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SM Journal of Cardiology and Cardiovascular Diseases

Research Article

Choice of Beta-Adrenoblocker Depending on the Level of Nerve Growth Factor in Elderly Patients with Coronary Artery (CAD) Disease and Heart Failure with Reduced Ejection Fraction (HFrEF)

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Article Information

Received date: Jan 12, 2018
Accepted date: Feb 05, 2018
Published date: Feb 06, 2018

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Keywords Chronic heart failure, Norepinephrine, Nerve growth factor, Beta blocker, Local inervation of the myocardium

Abstract

The Nerve Growth Factor (NGF) is a marker of the state of local sympathetic innervation of the myocardium. Patients with heart failure have changes in local sympathetic innervation, which must be considered when selecting therapy.

The purpose of the work: To study the effectiveness of the carvedilol (β-adrenoblocker (β-AB) with alpha-blocking and antioxidant effects) and the nebivolol (drug with NO-synthesizing function) in comparison with the bisoprolol (selective β-AB without additional properties) on the functional state of the myocardium, duration of ischemia, frequency of cardiac rhythm disturbances and quality of life in elderly patients with Coronary Heart Disease (CAD) and Heart Failure with reduced Ejection Fraction (HFrEF) and different levels of NGF.

Materials and methods: Was study 72 patients at the age of 69.4 ± 7.5 years with a diagnosis of CAD: angina pectoris, II - III functional class, HFrEF II-III class NYHA. Control group - 30 patients at the age of 68.7 ± 6.5 years with a diagnosis of CAD angina pectoris, II - III functional class without HF. Depending on the level of NGF, patients were divided into 2 groups: 1 group -26 patients with a level of NGF greater than the control group (average level NGF =101.8 ± 8.2 ng/ml). 2 group consisted of 46 patients whose level of NGF was sharply reduced compared to the first and control groups (average level NGF = 17.9 ± 3.2 ng/ml). Average level NGF in control group – 65.3 ± 4.1 ng/ml. Each random sample group was divided into 2 subgroups (A and B). Patients in group 1A in addition to basic therapy received nebivolol, patients in the subgroup 2A-carvedilol. Patients in subgroups B (1B and 2B) were assigned bisoprolol as a research drug.

Results: It has been shown that the β-AR blockade promotes stabilization of the NGF in patients with CAD and HFrEF, but the use of selective β-AB bisoprolol does not restore the level of neurotrophin in individuals with significant deviations in the level of NGF. At the same time, the efficacy of β-AB with additional properties (carvedilol and nebivolol), according to the theoretical preconditions, resulted in the expected stabilization of the level of NGF and reduction of norepinephrine levels and a significant reduction in the manifestations of pathological remodeling of the left heart, reduce the duration of myocardial ischemia, the number of cardiac arrhythmias (ventricular and supraventricular extrasystoles), and quality of life in elderly patients with CAD and HFrEF.

Conclusions: The obtained data indicate that the level of NGF is a sensitive indicator for a differentiated choice of beta-blockers in patients with CAD and HFrEF. According to the results, carvedilol may be recommended as a drug of choice for patients with an NGF below 20 ng/ml; patients with a level of NGF greater than 100 ng/ml - nebivolol.

Introduction

The search for new markers to optimize and individualize the choice of therapy for patients with CHF is an urgent task of modern cardiology. In this context, the newest data concerning to diagnostic and prognostic significance of the Nerve Growth Factor (NGF), as a marker for the local sympathetic innervation of the myocardium [1], are of great importance. Today, it is known that the NGF acts as the main regulator of the density of myocardial sympathetic neurons, whose functioning is closely related to the level of tissue norepinephrine and the functional state of beta-1 adrenergic receptors (β1-AR) [2,3]. It is local innervation, which is determined by the state of these indicators, carries out the processes of regulation of the vital activity of the heart muscle and determines the degree and rate of morphofunctional changes in the myocardium in the pathological process [4].

According to literary data, the level of the NGF has proven prognostic value for assessing the risk of developing early adverse events in patients with ischemic cardiomyopathy. Studies have shown that in the late period of chronic heart failure (CHF) tissue reserves of this neurotrophin may be exhausted, which is a manifestation of desensitization of the myocardium and the cause of rapid development and progress of CHF [4,5].

At the same time, the increase level of the NGF correlates with the excessive growth of sympathetic fibers in the myocardium, which leads to the inhomogeneity of the innervation of the myocardium and creates preconditions for the development of ventricular violations of the cardiac rhythm [6].

Given this, regulation of the level of the NGF and the search for possible medication methods to influence this indicator can be important for the treatment of this pathology.

Today, known theoretical ways to influence the level of NGF: the blockade of alpha-1 adrenergic receptors, decreased activity of peroxidation of lipids in the myocardium contributes to the increase of the level of neurotrophin. The reduction of the level of endothelin-1 and the severity of local inflammatory reactions can be attributed to the therapeutic possibilities of reducing the level of the NGF [7,8].

Considering that the main class of drugs for reducing the pathological effects of the sympathoadrenal system on the myocardium is beta-adrenergic blockers (β-AB), the recommended conditions for the treatment of patients with CHF in this class for patients with low levels of NGF are the theoretical preconditions for selecting β-AB with proven alpha-blocking and antioxidant effect of carvedilol. For patients with high levels of NGF, a choice of drugs may be β-AB with endothelial-protective properties of nebivolol.

Materials and Methods

The study 72 patients at the age of 69.4 ± 7.5 years with a diagnosis of CAD: angina pectoris, II - III functional class, HFrEF II-III class NYHA. Control group - 30 patients at the age of 68.7 ± 6.5 years with a diagnosis of CAD angina pectoris, II - III functional class without HF.

Patients in the main group received standard therapy according to guidelines for the treatment of CHF (2016), including an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker, mineralocorticoid receptor antagonists.

Depending on the level of NGF, patients were divided into 2 groups: 1 group -26 patients with a level of NGF greater than the control group (average level NGF =101.8 ± 8.2 ng/ml). 2 group consisted of 46 patients whose level of NGF was sharply reduced compared to the first and control groups (average level NGF = 17.9 ± 3.2 ng/ml). Average level NGF in control group – 65.3 ± 4.1 ng/ml. Each random sample group was divided into 2 subgroups (A and B). Patients in group 1A in addition to basic therapy received nebivolol, patients in the subgroup 2A-carvedilol. Patients in subgroups B (1B and 2B) were assigned bisoprolol as a research drug.

β-AB were prescribed by titration of doses to the maximum tolerated: (the average daily dose of carvedilol in the groups was 23 ± 2.5 mg; nebivolol - 9.5 ± 1.5; the average daily dose of bisoprolol in the groups was 7.5 ± 1.5 mg). Duration of follow up after a background examination of patients - 6 months.

Table 1: The level of NGF in the compared groups after therapy with β-AB.

Group Parameter	Control	Group I		Group II	
		A	B	A	B
NGF ng/ml	56.3± 4.2	49.1 ± 3.9	91.3 ± 4.2*	48.7 ± 2.1	33.8 ± 2.3*

Fn: * - P value <0.05 when compared in subgroups A and B.

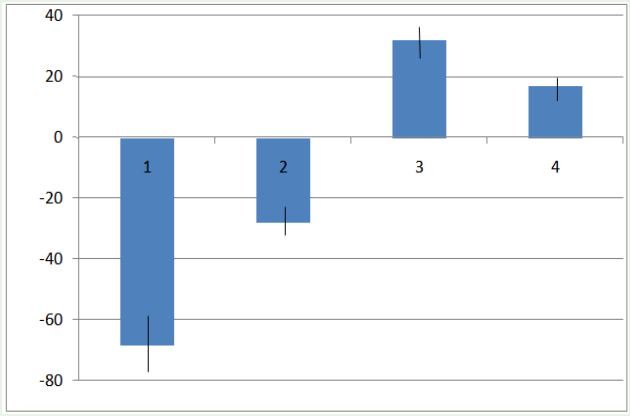

Figure 1: Dynamics of the level of NGF under therapy of β-AB.
Fn: 1- group 1A; 2- group 1B; 3-group 2A; 4-group 2B.

All patients at the stage of the primary examination and after 6 months of observation performed electrocardiography in 12 leads in rest, a daily Holter monitoring of the ECG on the device "DP-03250B" firm Solveig, echocardiography was performed using two-dimensional Echocardiography on the device "Khario SSA - 660a "Toshiba" firms. Determined the level of nerve growth factor by the method of immunoassay in serum samples using Human Beta - NGF ELISA Kit. Determined the level of norepinephrine by the method of immunoassay in blood plasma samples using "Noradrenalin (Norepinephrine) ELISA". The clinical evaluation was performed using a six minute walk test and Minnesota Living with Heart Failure Questionnaire (MLHFQ). Statistical data processing was carried out using the Statistica-10.0 program.

Results

The results of the study indicate that the β-AR blockade promotes stabilization of the NGF in patients with advanced CAD, but the use of selective β-AB bisoprolol does not lead to stabilization of the level of neurotrophin in subjects with significant deviations in the control-level (Table 1).

At the same time, the efficacy of β-AB with additional properties (carvedilol and nebivolol), according to the theoretical preconditions, led to the expected stabilization of the level of the NGF within the control group's indicator (Figure 1). According to the data obtained, the level of NGF in the groups treated with carvedilol and nebivolol after treatment was not different from that in the control group.

Together with the normalization of the level of NGF under the influence of β-AB, there was a decrease in the level of norepinephrine, indicating not only the local, but also the systemic effect of beta-blockers on the level of activity of the sympathe-adrenal system in patients with CAD and HFrEF (Table 2, Figure 2).

Table 2: Norepinephrine levels after treatment β-AB in compared groups.

Group Parameter	Control	Group I		Group II	
		A	B	A	B
NE ng/ml	567.2 ± 17.1	1085.4 ± 22.1	880.5 ± 36.4*	896.7 ± 21.2	841.6 ± 34.3*

Fn: * - P value <0.05 when compared in subgroups A and B.

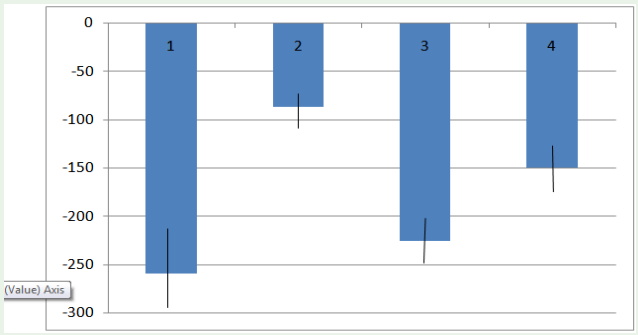

Figure 2: Dynamics of the level of NA under the influence of therapy with β-AB.

Fn: 1- group 1A; 2- group 1B; 3- group 2A; 4- group 2B.

Also, beta-adrenergic blocking therapy reduced pathological myocardial remodeling. On the background of treatment with drugs, there was a decrease in the size of the left atrium and the left ventricle, increase left ventricular ejection fraction (LVEF). LVEF after treatment with carvedilol increased from 36.3±4.8% to 48.6±3.9% (P < 0.05), after treatment with nebivolol increased from 48.7±2.5 % to 56.3±3.1 % (P < 0.05). LV end-systolic volume index, after treatment with carvedilol decrease from 45.8±7.2 to 26.6±5.4 mL/m^2 (P < 0.05), after treatment with nebivolol decrease from 27.8±5.7 to 22.4±3.4 mL/m^2 (P < 0.05), LV end-diastolic volume index, after treatment with carvedilol decrease from 73.7±8.4 to 51.2±6.1 mL/m^2 (P < 0.05), after treatment with nebivolol decrease from 68.4±5.3 to 49.2±4.8 mL/m^2 (P < 0,05). Diameter of LA, after treatment with carvedilol decrease from 4.8±0.3 to 4.3±0.2 cm, after treatment with nebivolol decrease from 4.43±0.3 to 4.1±0.1 (P<0.05) cm (Table 3).

The dynamics of these indicators in groups with carvedilol and bisoprolol was significantly greater than in the group in which bisoprolol was used. This can be explained by the need to simultaneously with beta-adrenergic receptors, the effect on additional mechanisms regulating the level of the NGF (alpha-adrenergic receptors for carvedilol and reducing endothelin-1 for nebivolol). In favor of this conclusion, the results of the previously obtained data suggest that patients with insignificant deviations of the level of NGF from the control indicators, the effectiveness of bisoprolol did not differ from the effectiveness of alternative used β-AB [9].

The drugs used had a different effect on the duration of daily myocardial ischemia, the frequency of ventricular and supraventricular extrasystole (Table 4). According to the data of 24-hour ECG monitoring, under the influence of carvedilol and nebivolol was observed a greater anti-ischemic and antiarrhythmic effect, than under the influence of bisoprolol.

Duration of ischemia per day after treatment with carvedilol decrease from 10.3±0.6 to 3.5±0.3 min (P < 0.05), after treatment with nebivolol decrease from 12.7±1.1 to 4.8±0.3 min. Number of supraventricular extrasystoles after treatment with carvedilol decrease from 245.2±65.1 to 89.6±0.2 per day (P< 0,05); after treatment with nebivolol decrease from 3245.2±65,1 to 371.4±4.4 per day (P < 0.05). Number of ventricular extrasystoles after treatment with carvedilol decrease from 23.5±3,2 to 7.4±0.5 per hour (P< 0,05); after treatment

Table 3: Indicators of the morpho-functional status of the myocardium in the study groups under the therapy of β-AB therapy.

Group	Control		Group IA		Group IB		Group IIA		Group II B	
Echocardiographic parameter	Before treatment	After Treatment	Before Treatment	After Treatment	Before treatment	After treatment	Before Treatment	After Treatment	Before treatment	After treatment
Diameter LA. cm	3.9±0.3	3.8±0.2	4.43±0.3	4.1±0.1*	4.5±0.1	4.4±0.3	4.8±0.3	4.3±0.2	4.7±0.2	4.7±0.3
LV end-systolic volume index. mL/m^2	17.9±3.3	17.3±4.1	27.8±5.7	22.4±3.4*	25.9±4.4	24.7±3.2	45.8±7.2	26.6±5.4*	41.7±4.9	30.3±4.1
LV end-diastolic volyme index. mL/m^2	46.3±5.4	44.5±4.6	68.4±5.3	49.2±4.8*	59.9±3.6	53.3±5.7	73.7±8.4	51.2±6.1*	61.5±7.1	58.3±7.3
LVEF. %	59.3±4.1	61.6±3.1	48.7±2.5	56.3±3.1*	49.3±2.1	51.3±3.3	36.3±4.8	48.6±3.9*	35.7±4.4	38.7±3.4
LV mass index. g/m^2	97.8± 14.5	94.1± 15.8	122.8± 17.3	104.3± 9.2*	119.9± 17.5	114.3± 11.2	166.8± 14.3	121.7± 19.4*	155.1± 17.4	150.4± 15.8
s/.см/с	7.6±0.3	7.8±0.2	6.1±0.3	7.0±0.3*	6.4±0.2	6.5±0.3	5.2±0.3	6.5±0.2*	5.0±0.2	5.4±0.1
e/.см/с	6.3±0.2	6.1±0.2	5.3±0.4	5.7±0.2	5.7±0.2	5.5±0.2	4.2±0.5	6.0±0.6	5.3±0.2	5.5±0.2
a/.см/с	12.1±0.4	11.8±0.6	10.7±0.5	13.1±0.5	12.7±0.4	11.5±0.5	9.8±0.3	12.4±0.3	10.7±0.6	9.1±0.3
E/e/	7.5±0.3	7.0±0.4	14.2±0.7	9.1±0.3*	12.4±0.6	10.3±0.4	16.8±0.7	10.4±0.4*	15.3±0.5	13.8±0.7

Fn: *- P value <0.05 when comparing results in groups before and after treatment.

Table 4: Duration of myocardial ischemia and ventricular and supraventricular extrasystoles in the study groups under the influence of β-AB therapy.

Group	Control		Group IA		Group IB		Group IIA		Group II B	
Parameter	Before treatment	After Treatment	Before treatment	After Treatment	Before treatment	After treatment	Before Treatment	After Treatment	Before treatment	After treatment
Duration of ischemia per day. min.	2.5±0.2	2.2±0.1	12.7±1.1	4.8±0.3*	14.5±0.9	10.8±0.3	10.3±0.6	3.5±0.3*	10.7±0.7	8.9±0.7
SVE. per day	12.4±2.2	11.3±2.1	3245.2±65.1	371.4±4.4*	3111.7±58.1	2290.8±41.3*	245.2±65.1	89.6±0.2*	111.7±18.1	90.8±11.3
VE. per hour	3.7±0.2	3.3±0.6	63.5±3.2	12.1±0.3*	60.3±11.8	55.5±8.2	23.5±3.2	7.4±0.5*	60.3±11.8	55.5±8.2

Fn: *- P value <0.05 when comparing results in groups before and after treatment.

Table 5: Indicators of quality of life of the examined patients against the background of β-AB therapy.

Group	Control		Group IA		Group IB		Group IIA		Group II B	
Parameter	Before Treatment	After Treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
six minute walk test. m	256.7±9.4	367.3±14.1	181.6 ±11.7	257.2 ±13.8*	187.4±9.3	198.5±7.4	186.4 ±7.3	252.2 ± 8.4*	177.7±12.8	209.4±7.8
MLHFQ	55.3±4.6	56.1±4.1	69.4 ± 2.4	54.2± 4.1*	65.3±7.1	60.3±6.2	68.5 ± 3.4	55.2± 3.2*	69.7±8.7	60.8±10.2

Fn: *- P value <0.05 when comparing results in groups before and after treatment.

with nebivolol decrease from 63.5±3.2 to 12.1±0,3 per hour (P < 0,05). You must note that an elevated level of NGF is associated with a high incidence of cardiac arrhythmias.

Obviously, the complex positive effect of the chosen therapy contributed to the improvement of the clinical status of the patients included in the study. When assessing a six minute walk test and MLHFQ, in patients with HFrEF, a decrease in the number of points indicating the presence of symptoms of heart failure and an increase in the distance passing by the patient in 6 minutes was determined. Distance in the test with six minutes of walking in the group, with carvedilol before treatment was 186.4 ±7.3 m, after treatment 252.2 ± 8.4 m (P<0.05). In the group with nebiwolol – 181.6 ±11.7 m and 257.2 ±13.8 m (P<0.05) (Table 5).

The obtained data indicate that the level of NGF is a sensitive indicator for a differentiated choice of beta-blockers in patients with HFrEF. According to the results, carvedilol may be recommended as a drug of choice for patients with an NGF below 17.9 ± 3.2 ng/ml; for patients with a level of NGF greater than 101.8 ± 8.2 ng/ml - nebivolol.

Discussion

According to generally accepted ideas, the systemic chronic hyperactivation of the Sympathoadrenal System (SAS) plays a key role in the development and progression of cardiovascular disease and its complications [10]. It is proved that excess catecholamines have a direct toxic effect on the myocardium leads to excessive stimulation of the receptor apparatus of the myocardium, unreasonable increase in energy consumption, vasoconstriction, delayed sodium and water in the body, increased postnal load on the left ventricle, impaired perfusion of organs and tissues, and development of complications [10]. At the same time, the pathogenetic role of SAS is not limited to systemic effects. Equally important, however, much less studied is the state of local innervation of the myocardium [11,12].

The local innervation, which is determined by the level of tissue norepinephrine, the density of neurons, the state of the adrenergic receptor apparatus, regulates the local processes of vital activity of the heart muscle and determines the degree and rate of development of morpho-functional changes in the myocardium during the pathological process [13].

It should be noted that diagnostic approaches to assessing the state of local myocardial innervation cannot be based on determining the plasma level of catecholamines, because a considerable amount of clinical and experimental studies show the inconsistency of systemic and local sympathetic regulation, primarily with the development of HF.

In studies, it was shown that prolonged toxic hypersympathicotonia leads to a decrease in the density and sensitivity of beta-adrenergic receptors [9] depletion of local tissue norepinephrine tissues by decreasing the level of nerve growth factor. This leads to a pathological decrease in neuronal density in the development of myocardial desensitis [14] and is the immediate cause of the rapid development and progression of HF [15].

Therefore, the evaluation of local sympathetic innervation of the myocardium is important for assessing the risk of development and prognosis of HF in patients with CAD. Unfortunately, there are no standardized methods for assessing this phenomenon today. The literature describes the diagnostic capabilities of assessing the level of tissue norepinephrine, functional activity and density of the beta receptor apparatus [16]. However, in recent years, more attention has been paid to determining the level of the NGF as the main regulator of myocardial neuronal density, the functioning of which is closely related to the level of tissue norepinephrine and the functional state of beta 1-adrenergic receptors [1,7]. According to the literature, the level of the NGF has been shown to be predictive in assessing the risk of developing early adverse events in patients with ischemic cardiomyopathy [5,8].

In earlier studies we have shown that a low level of NGF in patients with heart failure is associated with low contractility of the myocardium (LVEF <30%), large cavity size and left ventricular hypertrophy [17]. A significant increase in the NFR level was associated with the presence of frequent ventricular extrasystole [18]. The data obtained by us agree with the results of other authors [6].

All the data presented indicate the need to normalize the level of NGF to obtain good results in the treatment of patients with HF. The results of experimental studies show that the normalization of the level of NGF in model of HF myocardium leads to the restoration of the density of sympathetic fibers in the myocardium and activates the processes of regeneration of cardiomyocytes [11,12,19]. Taking into account that such results are obtained on experimental models, the shown possibility of influence on the level of NGF by drugs that are included in the protocols of CHF treatment is very important.

No less important result of the work is the conclusion that it is necessary to use beta-adrenoblockers with additional properties in patients with significant deviations in the level of NGF. This conclusion is consistent with data on the negative effect of beta-adrenoblockers without additional properties on the state of local sympathetic innervation of the myocardium [20]. Therefore, the proposed differential approach to the choice of beta-adrenoblockers for the treatment of patients with CHF, depending on the level of NGF can have a large clinical application.

Conclusions

1. Level NGF may be a criterion for choosing a beta blocker for patients with a CAD and HFrEF. In order to restore the level of the NGF within the control, the use of β-AB with additional

properties is necessary: for patients with an NGF below 17.9 ± 3.2 ng/ml may be recommended carvedilol; for patients with a level of NGF greater than 101.8 ± 8.2 ng/ml - nebivolol.

2. Normalization of the level of the NGF promotes the reduction of pathological modeling of the left ventricle, reduction of the duration of the daily myocardial ischemia, and the frequency of cardiac arrhythmias.

3. The clinical consequence of the normalization of the level of NGF is the improvement of the quality of life of elderly patients with IHD and HFrEF.

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