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Nebivolol: Does the Key Lie in β3 Agonism?

Hernán Cohen Arazi[1] and Miguel Gonzalez[2]*

[1]Department of Cardiology and Cardiovascular Surgery, Centro Médico Pilares, Buenos Aires Argentina CEMIC, Buenos Aires Argentina

[2]Department of Cardiovascular Surgery, Sanatorio Finochietto, Buenos Aires, Argentina

Abstract

Beta-blockers are drugs indicated in the treatment of multiple cardiovascular pathologies. The review highlights the mechanisms of action of Nebivolol and its particular potential effect on β3 receptors that increases nitric oxide that may mark very significant differences, which are traduced to benefits in clinical results. Nebivolol has an special place in the treatment of adrenergic hypertension associated with tachycardia and emotional stress, more frequently in young individuals, and may be considered adequate even in patients with glucose and lipid metabolism disorders due to its pleiotropic effect. In patients with heart failure, Nebivolol showed effectiveness and safety in patients over 75 years old. Nebivolol showed a reduction of cardiomyocyte apoptosis and improvement of contractile function through a mechanism related to β3 receptor agonism after an acute coronary syndrome. Because of all these actions Nebivolol should be considered not only a third-generation Beta-blocker.

Introduction

Beta-blockers are drugs indicated in the treatment of multiple cardiovascular pathologies, with different level of evidence. Despite the fact that they are divided into first-generation to third-generation drugs and according to their selectivity by beta and alpha receptors, they are often mentioned as belonging to the same group [1]. The purpose of this review is to highlight that the mechanisms of action of the beta-blockers may mark very significant differences, which are seen in clinical results [2,3]. In this sense, Nebivolol seems to be a drug that due to its pharmacodynamics and its particular potential effect on β3 receptors and the increase of Nitric Oxide (NO) [4], may be considered in a different place in comparison to a conventional beta-blocker.

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Correspondence:
Hernán Cohen Arazi, Department of Cardiology and Cardiovascular Surgery, Centro Médico Pilares, Buenos Aires Argentina CEMIC, Buenos Aires Argentina, Tel: +5491159938744; E-mail: h_c_arazi@yahoo.com

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Most Frequently Used Beta-Blockers

Propranolol is the oldest beta-blocker, dating back to the 1960s. It has an equal affinity for β1 and β2 receptors and is a non-selective beta-adrenergic antagonist. It is highly lipophilic and has a half-life of 3 to 5 hours, even though the duration of action is higher. It is indicated in cases of high blood pressure [5], angina [6] and some arrhythmias [7,8], frequently with two or more daily doses taken orally. It was one of the first beta-blockers that showed benefits.

Atenolol is a selective β1 receptor inhibitor, hydrophilic, highly used in spite of not having shown decrease of arrhythmias or mortality after myocardial infarction [9]. Compared with angiotensin-converting-enzyme inhibitors (ACE inhibitors), atenolol does not improve the arteriolar resistance in hypertensive patients [10] and has a short duration of action that does not allow for a homogeneous antihypertensive effect during 24 hours [11]. What is more, it was associated with an increase in diabetes and stroke risk and total mortality when compared with other agents [12], especially in elderly patients [13]. Bisoprolol, like atenolol, is also a second-generation beta-blocker, with greater selectivity for β1 receptors, is lipophilic and has a half-life of 11 to 17 hours. There are randomized clinical trials that have proven the benefits of bisoprolol in cases of heart failure [14]. However, despite the fact that the studies conducted on high blood pressure do not have the same methodological rigor, it is also approved for its use in cases of hypertension [15]. Carvedilol is a non-selective beta-blocker with additional blockades of ά receptors, which gives it a vasodilatory effect. At high doses, it blocks the entry of calcium. Milligram per milligram, it is two to four times more potent than propranolol as ß antagonist [17]. In the U.S. Carvedilol Heart Failure Program [18], it is used in the treatment of heart failure, and it is also indicated for high blood pressure and myocardial ischemia.

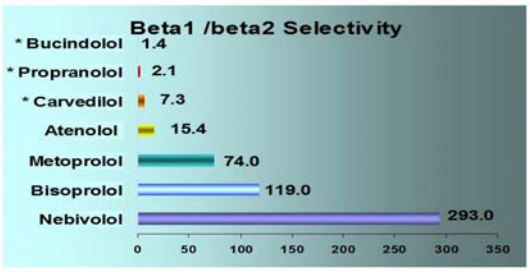

Figure 1: Comparison of Beta-blockers blockade selectivity of β1 receptors.

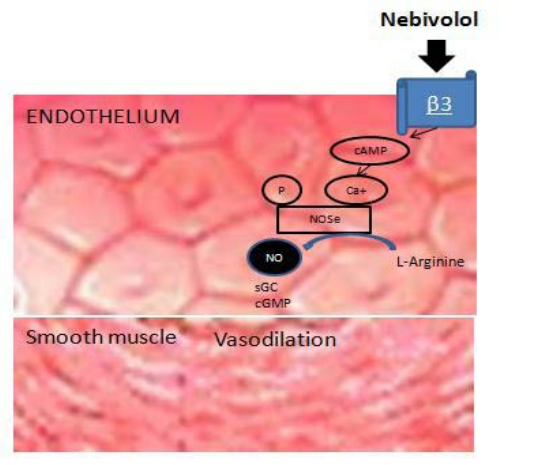

Figure 2: Vasodilation mediated by β3 receptors and NO of Nebivolol.

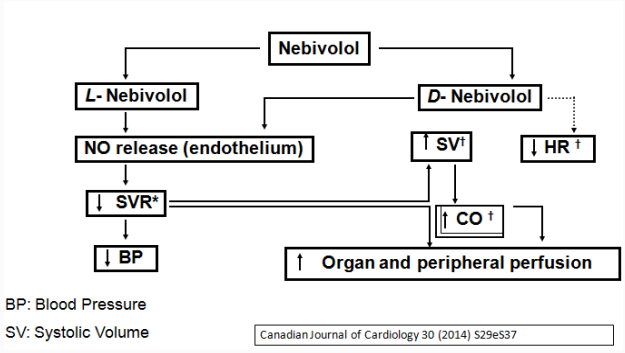

Figure 3: Synergy of combined action of beta-blockade and increase of NO with Nebivolol.

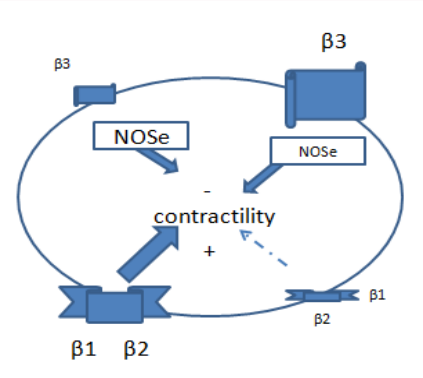

Figure 4: Modifications of β receptors in the cardiomyopathy.

Beta-Blockers in High Blood Pressure (HBP)

Even though beta-blockers have been used for almost half a century for the treatment of HBP, they are not drugs considered as first-line treatment by national [19] and international [20,21] treatment guidelines. The antihypertensive effect of second-generation beta-blockers is achieved through the reduction of the cardiac minute volume, the heart rate and the contractility, with no effect on peripheral vascular resistance [22]. Third-generation beta-blockers have vasodilatory properties through blockades of à receptors (carvedilol) or through the increase of nitric oxide (nebivolol), which lowers the peripheral resistance maintaining the minute volume [23]. The low effectiveness for the prevention of strokes with beta-blockers has been attributed to a low ability to decrease the central systolic pressure and the pulse pressure. However, they have proved effective in the prevention of cardiovascular events in patients with a recent myocardial infarction or with heart failure [24]. The national and international treatment guidelines clearly state that beta-blockers with a vasodilatory effect have advantages over other beta-blockers since they reduce the central pressure of the pulse and the aortic rigidity [25-27]. There is evidence that the central aortic pressure is an independent predictor of cardiovascular structural damage and clinical events [28-31].

Differences of nebivolol

Nebivolol has a greater selectivity of β1 receptor blockages than other beta-blockers [32] Figure 1. Unlike carvedilol, Nebivolol exercises its vasodilatory effect through the production of nitric oxide derived from the endothelium by stimulating the Nitric Oxide Synthase (NOS) mediated by β3 receptor agonism [33,34] Figure 2.

Endothelial dysfunction caused by oxidative stress is an essential mechanism involved in high blood pressure [35] and is associated with the prognosis in cardiovascular disease [36]. Nebivolol showed reduction of oxidative stress, which may also be an explanation for the better metabolic profile of Nebivolol in connection with glucose and lipids [37-39]. The studies that assessed Nebivolol against placebo in patients with high blood pressure showed a significant reduction of systolic (SBP) and Diastolic Blood Pressure (DBP) [40], with a broad safety margin, and few adverse effects (headache 7.1% versus 5.9 with placebo, fatigue 3.6% vs. 1.5% with placebo and dizziness 2.9 vs. 2.0% with placebo), without differences in the treatment discontinuation rate (2.6% with Nebivolol versus 2.0% with placebo). These results were concordant in the subgroup analysis [41] and especially beneficial in the group of young patients [42], a special target for the incidence of adrenergic hypertension. Compared with Angiotensin-Converting-Enzyme inhibitors (ACE inhibitors), Nebivolol showed a greater percentage of patients that reached the target values and was comparable to the angiotensin 2 receptor antagonists (AT2) and calcium channel blockers [43]. Maximum antihypertensive action is observed between week 2 and 8 of treatment, which is intermediate between the ACE inhibitors (slower) and amlodipine (faster) [44]. The action on nitric oxide may be of great benefit, preventing erectile dysfunction [45] reported with other beta-blockers [46,47], which is one of the main adverse effects feared by young patients. These additional benefits reinforce the potential role of Nebivolol in the treatment of adrenergic hypertension associated with tachycardia and emotional stress, more frequently in young individuals, and may be considered adequate even in patients with glucose and lipid metabolism disorders [48] due to its pleiotropic effect [49]. In patients with hypertension and type 2 diabetes, Nebivolol has

demonstrated reductions in mean glucose levels and HbA1c across several age groups [50] and increases in HDL cholesterol (5 mg/dl) were observed [51].

Beta-Blockers in Cases of Heart Failure (HF)

There are no doubts about the benefit of beta-blockers in the treatment of heart failure [52]. They reduce mortality and morbidity by approximately 30% over 5 years [53]. They have a grade I recommendation, with a level of evidence A in all international and national treatment guidelines together with the ACE inhibitors. The beneficial effect in this pathology would be associated with a reduction of adrenergic stimulation modulating the sympathetic-vagal balance and the variability of the heart rate, in addition to improving heart performance. The deleterious effects of beta-blockers are related to the reduction of inotropism and chronotropism, which is why they must be administered in patients that are hemodynamically stable.

Differential aspects of nebivolol

The distinctive pharmacologic profile of Nebivolol is explained by some relevant hemodynamic effects: 1- The highly selective β1 blockade reduces heart rate at rest and on exertion as well as SBP and DBP, without causing adverse effects related to the β2 receptor blockade [54] and maintaining the balance with the alpha receptors at vascular level. 2- Vasodilation mediated by NO results in the reduction of peripheral vascular resistance, the improvement of remodeling and of arterial stiffness [55,56] and in the increase of systolic volume and ejection fraction maintaining the minute volume [57]. When compared to other beta-blockers, Nebivolol did not cause negative hemodynamic effects such as increase of pulmonary artery pressure and Pulmonary Capillary Pressure (PCP) and decrease of cardiac minute volume [58], unlike Metoprolol tartrate. The hemodynamic profile and tolerance to exertion was also better in comparison to Atenolol [59], and when compared to Carvedilol (CARNEBI (Multiparametric comparison of CARvedilol, *vs.* NEbivolol, *vs.* BIsoprolol in moderate heart failure cardiopulmonary trial), patients with moderate HF had better physical capacity [60]. Nebivolol is a 1:1 racemic combination of a D- and an L-isomer. The D-isomer grants it a blocking effect for β1 receptors and the L-isomer is mainly responsible for the stimulating action of NOSe Figure 3. When studying the Randomized Clinical Trials (RCT) conducted on patients with heart failure, it is observed that they included younger populations than the average age of patients that are hospitalized in real life due to this pathology. The average age of RCT patients is around 60 years old and only 25% are >75 years old. In our country, according to the last census [61], there are more than 4 million people older than 70, and in accordance with the prevalence of the disease, it is estimated that there are more than 300,000 people with heart failure in that age group [62]. Although some of the studies that have assessed the treatment with beta-blockers in HF have analyzed the results in elderly patients, these studies were not designed to reach statistically significant conclusions [63,64]. The SENIORS study (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) [65] enrolled patients with heart failure, and established as inclusion criteria that the patients were 70 years old or older and incorporated a high percentage of women and patients with preserved systolic function. It showed a reduction of 14% in the mortality from all causes, and there were no more adverse effects than with placebo. This last datum is also relevant considering that, in the treatment with other beta-blockers, advanced age was a determining factor of intolerance risk [66]. The SENIORS study reported an improvement in cardiac function and diameter, but the hospitalization rate had not decreased. In patients under 75 years old (median age of the population) and with ejection fraction <35%, a decrease of the primary final event of 38% (hazard ratio of 0.62) was observed, in concordance with other beta-blockers in previous studies.

Nebivolol in cases of coronary disease

Treatment with beta-blockers is indicated in patients with acute and chronic coronary artery disease (67-69). Although in some countries Nebivolol is not indicated in this pathology, there is evidence that, in comparison to Atenolol, it improves exercise tolerance and the time until the onset of angina in the exercise test in patients with stable coronary artery disease [70] and also improves coronary flow reserve [72]. Even in patients with cardiac syndrome X and endothelial dysfunction, Nebivolol was associated with an improvement of the exercise time, less exercise-induced ischemia and less angina attacks than Metoprolol [72]. In acute coronary syndromes, a small-scale study showed that patients that had an infraction with ventricular dysfunction had fewer events (infarction/death/hospitalization due to coronary syndrome/stroke or need of revascularization) over 12 months than those patients treated with Metoprolol and similar to those treated with Carvedilol [73]. The additional benefit may be related to an antiplatelet effect showed with Nebivolol [74,75]. However, there is a new paradigm related to the agonist effect of β3 receptor.

New paradigm: the importance of β3 receptor

For many years we understood the hemodynamic and myocardial functioning based on two beta receptors at myocardial level: β1 and β2 and the ά receptors at a vascular level, together with the neurohumoral behavior of the Renin-Angiotensin-Aldosterone System (RAAS). The endogenous catecholamines act at a myocardial level through the union to these β myocardial receptors regulating heart rate and contractility. Special situations may cause an increase of the catecholamine levels and an increase of the cardiac activity, as occurs, for instance, in adrenergic hypertension or in heart failure. In this last case, a mechanism that is initially compensatory becomes harmful due to cellular toxicity and apoptosis, consequence of the activation and *"overstimulation"* of β1 receptors at myocardial level. The discovery of β3 receptors in atria and in ventricles [76] forces us to redefine the model. These receptors, encoded in chromosome 8 [77], were known in the adipose tissue, where they regulate thermogenesis, and were also described at the muscular level of bladder and gallbladder. In the myocardium, it was observed that in situations where there are high levels of catecholamines, the upregulation of β3 receptors occurs [78,79]. The union to these receptors causes attenuation of inotropism, favoring a counterbalance of β1 receptors against "deleterious overexposure" of catecholamines that may derive in hypertrophy, fibrosis and apoptosis. Thus, the β3 receptor agonism may exercise a protective effect at myocardial level [80,81]. The activation of one or another β receptor depends on the clinical situation and the circulating catecholamine levels. The β3 effect is connected with the activation through NO. There are 3 isoforms of NO synthase (NOS). In patients with heart failure, the NOSe (endothelial) and ONSn (neural) are the ones responsible for the protective effect through the increase of NO at myocardial level [82,83]. Several studies have shown that Nebivolol causes its effect through the combined action of β1 receptors blockade and β3 receptors agonism. At a vascular level, the increase of NO causes vasodilation, and at a myocardial

level, it favors the necessary balance to achieve a balanced inotropic effect, preventing the increase of catecholamines from becoming deleterious Figure 4. β3 receptor agonism at a coronary vascular level causes vasorelaxation mediated by Nitric Oxide (NO), especially in microvasculature. Considering that an important component of cardiac remodeling is the adaptation of the capillary density under hemodynamic stress and neoangiogenesis [84], the action at the vascular level of β3 agonists may be part of the improvement of post-infarction remodeling [85] observed with Nebivolol, jointly with a paracrine effect at fibroblast level that improves the formation of scar tissue and peripheral vasodilation contributing to the improvement of ventricular relaxation. In experimental studies in animals with recent myocardial infarction, treatment with Nebivolol showed a reduction of cardiomyocyte apoptosis and improvement of contractile function through a mechanism related to β3 receptor agonism. These same mechanisms could explain part of the benefit observed in the SENIOR study in patients with chronic heart failure.

Conclusion

Beta-blockers proved beneficial in different clinical scenarios. A big part of the benefit was explained by the antiarrhythmic and antihypertensive effect of these drugs, added to a decrease of the deleterious action of catecholamines against excessively high levels. The initial approach was to differentiate beta-blockers according to their affinity to β1 and β2 receptors. Then, focusing on the neurohumoral hypothesis and reassessing the hemodynamic control of ventricular dysfunction, an action on peripheral resistance was considered essential, and carvedilol differed due to its vasodilatory effect through blockade of ȁ receptors at vascular level. However, NO is a more potent vasodilator and is physiologically present in situations of ischemia. The discovery of the β3 agonist action with the consequent action of NO at myocardial and vascular level could change the paradigm. Nebivolol acting as agonist would have additional beneficial effects, at the level of ventricular remodeling, in patients with different degrees of ventricular dysfunction and in subpopulations specifically assessed as elderly patients.

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