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Features antihypertensive therapy in patients with essential hypertension based vegetative heart rate regulation

Gahramanova S.M.[1], Bakhshaliyev A.B.[1]

In recent years, the growing interest of researchers to study the state of the autonomic nervous system in EH, which was made possible thanks to the introduction into clinical practice of noninvasive examination of the heart rate variability (HRV) as autonomic dysfunction in the form of reducing the activity of parasympathetic effects, is associated with increased risk of cardiovascular morbidity and mortality [1,2,5]. HRV can be used to quantify and assess the effects of antihypertensive drugs on the autonomic nervous system. Known in the literature data on the effect of angiotensin converting enzyme inhibitors, angiotensin-2 receptor antagonists, calcium antagonists, beta-blockers on heart rate variability [2,4]. But there are no data on the use of antihypertensive drugs with the type of autonomic regulation. With HRV analysis can be carried out individual selection of therapy to achieve a favorable simpato-vaqal balance

Keywords: hypertension, heart rate variation, antihypertensive therapy

Essential hypertension (EH) is one of the most common diseases of the internal organs. Elevated levels of blood pressure in 50% of cases is the direct cause of death from stroke and coronary heart disease. Despite progress in recent years, advances in the prevention and treatment of cardiovascular disease, the effectiveness of the treatment of essential hypertension in different countries ranging from 2.5% to 27.4% [10].

In recent years, the growing interest of researchers to study the state of the autonomic nervous system in EH, which was made possible thanks to the introduction into clinical practice of noninvasive examination of the heart rate variability (HRV) as autonomic dysfunction in the form of reducing the activity of parasympathetic effects, is associated with increased risk of cardiovascular morbidity and mortality [1,2,5]. HRV can be used to quantify and assess the effects of antihypertensive drugs on the autonomic nervous system. Known in the literature data on the effect of

Yazışma üçün əlaqə:
Gahramanova S.M.[1], Bakhshaliyev A.B.[1]
1 Scientific-Research Institute of Cardiology named after acad. J.Abdullayev, Azerbaijan Baku
Email: sonaxanum@mail.ru

angiotensin converting enzyme inhibitors, angiotensin-2 receptor antagonists, calcium antagonists, beta-blockers on heart rate variability [2,4]. But there are no data on the use of antihypertensive drugs with the type of autonomic regulation. With HRV analysis can be carried out individual selection of therapy to achieve a favorable simpato-vaqal balance The purpose of the study:
Use the time and spectral analysis of heart rate variability to optimize the selection of antihypertensive therapy based on the autonomic regulation of heart rhythm.
Material and Methods.

The results of clinical and instrumental study of 142 patients with essential hypertension (EH) I-II stage hypertension (HT) 1-3 degrees in accordance with the recommendations of the Joint National Committee on Prevention, Recognition, Evaluation, and Treatment of High Blood Pressure (JNC, USA) in 2003, the European Society of Hypertension (ESH) / European Society of Cardiology (ESC) 2007. For the diagnosis of all patients underwent a thorough physical examination with laboratory and imaging studies.
For the study of HRV in patients with EH used the method of Holter ECG monitoring using noninvasive system "ESGproHolter" (Germany). HRV analysis methodology consistent standards of measurement, physiological interpretation and clinical use, to develop a working group of the European Society of Cardiology and the North American Society of pacing and electrophysiology (1996) [8].
Our approach to pharmacotherapy been the need to highlight individual clinical and pathogenetic types of EH based on data on the autonomic regulation of heart rate, obtained by analysis of heart rate variability. Vagotonia at rest and / or a reduced activation of the sympathetic nervous system during active orthostatic test 41 patients (21 men and 20 women with the first degree of hypertension was observed in 33, second degree - in 8 patients) was given a prolonged slow calcium channel blocker amlodipine (normodipin, Gedeon Richter, Hungary) with titrated from 5 to 10 mg every 2 weeks (mean dose - 7,5 ± 0,09 mg) to achieve target levels of blood pressure (not higher than 140/90 mm Hg .) or optimal blood pressure reduction by 10-20% from baseline within 1 month. 17 patients (first subgroup), in which there was a decrease in blood pressure to target levels, continued treatment with individually dosed. 24 patients (second subgroup) with low blood pressure reduction to target levels, joined by a second treatment drug from the group of angiotensin converting enzyme (ACE) inhibitors - lisinopril (Diroton, Gedeon Richter, Hungary) titrated from 5 to 10 mg (in average - 8,9 ± 0,11 mg) every 2 weeks until the target level of blood pressure reduction. Repeated studies of heart rate variability were performed at 1 and 6 months. With the predominance of sympathetic tone at rest and / or in case of its excessive activation during an orthostatic test, used neurohumoral modulators of group ACEI and beta-blockers in combination with the diuretic indapamide (Arifon, Servier, France) in the standard dose of 12.5 mg. Thus, 51 patients (32 men and 19 women, including first degree hypertension was observed in 7, the second in 29 degree and third degree - in 15 patients) were allocated to ACE inhibitors - lisinopril (Diroton, Gedeon Richter, Hungary) with indapamide with titration of the first from 5 to 10 mg (day average 9,6 ± 0,12 mg) every 2 weeks until the desired effect . 23 patients have reduced blood pressure to target levels, continued treatment with individually selected doses. 28 patients with low blood pressure reduction to the target level, attached to the treatment of Bisoprolol (Concor, Novartis,

Sweden) with a dose titration of 5 to 10 mg (mean 7,7 ± 0,31 mg) every 2 weeks until the target BP . Repeated studies of HRV was performed at 1 and 6 months of the study. 50 patients (25 men and 25 women, including first degree hypertension occurred in 5, second degree AG - in 24, third degree of hypertension - in 21 patients) were allocated to bisoprolol (Concor, Novartis, Sweden) with indapamide with titration of the first from 5 to 10 mg (mean dose of 9,7 ± 0,31 mg) every 2 weeks until the target BP. 24 patients, who had managed to sufficiently reduce blood pressure, continued treatment with drugs in appropriate doses. 26 patients failed to reduce blood pressure to target levels, and therefore attached to their treatment amlodipine (normodipin, Gedeon Richter, Hungary) titrated from 5 to 10 mg (mean 8,9 ± 0,21 mg) every 2 weeks to achieve the desired effect. Repeated studies of HRV were also conducted at 1 and 6 months of treatment.

A statistical analysis of the results of research used a software package Statistica6, 0 firms StatSoft.Inc (USA). The data were presented as the number of observations (n), the mean trait (M), the minimum and maximum values of the attribute. In view of the asymmetric distribution of the null hypothesis test was performed using nonparametric U (Wilcoxon-Mann-Whitney test). As the threshold of statistical significance was assumed value p <0,05.

Results and Discussion.

Mean systolic and diastolic blood pressure (SBP and DBP) in patients with EH to amlodipine, were 152,4 ± 3,7 / 99,6 ± 0,9 mm Hg. By the end of one month of treatment, the average levels of blood pressure dropped an average of 132,5 ± 2,1 / 87,9 ± 1,1 mm Hg. Among the side effects in patients receiving amlodipine in 2 patients had headaches, in 4 - feeling of the heart, in 3 women have evolved not expressed swelling leg. However, these adverse effects were not severe and did not show a cause for discontinuation.

In our study, one month of the initial treatment of patients with vagotonic amlodipine did not lead to excessive sympathetic stimulation of the time parameters of HRV. Changes in the spectral parameters were as slight strengthening of humoral-metabolic effects on the heart rate of the manifestations of relative sympathic by significantly reducing parasympathetic effects without excessive sympathetic stimulation. For 6-month treatment with amlodipine is also no impairment of time and spectral (both sympathetic and parasympathetic) parameters of HRV.

To improve the effectiveness of treatment of 24 patients with EH, who for one month of therapy was not achieved target BP levels and a side effect of amlodipine treatment attached a second drug - lisinopril. Adding to lisinopril monotherapy with amlodipine resulted in efficient reduction of blood pressure and leveling of the side effects of amlodipine by eliminating relative sympathic and parasympathetic failure. However, the trend to an increase in humoral-metabolic effects found during one month amlodipine monotherapy, aggravated by prolonged 6-month combination therapy with amlodipine + lisinopril, possibly due to the ability of long-term treatment with lisinopril lead to accumulation of renin and secondary stimulation of the humoral system, which was confirmed and in several other studies with ACE inhibitors [3,6,7].

To study the effects of neurohumoral modulators on the autonomic regulation of heart rate in 51 patients with EH and sympathicotonia was appointed ACE inhibitors lisinopril in combination with indapamide to enhance the hypotensive effect. Mean levels of systolic and diastolic

blood pressure in patients before treatment were 170,2 ± 4,4 / 105,1 ± 0,8 mm Hg. By the end of one month of treatment, the average levels of blood pressure decreased, on average, up to 149,6 ± 3,2 / 92,2 ± 1,9 mm Hg. Among the side effects in patients receiving lisinopril + indapamide in 2 patients had dry cough, in 4 - headaches caused by insufficient blood pressure reduction. These side effects were not severe and did not show the reason for drug withdrawal.

In our study, changes in the time parameters of HRV against one month therapy with lisinopril + indapamide, is to improve HRV by a slight decline in the sympathetic and parasympathetic gain significant effects on heart rate.

Changes in the spectral HRV characterized decrease sympathetic tone to eliminate the signs of relative sympathicotonia. However, there was a trend to an increase in humoral activity against the background of relative parasympathicotonia.

Improve the time and spectral parameters of HRV identified for 1 month of therapy with, save, and the end of 6 months of treatment. However, a significant increase in activity of humoral systems took place only at the end of 6 months of therapy with what was probably connected with the so-called phenomenon of escaping the effect of ACE inhibitors, long-term use of which causes a compensatory increase in the concentration of renin in the blood and other components of the RAAS that are in the initial stage of its . Similar results were obtained in other studies [9,10,11]. To attempt to overcome this phenomenon is to use a combination of ACE inhibitors and beta-blockers, inhibits the synthesis of renin. Therefore, the treatment of 28 patients with insufficient efficacy of lisinopril the end of 1 month of therapy, joined by a third drug from the group of selective beta-blockers - bisoprolol. In our study, adherence bisoprolol to the double combination of lisinopril + indapamide than effectively reduce blood pressure to target levels, led to a significant improvement in the time parameters of HRV, mainly through increased parasympathetic activity. Changes in the spectral parameters of HRV in addition to treatment bisoprolol, characterized by normalization of humoral-metabolic activity against additional development sympatholytic and parasympathotonic effects.

To study the effect of different neurohormonal modulators HRV 50 patients with EH and the original sympathicotonia, was appointed a selective beta-blocker bisoprolol in combination with indapamide. With mean SBP and DBP in patients before treatment were 174,6 ± 3,2 / 109,2 ± 1,4 mm Hg. By the end of one month of treatment, the average levels of blood pressure dropped an average of 155,4 ± 2,9 / 95,4 ± 1,9 mmHg. Among the side effects during treatment with bisoprolol + indapamide 1 patient developed bronchospasm, in 4 - sinus bradycardia, which required a dose adjustment bisoprolol without discontinuation therapy.

In our study, at 1 and 6 months of treatment in patients with initial sympathicotonia bisoprolol + indapamide had improved the time parameters of HRV due to a significant increase in parasympathetic and a slight weakening of the sympathetic tone. Especially changes in the spectral parameters were characterized with marked decrease humoral activity and signs of relative sympathicotonia. Traced simultaneously eliminating peripheral parasympathetic failure with the development of severe parasympathicotonia.

In order to increase the effectiveness of therapy and leveling side effects of drugs to treat 26 patients in whom the end of 1 month failed to reduce blood pressure to target

levels, the treatment added a third drug from the group of calcium antagonists, long-acting dihydropyridine - amlodipine. In our work, adherence to the double combination of amlodipine + indapamide bisoprolol at 6 months of treatment, in addition to effective blood pressure reduction was not accompanied by deterioration of the time and spectral parameters of the humoral, the sympathetic and parasympathetic activity. The combined use of drugs contributed to the leveling of the side effects of bisoprolol in the form of sinus bradycardia due to elimination of peripheral sympathetic failure. Thus, the study of HRV at baseline and against him confirm the usefulness of the analysis of autonomic regulation of heart rate as a possible way to optimize pharmacotherapy patients with EH with clinical- pathogenetic positions.

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XÜLASƏ

Essential hipertoniyalı xəstələrdə ürək ritminin vegetativ idarə olunmasından asılı olaraq antihipertenziv terapiyanın xüsusiyyətləri

Qəhrəmanova S.M., Baxşəliyev A.B.
Akademik C.Abdullayev adına Elmi-Tədqiqat Kardiologiya İnstitutu

İşin məqsədi: Ürək ritminin dəyişkənliyinin (ÜRD) zaman və spektral analizlərini istifadə edərək ürək ritminin vegetativ idarə olunmasından asılı antihipertenziv terapiyanın seçiminin optamallaşdırılması. Tədqiqata I-II mərhələ, 1-3 dərəcəli 142 essensial hipertoniyalı (EH) xəstə daxil olmuşdur. ÜRD-nin öyrənilməsi ücün "ECG pro Holter" (Almaniya) sisteminin köməyi ilə elektrokardioqrammanın sutkaliq Holter monitorinqi metodundan istifadə olunmuşdur. Vaqotoniyali 41 xəstəyə ləng tipli kalsium kanallarının blokatoru qrupundan olan amlodipin təyin olunmuşdur. Simpatikotoniyalı 51 xəstəyə AÇF ingibitoru lizinopril, 50 xəstəyə isə β-adrenoblokator bisoprolol təyin edilmidir. Nəticədə amlodipinlə müalicə zamanı ÜRD-nin simpatik və parasimpatik parametrlərinin göstəriciləri pisləşməmişdir. Lizinopril ilə terapiya zamanı nisbi parasimpatikotoniya fonunda humoral aktivliyin artmasına meyillik yaranmıdır. Bisoprololla müalicə humoral aktivliyin və nisbi simpatikotoniya əlamətlərinin azalmasına, periferik parasimpatik çatışmazlığının aradan götürülməsinə və nəzərə çarpan dərəcədə parasimpatikotoniyanın inkaşafına gətirib çıxarırdı.

Açar sözlər: hipertenziya, ürək yığılmaları tezliyinin variasiyası, antihipertenziv terapiya.

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Details about the authors.
1. Scientific-Research Institute of Cardiology named after acad. J.Abdullayev, Azerbaijan Baku

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