ASSESSMENT OF THE VEGETATIVE STATUS AND DYNAMICS OF HEART RATE VARIABILITY OF PATIENTS WITH CHRONIC KIDNEY DISEASE UNDER THE INFLUENCE OF ANTIHYPERTENSIVE THERAPY

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In this paper the authors present information on the study of heart rate variability of patients with chronic kidney disease. Hypersympathicotonia is observed in patients with renal disease and hypertension. Arguments are given in favor of the use of angiotensin-converting enzyme. The issue of the place of beta-blockers is debated.

Keywords: chronic kidney disease, heart rate variability, angiotensin-converting enzyme.

In recent years, more attention has been given to identifying predictors of sudden death in patients with chronic kidney disease: glomerulonephritis, a heart rhythm disorder, the presence of concomitant coronary artery disease and hypertension. Monitoring of blood pressure and heart rate helps to clarify aspects of the pathogenesis of the disease, prescribe adequate treatment to nephrology patients and prevent complications of the cardio-vascular system.

This paper presents the results of a study of heart rate variability (HRV) in patients with chronic kidney disease of I-III stages: glomerulonephritis, the dynamics of these parameters under the influence of antihypertensive therapy, the appropriateness of the use of beta-blockers (nebivolol) and/or ACE inhibitors (perindopril). We have studied patients with chronic kidney disease (glomerulonephritis; hypertensive), who, unlike healthy ones, faced prevalence of sympathetic tone, accompanied by a temporary decrease in HRV. Thus, the daily value of SDNNi, characterizing the total HRV, was on average by 41.1% lower in the healthy group, in the passive period - by 94.23% during the active period - at 41.26 (p<0.001). Accurate daily measurement of the heart rate interval difference, rMSSD, was 42.64% lower in patients with hypertension than in those without, respectively rMSSD in the active period was lower by 42.33%, rMSSD in the passive period - by 53.23% (p<0.001).

The average value of pNN50 among three subgroups of patients was reduced by 70.45%, pNN50 during the active period - at 62.13% and pNN50 in the passive period - by 72.58% compared to the healthy group (p<0.001).

HF daily index reflecting the influence of the parasympathetic division of the ANS on cardiac activity was lower by an average of 41.42% as compared to healthy individuals, respectively HF during the active period was at 42.15% in the passive period - at 43.72%.

In contrast, the daily output was higher for low frequency spectrum night LF, reflecting the sympathetic influence on the heart rate: respectively, in average – at 14.64%, the active period – at 21.15%, in the passive period - 3.12% (p<0.001) as compared with the group of healthy.

In the main group sympathetic/parasympathetic balance offset was also observed in favor of the sympathetic division of the ANS, the rate of daily LF/HF was high erg by an average of 49.34%, i.e. patients with hypertension showed the predominance of sympathetic activity.

In a study of 17 patients in the control group receiving antihypertensive drug enalapril maleate 20mg twice a day, it was found out that its influence has improved baroreflex regulation of hemodynamics, reduced sympathetic activity.

When comparing the percentage of fluctuations of high, low and very low frequencies of patients in the control group we marked the decline in the percentage of slow-wave 1 - the first order with 16.72 ± 2.07 to 13.27 ± 2.12; slow waves of 2 order - with 51.18 ± 6.94 to 45.90 ± 6.46, increase in the proportion of tidal waves from 32.27 ± 6.77 to 40.81 ± 7.57 (Fig.1, Table 1).

Under the influence of enalapril maleate in the control group, there was a significant decrease in both systolic blood pressure by 26.08 mm Hg and diastolic – by 13.90 mm Hg (Table 2).

| Parameters | Before treatment | After treatment | p I-II |
|------------|-----------------|----------------|-------|
| LF M ± m, mc² | 1190±304 | 420±213 | p < 0,05 |
| VLF M ± m, mc² | 4698±1540 | 1212±616 | p < 0,05 |
| HF M ± m, mc² | 1416±323 | 769±299 | p < 0,05 |
Stable positive effect in hypertensive patients in the control group was accompanied by subjective improvement of a general state (decreasing intensity of the brain and anginal pain, memory improvement, decrease of the overall weakness etc.) and was confirmed by echocardiography (reduction of left ventricular hypertrophy in 48% of patients), electrocardiogram (the tendency to normalization of the ST segment in 51% of patients).

The decrease in sympathetic nervous system in patients with glomerulonephritis under the influence of ACE inhibitor treatment is a positive predictor in the progression of chronic kidney disease. Correction of autonomic imbalance with enalapril maleate is suitable both in the complex treatment of patients with chronic kidney disease and in the prevention of cardio-vascular complications in the rehabilitation of nephrology patients. There was a relation between the magnitude of blood pressure and weakening of baroreflex regulation with increased sympathetic influences (in patients with severe hypertension power VLF increases, the power of LF-components therein is low).

Under the influence of antihypertensive therapy along with antihypertensive effect there was a positive change of HRV. In the study group (n = 32) treated with perindopril reduction of clinical manifestations of the underlying disease, lowering blood pressure, the positive dynamics of the autonomic regulation of the cardiovascular system was observed (Table 3), namely the reduction of sympathetic activity (reduction of low-frequency power of the spectral components of heart rate - VLF from 51.64±13.98% to 35.38±11.56%) and an increase in parasympathetic activity (increased power of high-frequency components - HF from 28.67±9.54% to 31.34±9.54%). An effect on the baroreflex regulation is marked: the capacity of the midrange spectrum component has been increased - LF from 21.34±8.05% to 28.38±9.54%, p < 0.05.

In the group of patients (n = 34) treated with nebivolol reduction of the clinical manifestations of the underlying diseases was also observed; antihypertensive effect was received. According to cardiointervalography (Table 4) there was a decrease in sympathetic activity - VLF from 42.28±10.06% to 32.79±10.06%, p < 0.05, and an increase in parasympathetic activity - HF from 32.46±10.06% to 42.56±10.06%, p < 0.05. There was no effect on baroreflex regulation - LF (p > 0.1).

**Fig. 1. Percentage of LF, VLF, HF patients in the control group**

**Tab. 2**

Dynamics of changes in systolic and diastolic blood pressure in patients in the control group (n = 17) under the influence of enalapril maleate

| Kind of blood pressure | Before treatment | After treatment | p I-II |
|------------------------|-----------------|----------------|-------|
| Systolic               | 160.00±28.16    | 133.92±15.39  | p < 0.05 |
| Diastolic              | 93.70±13.22     | 79.80±7.70    | p < 0.05 |

**Tab. 3**

Dynamics of HRV in patients with chronic kidney disease (glomerulonephritis) who received ACE inhibitors, perindopril

| Index Cardiointervalographic | Chronic kidney disease: glomerulonephritis, perindopril | p |
|------------------------------|-------------------------------------------------------|---|
|                              | Before treatment (M±σ) | After treatment (M±σ) |     |
| LF,%                         | 21.34±8.05            | 28.38±9.54            | p < 0.05 |
| VLF,%                        | 51.64±13.98           | 35.38±11.56           | p < 0.05 |
| HF,%                         | 28.87±9.54            | 31.34±9.54            | p < 0.05 |
| Sympathetic- vagal index, LF/ HF | 0.74±0.07        | 0.86±0.07             | p < 0.05 |
At 6 months after the combined treatment (perindopril+nebivolol) alignment of the balance between sympathetic and parasympathetic divisions of the autonomic nervous system was observed.

This was observed in a statistically significant (p<0.001) increase of the time parameters of ANS: SDNNi daily in a group of perindopril+nebivolol has increased by 35.8% - more than in the control group (standard) - by 32.2%, SDNNi in active period - at 32.7%, in the control group at 28.3%, SDNNi in passive period - 36.23% (27.5%) (p<0.001). Daily SDNN in a group of perindopril+nebivolol has increased by 34.3% (control – 23.6%), SDNN during the active period has increased by 33.1% (control - 22.2%), SDNN in the passive period has increased by 19.3% (control - 11.8%). Other time parameters changed similarly: daily rMSSD has decreased by 54.5% (control - 39.8%), rMSSD in the active period has increased by 51.3% (control - 45.6%), rMSSD in the passive period has increased by 57.2% (control - 39.4%, p < 0.001).

Under the influence of antihypertensive therapy sympathetic-parasympathetic balance has returned to normal in most patients (decline by 34.45% in the group of perindopril+nebivolol; by 39.2% in the control group).

HF indicator, showing the effect of parasympathetic cardiac activity grew by 38.9%, in the control group - by 32.4%, the power spectrum of low frequencies, on the contrary, tended to lower: in the group with perindopril+nebivolol by 23.4%, in the control group - by 15.4%. No statistically significant differences between the groups of perindopril, nebivolol and perindopril+nebivolol were fixed, but the trend towards normalization in the perindopril+nebivolol group was more expressed in comparison with the groups of perindopril and control. The use of enalapril was positive changes observed in the HRV perindopril group (Figure 2).

It should be noted that the effectiveness of treatment of vasoregulatory disorders was higher in patients with chronic kidney disease at the stage I: glomerulonephritis. In patients with nephrotic form and pronounced chronic kidney disease at the stage III: glomerulonephritis, in 34.5% of cases it was failed to achieve correction of autonomic regulation. Thus, the research has revealed signs of autonomic dysfunction in patients with chronic kidney disease: glomerulonephritis with hypertension. Its incidence increases with the decrease in the glomerular filtration rate. Autonomic imbalance manifests by alterations in sympatho-vagal balance.

Nebivolol therapy provides positive changes observed in the HRV perindopril group (Figure 2). The use of enalapril was also positive changes observed in the HRV perindopril group.

Thus, the research has revealed signs of autonomic dysfunction in patients with chronic kidney disease: glomerulonephritis with hypertension. Its incidence increases with the decrease in the glomerular filtration rate. Autonomic imbalance manifests by alterations in sympatho-vagal balance. Nebivolol therapy provides positive changes observed in the HRV perindopril group (Figure 2). The use of enalapril was also positive changes observed in the HRV perindopril group.

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Tab. 4

### Dynamics of HRV in patients with chronic kidney disease (glomerulonephritis) who received ACE inhibitors, perindopril, nebivolol and perindopril+nebivolol

| Index Cardiointervalographic | CKD: glomerulonephritis, nebivolol (n = 26) | P |
|-----------------------------|-----------------------------------------|---|
|                             | Before treatment (M±σ) | After treatment (M±σ) |       |
| LF,%                        | 26,42±8,37                 | 25,78±8,42               | p > 0,1 |
| VLF,%                       | 42,28±10,06                | 32,79±10,06              | p < 0,05 |
| HF,%                        | 32,46±10,06                | 42,56±10,06              | p < 0,05 |
| Sympathetic-vagal index, LF/HF | 0,76±0,06                  | 0,60±0,04                | p < 0,05 |
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