or equal to 25 mg bid it blocks both β1- and β2-receptors [13••]. It has no intrinsic sympathomimetic activity but, for its atypical binding characteristics, it does not upregulate myocardial β1-receptors [29]. Its vasodilating action is caused by α1-receptor blockade with a two- to threefold selectivity for β1 versus β2-receptors [12•,13••,29]. In addition, it has antiproliferative and antioxidant effects, which may be important for the inhibition of the progression of heart failure [30•].

Bucindolol is nonselective and has a mild vasodilating activity likely mediated by weak α1-receptor blockade [13••]. Recently, discussion of whether it also has intrinsic sympathomimetic activity has arisen [31,32]. This is important for the interpretation of the neutral effects it had on mortality in the β-blocker Evaluation of Survival Trial (BEST) [13••]. According to other data, however, it has no intrinsic sympathomimetic activity and, compared with other β-blockers, has the lowest amount of inverse agonism, that is to say, the property to inactivate active-state receptors [13••,29]. This last property should explain the low incidence of symptomatic bradycardia after bucindolol, reported in clinical studies.

Short-term effects

The peripheral vasodilating activity of third generation β-blockers is important when the therapy is initiated as it may counteract the negative inotropic effect of myocardial β1- and β2-receptors blockade and the vasoconstrictor effects of vascular β2-receptors blockade. Accordingly, differently from second generation agents, the acute administration of carvedilol does not decrease the cardiac output and stroke volume and may slightly reduce the pulmonary wedge pressure in patients with heart failure [27,33]. This also explains the higher incidence of hypotension and dizziness with a similar incidence of worsening heart failure, compared with placebo, as adverse effects in controlled trials [1].

Thus, differences between selective and nonselective β-blockers affect their acute hemodynamic effects and their side effects during initiation of therapy. They may, however, be important also for their long-term effects. Particularly, it has been hypothesized that the greater antidrenergic activity of nonselective agents may yield additional advantages also in the long-term treatment of the patients with heart failure [12•,16,34•].

β1-receptor density

A first distinction regards the effects on β1-receptor density. This is increased by second generation agents [19,26], consistently with the observation that β1-receptor downregula-