Prevention of Remodeling of the Heart

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Abstract. A comparative study was carried out of the effect of prophylactic administration of two beta blockers with different mechanisms of action on the morpho-functional parameters of the cardiovascular system in SHRSP rats and their genetic control - WKY rats. We studied blood pressure, the concentration of nitrates and nitrites in the blood plasma, endothelium-dependent vascular relaxation, the structural component of vascular resistance and heart mass index during chronic administration of the cardioselective beta-blocker nebivolol, which has the ability to modulate the synthesis of NO in the vascular endothelium, and the cardioselective beta-blocker metoprolol, which does not have this effect. A more effective reduction in blood pressure, myocardial mass, normalization of nitrates and nitrites in the blood, a pronounced effect on endothelium-dependent vascular relaxation and effective inhibition of vascular remodeling were revealed when using nebivolol, compared to metoprolol.

Key words: arterial hypertension, nebivolol, nitric oxide, cardiovascular remodeling.

The requirements for modern antihypertensive therapy provide for an effective effect not only on the functional parameters of hemodynamics - blood pressure, heart rate, peripheral vascular resistance, but also an inhibitory effect on the processes of structural restructuring (remodeling) of the heart and blood vessels. Discovering the role of local regulatory factors of the endothelium - endothelin, nitric oxide (NO) - allows us to re-evaluate the possibilities of antihypertensive therapy. Thus, depression of the synthesis of endothelial NO, a powerful vasodilating and vasoprotective agent, usually observed in patients with developed arterial hypertension (AH), may contribute to the progression of hypertension and accelerated remodeling of the cardiovascular system [1]. Therefore, the use of effects and drugs that stimulate the synthesis of NO in the vascular endothelium seems theoretically justified.

In this regard, of particular interest is the study of the anti-remodeling effects of the new lipophilic, highly cardioselective beta-blocker nebivolol, which has the ability to modulate NO synthesis in the vascular endothelium [2]. There are clinical data in the literature showing that nebivolol stimulates endothelium-dependent vascular relaxation (EDV) in both acute [3] and chronic [4] use. However, few experimental studies have been conducted to evaluate the NO-dependent mechanisms of the antihypertensive effect of nebivolol in animals. Meanwhile, nebivolol apparently acquires the ability to stimulate NO synthesis only after metabolization in the body [5].

In this regard, the purpose of this study was to comparatively study the effect on NO-dependent parameters of the cardiovascular system in rats with spontaneous hypertension of chronic
administration of two lipophilic cardioselective beta-blockers - nebivolol, which modulates NO synthesis in the vascular endothelium, and metoprolol, which does not affect NO synthesis.

**Material and methods**

Experiments were conducted on male spontaneously hypertensive stroke-prone rats (SHRSP) and male normotensive Wistar-Kyoto (WKY) rats, which are genetically related controls to the SHRSP strain. The rats were administered a cardioselective lipophilic beta-adrenergic blocker with NO-modulating activity - nebivolol (1.25 mg/kg, i.p.) and a reference drug - a cardioselective lipophilic beta-adrenergic blocker metoprolol (30 mg/kg, i.p.) daily for 10 weeks. The administration of drugs began at the age of 5 weeks, which corresponded to the early hypertensive stage in SHRSP, and ended at the age of 15 weeks, which corresponded to the stage of developed hypertension in SHRSP. The course of drug administration was 5 and 10 weeks. Each experimental group included at least 9 animals. Blood pressure was measured in awake rats by an indirect bloodless method on the tail artery using a Physiograph DMP-4F unit (Narco Bio-Systems, USA).

Rats were sacrificed by decapitation 24 hours after the last drug administration. Immediately after decapitation, the thoracic aorta was removed from the rats and cleared of surrounding tissue. A 3.5 mm long ring specimen was then cut from the aorta. The drug was placed in a thermostated (37°C) chamber containing 30 ml of Krebs solution (130 mM NaCl, 11 mM glucose, 14.9 mM NaHCO, 4.7 mM KCl, 2.5 mM CaCl, 1.2 mM MgSO, 1.18 mM KHPO, pH 7.4), which was constantly aerated with a mixture of 95% O and 5% CO. The stabilization period was 60 minutes with a residual voltage of the drug of 1.2 g. Voltage recording was carried out on a two-channel recorder (Ugo Basile, Italy). Aortic contractions were induced by the cumulative addition of norepinephrine (10⁻⁸ - 5x10⁻⁷ M) to the chamber. Endothelium-dependent relaxation was induced by acetylcholine (10⁻⁸ - 10⁻⁵ M) against the background of contraction caused by norepinephrine (5x10⁻⁷ M).

**Results**

A study of the dynamics of blood pressure (Fig. 1) showed that in the SHRSP group who did not receive treatment, blood pressure increased with age from 135 ± 3.6 to 219 ± 4.6 mm Hg. (p<0.05). Treatment started at an early hypertensive stage slowed the development of hypertension. At the same time, the hypotensive effect of metoprolol was more pronounced after 5 weeks, while the hypotensive effect of nebivolol increased more slowly, but after 10 weeks of treatment it turned out to be significantly stronger than that of metoprolol. In normotensive rats, nebivolol did not have a significant effect on normal blood pressure values, while metoprolol slightly reduced it after 10 weeks of administration.

In 5-week SHRSP, plasma nitrite and nitrate concentrations did not differ from WKY (Fig. 2). By the ages of 10 and 15 weeks in SHRSP it increased from 28.4±11.8 μM to 64.7±7.5 μM (p<0.05) and 68.8±7.5 μM (p<0.05), respectively, while in WKY, on the contrary, it decreased slightly compared to 5-week-old animals. In SHRSP treated with nebivolol for 5 and 10 weeks, plasma nitrite and nitrate levels did not increase and remained at 20.1 ± 4.8 μM and 25.9 ± 7.6 μM, respectively. These indicators did not differ from those in WKY of the same age who received nebivolol. At the same time, in SHRSP who received metoprolol, the level of nitrites and nitrates in plasma after 5 weeks of administration remained elevated compared to WKY and decreased only after 10 weeks of treatment.

In Fig. Figure 3 shows that with age, spontaneously hypertensive rats develop pronounced endothelial dysfunction, which manifests itself in the inhibition of endothelium-dependent vascular relaxation. Endothelium-dependent relaxation in untreated WKY rats did not change until the age of 10 weeks, but by 15 weeks of age its decrease was noted (51.4±3.9% vs. 34.0±3.2%, p<0.05). Nebivolol significantly prevented the decline in this indicator in both groups and even significantly improved it in SHRSP after
10 and 15 weeks of administration. In rats treated with metoprolol, endothelium-dependent relaxation was 30.3±0.6% and 23.5±0.7%, respectively. Thus, in terms of endothelium-dependent relaxation, the effect of nebivolol was more durable than the effect of metoprolol.

A study of cardiac mass index (Fig. 4) shows that myocardial hypertrophy developed in SHRSP by the age of 15 weeks. The hypertrophy index (percentage of heart weight to the body weight of the animal) in SHRSP increased from 0.39±0.0075 to 0.59±0.018 (p<0.05), while in WKY of any age it did not exceed 0.38. Both nebivolol and metoprolol slowed the development of hypertrophy, however, while SHRSP who received nebivolol for 15 weeks did not differ from the control (0.31 vs. 0.38), then those who received metoprolol it remained elevated (0.43±0.024). In groups of normotensive rats, no significant changes in heart mass index were detected either in the control group or during the administration of beta blockers.

In Fig. Figure 5 shows that the structural component of the resistance of the vascular basin, reflecting the remodeling of the vessel, in SHRSP significantly increased with age, as evidenced by the shift of the “flow-pressure” curve to the region of higher pressure values. Treatment with metoprolol and nebivolol significantly limited the increase in the structural component. This effect was more pronounced for nebivolol. This pattern persisted both after 5 and 10 weeks of drug administration. In WKY, age-related changes in the structural component of vascular resistance were practically absent. Metoprolol and nebivolol did not have a significant effect on this indicator.

Thus, nebivolol has a more effective antihypertensive effect than the comparison drug, the b-blocker metoprolol, and more effectively prevents NO-dependent disorders that accompany hypertension, the development of myocardial hypertrophy and vascular remodeling.

The discussion of the results
In recent years, sufficient evidence has accumulated to believe that endothelial dysfunction (ED) and deficiency of endothelial NO synthesis are not only an early marker of vascular damage in hypertension and atherosclerosis, but also make a significant contribution to the formation and progression of hypertension [1,7]. It should be noted that even successful antihypertensive therapy does not always lead to normalization of endothelium-dependent vascular relaxation [8]. Therefore, preferable are drugs that can not only lower blood pressure, but also correct ED, as a key and early link in the pathogenesis of hypertension. Beta-blockers are widely used in the clinic for the treatment of hypertension, heart failure and coronary heart disease. As a result of the evolution of the class of b-blockers, in recent years new third-generation b-blockers have been introduced into clinical practice, differing not only in their pharmacological characteristics, but also having additional vasodilator properties [9]. Moreover, the mechanisms of vasodilation in these drugs are different - from alpha-adrenergic blockade in carvedilol and intrinsic sympathomimetic activity in busindolol and celiprolol, to modulation of NO synthesis in the vascular endothelium in nebivolol [3].

It is the property of directly modulating NO synthesis in the endothelium that fundamentally distinguishes nebivolol from most antihypertensive drugs and significantly expands the range of protective effects of nebivolol, since the function of NO in the body is not limited to its direct vasodilator and hypotensive effects. Thus, studies have shown that, due to the correction of NO synthesis in the body, nebivolol inhibits platelet aggregation [10], increases cell sensitivity to insulin [11] and prevents the proliferation of vascular smooth muscle cells [12]. All these properties of nebivolol are not associated with a beta-blocking effect and constitute its advantages over other beta-blockers.

In the present study, the antihypertensive effect of nebivolol at a dose that did not affect blood pressure in normotensive rats after 5 weeks of treatment was less pronounced than that of the comparator drug.
metoprolol. However, with further administration it intensified and by the end of the experiment, blood pressure in SHRSPs receiving nebivolol was significantly lower than in rats receiving metoprolol, although metoprolol, unlike nebivolol, significantly reduced blood pressure not only in spontaneously hypertensive animals, but also in normotensive rats. Thus, long-term use of nebivolol reduces high blood pressure and does not affect normal blood pressure. SHRSP is characterized by the rapid development of endothelial dysfunction, which, according to some data, occurs even earlier than the increase in blood pressure [13]. In our experiments, endothelium-dependent relaxation (EDR) of the SHRSP aorta, already at the early hypertensive stage, was significantly different from that in WKY. Nebivolol prevented the suppression of EZR, and after 10 weeks of nebivolol administration, the indicator in SHRSP was practically no different from that in intact WKY of the same age. In WKY, nebivolol also limited the age-related decline in endothelial function observed in 15-week-old animals.

Metoprolol after 10 and 15 weeks of administration also had a significant beneficial effect on the aortic ERD, although its effect was significantly weaker than that of nebivolol. Apparently, the effect of metoprolol can be explained by the fact that any long-term decrease in blood pressure, regardless of the cause that caused it, partially improves endothelium-dependent vascular relaxation [14].

Endothelial dysfunction in SHRSP was accompanied by a significant increase in the total production of NO in the body, which manifested itself in increased plasma concentrations of stable NO metabolites – nitrites and nitrates. Similar data were obtained by other authors [14]. This seemingly paradoxical combination of a decrease in NO-dependent endothelial function and an increase in the overall synthesis of NO in the body is explained by the fact that rats with spontaneous hypertension are characterized by a simultaneous weakening of the activity and expression of the eNOS protein in the endothelium and high iNOS activity, which appears in these rats in vascular smooth muscle and macrophages at the early hypertensive stage [14, 15]. Excess NO in smooth muscle suppresses eNOS activity and directly damages endothelial cells by inhibiting mitochondrial respiration and DNA synthesis [14]. As a result, the production of endothelial NO progressively decreases, which makes a major contribution to the development of endothelial dysfunction and an increase in blood pressure. Since iNOS produces NO in quantities several orders of magnitude higher than the production of NO eNOS, then under conditions of iNOS induction, changes in the level of NO in plasma reflect the intensity of NO synthesis precisely by the inducible NOS isoform, which normally absent in the vascular wall [16].

In the present experiments, nebivolol completely prevented NO hyperproduction in SHRSP after 5 weeks of administration, and this effect persisted throughout the course of nebivolol treatment. The normalizing effect of metoprolol appeared much later and was less pronounced. This benefit of nebivolol appears to be due to its stimulatory effect on eNOS. It is well known that a moderate increase in NO levels in the body, regardless of the source of this factor, effectively prevents NO overproduction and associated damage. This effect may be based on a negative feedback mechanism, i.e. limitation of iNOS activity by NO itself, and NO-dependent induction of secondary protective factors - antioxidants, stress proteins, etc. [17, 18, 19]. This mechanism apparently also mediates the antihypertensive effect of non-pharmacological physical factors that stimulate gene expression and the activity of the eNOS enzyme - for example, adaptation to hypoxia [20], adaptation to physical activity [21], etc.

In our experiments, in SHRSP, as blood pressure increased, an increase in the structural component of peripheral vascular resistance was observed. Endothelial NO is considered one of the leading factors in maintaining the normal structure of the vascular wall, not only due to its powerful vasodilator effect, but also due to its antiproliferative effect, inhibition of platelet aggregation and leukocyte adhesion to the endothelium. Nebivo-lol, faster and more effectively than metoprolol, prevented an upward shift in the flow-perfusion pressure curve, which reflects the structural component of resistance, i.e. wall
thickness of peripheral resistive vessels. Indeed, it is the process of thickening of the vascular wall that is initiated during chronic inhibition of NOS, even in conditions of compensation for increased blood pressure and, therefore, is NO-dependent [22]. Therefore, stimulation of eNOS with nebivolol may prevent pathological vascular remodeling.

Clinical studies have shown that cardiac hypertrophy is reversible under the influence of b-blockers, in particular metoprolol, but this process occurs very slowly, and the effect quickly disappears after discontinuation of the drug [23, 24]. Studies on the preventive effect of b1-adrenergic blockers, as well as on the effect of stimulation of endogenous NO production on myocardial hypertrophy in hypertension, have not previously been conducted. Myocardial hypertrophy, which is naturally detected in the development of persistent hypertension, is the result of the interaction between chronic hemodynamic overload and non-hemodynamic factors, the most important of which is NO [25]. NO prevents cardiac hypertrophy due to hemodynamic unloading of the heart, reducing arterial tone and afterload, as well as due to venodilation, reducing preload. An additional contribution to the protective effect of NO against the development of hypertrophy is made by its antiproliferative effect [26].

We were able to prevent the increase in heart weight in SHRSP using nebivolol and metoprolol, although the effectiveness of these drugs varied. Myocardial hypertrophy was detected in SHRSP only at 15 weeks of age. Both β-blockers had no effect on normal rat heart weight. At the same time, the preventive effect of nebivolol turned out to be more pronounced than the effect of metoprolol, which may be due to the NO-stimulating effect of nebivolol.

In general, the data obtained in this study show that nebivolol is more effective than metoprolol in reducing blood pressure and vascular resistance in rats with experimental hypertension. Unlike metoprolol, nebivolol prevents the development of endothelial dysfunction. Finally, nebivolol is more effective than metoprolol in preventing remodeling of the vascular wall and heart.

In hypertension, the prognosis is determined by the degree of damage to target organs, the most important of which are the heart and blood vessels. Apparently, the ability of nebivolol to stimulate the synthesis of NO in the endothelium allows improving treatment results due to the additional vasoprotective and cardioprotective effects of this drug and, thereby, provides its significant advantages over the already classic metoprolol. In addition, according to clinical trial data, in terms of its efficacy and safety profile, nebivolol also has significant advantages over other b-blockers [27]. It can be assumed that further studies will reveal other properties of nebivolol associated with its positive effect on the synthesis of endothelial NO. But it is already obvious that this direction of antihypertensive therapy expands its capabilities and is promising.

Reference

6. MLA


