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MODERN POSSIBILITIES OF RATIONAL RENOPROTECTION IN PATIENTS WITH HYPERTENSIVE DISEASE

Fushtei I.M., Chabanna O.S.*, Podsievakhina S.L.

Department of Therapy, Clinical Pharmacology and Endocrinology, State Institution "Zaporozhye Medical Academy of Postgraduate Education of Ministry of Health of Ukraine", Zaporozhye, Ukraine

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Abstract

The aim of the study was to determine the renoprotective effect of antihypertensive therapy and to develop differential approach within rational renoprotective strategy in hypertonic disease.

According to research protocol all patients without clinically significant kidney failure (107 persons with essential hypertension) were examined through clinical, laboratory and instrumental studies. Patients were divided into 5 groups according to the combinations of antihypertensive therapy (all patients during thiazide-like diuretic Indapamide in a dose of 1.5 mg were prescribed): 1 – angiotensin-converting-enzyme inhibitor, 2 – angiotensin-2 receptor antagonists, 3 – long-acting dihydropyridine calcium antagonists, 4 – beta-adrenergic blocking agents, 5 – imidazoline receptor agonists. After 12 weeks the studies showed that despite comparable antihypertensive effect of the therapy (according to both the data of office blood pressure and to the data of 24-hour blood pressure monitoring), groups were different in achieving renoprotective effect. The most pronounced certain positive dynamics of blood pressure under therapy was in III group. Although, maximally certainly significant reduction of urinary microprotein excretion level (of albuminuria – by 85.24% and of macroglobulinuria – by 67.13%), in parallel with normalization of intrarenal hemodynamics (the increase of renal functional reserve in 2.9 and 2.7 times and regress of interlobar branches of renal arteries resistance by 65.69% and 64.76% respectively) were recorded in I and II groups (χ^2=3.91, p=0.041 and $\chi^2$2=4.02, p=0.014). In the detection frequency of beta-2-microglobulin in most cases there also was a significant reduction in groups 1.2 and 5 (χ^2=13.86, p<0.01, χ^2=13.12, p<0.01 and χ^2=5.29, p=0.022). In such a way, the most certain renoprotective effect was noted in patients who received angiotensin-converting-enzyme inhibitors, angiotensin-2 receptor antagonists and imidazoline receptor antagonists during diuretic therapy.

Keywords: *hypertension, markers of nephropathy, antihypertensive therapy, renoprotection.*

Introduction

To date, despite the long-term period of kidney failure research in patients with essential hypertension (EH) the patterns of nephropathy development, the assessment of renal dysfunction status and also researches of diagnostic significance of markers of nephropathy (NP), the range of issues concerning the adequacy of renoprotection during antihypertensive therapy still have not been adequately investigated [*Schmierder R, 2010; Svischenko E, 2014; Chikhladze N, Chazova I, 2015*]. It also should be noted that the variability of researchers' beliefs concerning the pathogenesis of NP in EH was reflected in various reviews of treatment strategies and assessment of renotrophic role of the therapy [*Levey A et al., 2011; Ivanov D, 2016*] It should be denoted that the research of autoregulation mechanisms of normal perfusion pressure and glomerular filtrate rate (GFR) control with the assessment of renoprotective effect in EH in conditions of arterial hypertension (AH) is as much important as data about the effect of modern hypotensive drugs on the state of intrarenal haemodynamics, since medication decrease of arterial pressure (AP) against the progressive decrease of renal blood flow and increase of renal vessels resistance

Address for Correspondence:
Olena S. Chabanna, PhD, assistant
232|60 Sobornyi avenue, Zaporozhye 69005, Ukraine
Tel.: (+380953928580)
E-mail: ek325482@gmail.com

can potentiate the dysfunction of autoregulation of renal blood flow processes and changes of GFR [*Sirenko Iu, 2008*] . Since the medication decrease of arterial pressure (AP) against the progressive decrease of renal blood flow and increase of renal vessels resistance can exacerbate the dysfunction of intrarenal haemodynamics and change GFR, which is a very adverse factor, especially in aged patients and in patients with kidney dysfunction [*Dziak G et al., 2009; Mischenko L et al., 2012; 2013 ESH/ESC Guidelines*]. Moreover, kidney dysfunction in NP in patients with EH can prevent to the decrease of filtration fraction, which affects pharmacokinetics of medicine, which have kidney elimination or preferentially kidney elimination [*Zagorodnyi M, 2017*]. So, in EH treatment it's preferably to use drugs that reduce selectively renal vessel resistance and in this way don't allow the reduction of glomerular filtration in AP normalization [*Vander A, 2000; Dudar I, 2013*].

Among existing at date classes of antihypertensive medication for the therapist it's sometimes hard to figure, which of the drugs, in addition to decrease and normalization of AP, are better at improving disordered renal haemodynamics, decreasing proteinuria, hypertrophy and hyperplasia of gromerular cells, slowing down the progression of hypertensive nephrosclerosis, so have certain renoprotective properties. Literature data concerning the effect of antihypertensive therapy on hypertensive angionephrosclerosis progressing in patients with mild AH in EH are sometimes contradictory, fragmentary and deal with combined pathology of diabetes and AH within assessment of nephroprotective potential. And usually this way are tested persons predisposed to faster progressing of chronic kidney disease (black people and aged patients) [*Svischenko E, 2015*].

Accordingly the aim of the study was to determine the renoprotective effect of different types of antihypertensive therapy and to develop differential approach within rational renoprotective strategy in essential hypertension.

Material and methods

In total 107 patients were examined with EH of both sexes aged 45-71 (the average age 50.5±0.097; the proportion of men and women is 48.84/51.16%), II stage of the disease with the AH level of I-III stage, various cardiovascular risk, without adequate therapy and chronic kidney diseases/kidney vessels affects. All patients gave their consent to participate in the study and it was endorsed by Institutional Committee on Bioethics and complies with the principles, set out in Declaration of Helsinki (Br. Med. J. 1964; p. 177), with the following additions. The study results were assessed initially and after 12 weeks of the therapy.

The 24-hour ambulatory AP monitoring was made with the help of the device "CARDIOTENS" ("Meditech", Hungary) under the standard protocol [*Dziak G et al., 2005*]. The average level of systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) and pulse arterial pressure (PAP), mean frequency of heart contractions (FHC), variability of SAP, DAP and FHC was analyzed within 24 hours, at day time and at night time. Pressure loads were assessed according to pressure time index (PTI) and pressure area index (PAI). Variability of AP at wake and sleep period was determined according to variability index. The diurnal index (DI) was determined and there were outlined four standard types of AP diurnal profile: "dipper" DI=10-20%; "non-dipper" DI=0-10%; "night-peaker" DI<10% and "over-dipper" in DI >20%.

The level of albumin excretion (Lot 5MA61307, 5MA72232) and Beta-2 microglobulin (MG) (Lot 5BM70418, 5BM71922) with urine was examined through immunoenzyme method using the kits by ORGenTecGmbH, (Germany) according to the attached instructions. There was also calculated a glomerular filtration index, which reflects the mean concentration of albumin in gromerular ultrafiltrate, through the formula $P\chi^2V/GFR$, where P – is a concentration of egested albumin with urine (mg/l); minute diuresis (*ml/min*); GFR – glomerular filtrate rate (ml/min) [*Chuba L, Vinnichenko L, 2008*]. There was the ratio of urine albumin-to-creatinine calculated. For the semi-quantitative express-assessment of albumin excretion rate (Microalbuminuria) with urine were used original reagent indicative test-stripes – stripe-test (Combur9Test® D, RocheDiagnosticsGmbH (Germany).

The condition of renal haemodynamics was studied in recumbent position on the equipment "SonolineVersaPlus" (SIEMENS, Germany) with the application of color Doppler mapping and pulse wave Doppler with curvilinear transducer [*Noble V, Brown D, 2004; Mankovskiy B, Ivanov D; 2010*]. Blood flow in renal arteries was exam-

ined on the level of common trunk of segmental and interlobar branches of renal arteries (SBRA and ILBRA) in spectral Doppler mode, assessing peak systolic (V_{max}), end-diastolic (V_{min}) and time-averaged (Vmean) blood flow speed. The calculations of vascular resistance of renal vessels (PI and RI) were made automatically by dopplerographic curve-fitting through formulas: GFR was calculated through the formula Cocroft-Gault and Modification of Diet in Renal Disease (MDRD) [*Bakris G, 2010*].

The assessment of renal functional reserve, which is the marker of intraglomerular hyperfiltration and hypertension, was made through modified method, using extraction ratio indices of endogenic creatinine before and 2 hours after oral protein load in conditions of adequate water schedule [*Karpov R et al., 1999*].

In studying of vasorefulative brachial artery function (method of Celermajer D.S. (1992)) the diameter changes, blood flow speed initially was assessed, in conditions of assaying with reactive hyperemia (temporary suprasystolic arterial occlusion by tonometer cuff) and after sublingual administration of 1 *mg* of nitroglycerin [*Balakhonova T et al., 1998*].

Echoscopy of brachial artery with imaging of its internal diameter was realized in the middle third of the arm. The record of echograms in B-mode and spectrum of blood flow with the help of pulse wave dopplerography was made on the equipment "SonolineVersaPlus" (SIEMENS, Germany). Also the total shift on endothelium (τ) and sensitivity coefficient of brachial artery to the shear stress were calculated. The change of internal diameter of brachial artery (the rate of endothelium-dependent vasodilation) was calculated as a diameter percentage, which was received after temporary compression, versus source value. Similar to occlusal assay, a calculation of endothelium-independent vasodilation rate was made after taking nitroglycerin (%); there was assessed the vasodilatation index proportionally to increase rate of endothelium-independent vasodilation to endothelium-dependent vasodilation increase rate, the rate of reactive hyperemia was calculated through the increase of blood flow speed after making a temporary occlusion in comparison with initial at rest.

Taking into account that antihypertensive monotherapy is effective more than in 30-40 % of patients with mild and medium AH forms [*Gavriliuk V, 2011*] and for reduction of AP to target level in 74% of patients with AH the combined antihypertensive therapy is required [*Sirenko Iu, Rekovets O, 2017b*], which has a range of advantages and that also now, the combined therapy with low doses of drugs, which has improved their effectiveness and safety as a monotherapy, is recommended on the first stage of treatment, we assessed nephroprotective effect of various combinations of antihypertensive drugs. In our work we used background therapy using thiazide-like diuretic Indapamide (1.5 *mg*) in parallel with adding such medicine: ACE inhibitor – Perindopril (subgroup 1, 24 persons), angiotensin-2 receptor antagonists (ARBs) – Valsartan (subgroup 2, 21 persons), long-acting dihydropyridine calcium antagonists (CCBs) – Amlodipin (subgroup 3, 23 persons), beta-adrenergic blocking agents (BAB) – Bisoprolol (subgroup 4, 20 persons) and imidazoline receptor agonists (IRA) – Moxonidine (subgroup 5, 19 persons). Groups were almost equitable in indicators, including such defining cardiovascular risk and possible predictors of the therapy effectiveness as the amount of smokers, the level of fibrinogen, the glycemia rate and the duration of the disease.

By analyzing treatment affecting test items in a case of normal variable distribution the procedure of unifactor repeated measures analysis of variance was used with the following usage of Newman-Keuls or Games-Howell taking into account most of the comparisons; in those cases when the distribution of variables studied didn't comply with normal law, there was used nonparametric repeated measures analysis of variance analogue – the Fridman criteria. In the case of amount of two groups the comparisons were made through the Wilcoxon criteria. In assessing the treatment effectiveness there was calculated a 95% confidence interval (95 % CI). The comparison of groups according to qualitative data and also studying the degree of incidence rate was made using the χ^2 criteria. The research results are processed using statistical package of license program "STATISTICA for Windows 6.0" (StatSoftInc., No AXXR712D833214FAN5), and also "SPSS 16.0", "Microsoft Excel 2003".

Results and discussion

The data analysis after 12 weeks allows to point out that at the end of the treatment on average among the groups of patients that received combined Indapamide treatment including agiotensin converting enzyme inhibitors it was noted the certain reduction of office value of SAP and DAP (by 29.41% and 23% respectively) with parallel reduction of mean and pulse arterial pressure by 26.4% and 35.71% respectively. While about 87.5% of patients in this group achieved target AP rates. On average among the groups according to office measurements, the best hypotensive effect was in III and V groups, while the reduction of SAP and DAP amounted to 37.91% and 31.74% for subgroup 3 and 35.85% and 34.35% for subgroup 3 respectively, and about 95% of patients have AP less than 140/90 *mm HG*. The similar dynamics occurred also regarding the mean haemodynamic AP. The sharpest reduction of pulse AP was shown in II and III groups (51.5 % and 53.33%).

Analyzing the parameter change of 24-hour blood pressure monitoring and class divisions in hypertensive effect under the treatment there was noted high, statistically significant effectiveness of CCBs either in terms of impact on average value SAP and DAP (-23.44% and -20.62%), or in terms of maximum values of AP without FHC (-3.77%), and therefore without signs of neurohumoral activity increase. This effect can be seen either upon median diurnal rates, or separate analysis of wake and sleep periods. The diagnostic and prognostic significance of average of medium and medium-integrated indexes is beyond doubt. Analyzing the reduction of these values in dynamics their specific character must be taken into account – they indicate the result of big amount of measurement results, not connected with anxious reaction of the patient. So, the reduction of average values of DAP even by 3-5 *mm HG* shows the certain antihypertensive effect. The positive moment in therapy with ARB (II group) as in office assessments was the certain reduction of pulse pressure after 12 weeks of treatment with its normalization in 20 patients, who initially have its level increased, as it has been proven that patients with PAP>50 *mm* AG have higher incidence of cardiovascular complications than organ failures [*Gavriliuk V, 2011*].

The assessment of "load indexes" – pressure time index and pressure area index in dynamics provide visualization of hypertensive effect development. Particularly sensitive is hypertension area index, because it constitutes double product of AP values by the time, during which this AP reduces a haemodynamic load on target organs. Foremost after 12 weeks there was a reduction of diurnal pressure time indexes of SAP and DAP by 87.01% and 85.95% in I group, by 92.15% and 89.75% in II group and by 90.43% and 92.15% in III group. In wake period there is also a high-grade dynamics (-82.11% and -67.94%) for V group with combined receiving of IRA. At night period the incidence of AP increase assessing APTI foremost was controlled by receive of CCB and ACE inhibitor (III and I groups). However, in high levels of AP this rate, approaching to 100%, loses its informativeness. In such cases APTI is calculated as area under influence curve of AP on time – APTI. The research of area index for SAP and DAP under the therapy showed that Foremost the hyperbaric load is decreased by using the combination of Indapamid with ACE inhibitor representor (-91.08% and -91.07%), CCB (95.27% and -92.17%) and IRA (-82.41% and -66.42%), what is more, in III group the rates after the treatment occurred equitable to the group of almost healthy persons.

In such a way it can be noted that the most positive AP dynamics under the therapy was in group "Indapamid+CCB" (according to 24-hour blood pressure monitoring (diurnal rates)) 95% CI for SAP reduction from 22.24 to 44.67 *mm HG*, for DAP 11.83-24.05 *mm HG*, for PAI SAP and PAI SAD the limits of CI were 87.7-817.59 and 38.68-152.38 *mm* AG per hour/24 hours respectively. At the same time the maximal reduction of urinary microprotein excretion level (of albuminuria – by 85.24% and of macroglobulinuria – by 67.13%) and also normalization of intrarenal haemodynamics (the increase of renal functional reserve in 2.9 times and reduction of in the pulse index of the interlobar branches of the renal arteries by 65.69%) was recorded in groups "Indapamide+ACE inhibitors" and "Indapamide+ARB".

As is known, the independent factor of target organs failure in patients with EH is a high variability of AP. The lack of negative impact of examined medicine on this rate meets one of the modern requirements to antihypertensive medicine. At the

end of the study foremost the reduction of variability SAP and DAP, is noted especially at daytime, in V group IRA (-20.5% and -27.96%, $p<0.05$) and IV group BAB (-23.12% and -23.81%, $p<0.05$). At nighttime there also was a reduction in variations of AP CCB (-20.94% and -28.24%). The similar positive dynamics of SAP and DAP variability also was noted both at daytime and nighttime for groups under usage ACE inhibitor and ARB. That happened because of normalization of AP variability in patients with its initially increased level and there is the positive moment in treatment of patients with EH. The differences in standard rate deviation from mean diurnal AP wasn't studied, since they include also physiological AP variability during 24 record hours.

The insufficient reduction of night AP and night hypertension in patients with AH is an adverse prognostic factor regardless of the AP level at nighttime and is associated with left ventricular myocardium mass index increase and early arterial sclerotic lesion of extracranial part of the carotid artery, being in close correlation with evidence of organ lesions in comparison with patients with normal reduction of AP during sleep. In our work there is noted the biggest positive drug influence on the phase structure of individual diurnal AP profile in I and III groups. By normalization of circadian rhythm and physiological AP variability was characterized also therapy with ARB (II group). Described results are the consequence of main feature of mechanism of CCB and ACE inhibitor action mechanism, which is reflected in gradual and smooth increase of hypertension effect without rough haemodynamic manifestations that actually had an impact on DA rates. It should be noted that initially in III group there were 15 patients with insufficient reduction of AP ("non-dipper" and "night-peaker") and one patient with excessive degree of AP reduction ("over-dipper"). After 12 weeks of the therapy 20 patients had normal degree of night AP reduction. Patients from I group with initially insufficient reduction of night AP had an increase of rates of DI SAP and DAP by 53.69% and 32.93% respectively. It's important that IRA (V group) almost didn't change initially normal AP varieties ("dipper").

Choosing antihypertensive therapy it's necessary to strive to achieve the normalization of AP both in the day and at night, and also taking into account the possibility of excessive hypotension at nighttime in certain patients [*Balakhonova T et al., 1998*]. In our research the biggest amount of patients after therapy with "over-dipper" profile was in II group (5 persons), and in IV group there was no excessive degree of AP reduction recorded after therapy.

Various studies show that the majority of cardiovascular accidents happens in morning hours when there is AP peak, the most studied characteristic of which is the value of morning AP increase [*Spinara J et al., 2014*]. In our work we pointed out the biggest reduction of mentioned rate for SAP and DAP under treatment in I group (by 26.04% and 22.03%) and III group (by 32.1% and 26.42%). However this rate is not an indicator of morning peak, especially in patients with "monotonous" rigid diurnal rhythm, who are part of studied patients. For this it's essential to calculate the speed of morning AP increase. The assessment of the influence of various therapy on rates of morning AP increase showed that IRA and CCB with Indapamide statistically certainly reduce the speed of morning AP increase both for SAP (by 56.68% and 42.22% respectively) and for DAP (by 45.2% and 67.35% respectively) that is very important for cardiovascular complications prevention. The rates of morning maximum of SAP and DAP certainly reduced after 12 weeks of treatment ($p<0.05$) and in groups with ACE inhibitor and ARB, which is a positive factor, because it's known that most heart attacks, strokes and oxymortia cases are recorded in the morning [*Sirenko Iu, Rekovets O, 2017a*]. Foremost there is noted prognosticate and logical reduction of FHC in all recording periods for IV group (-21.24%, -22.18% and -14.81% respectively diurnal, at daytime and nighttime).

As data about effects of EH and its possible treatment was accumulated and reflected, the most argued is a point of view about necessity of not only rigid AP control, but also not in a lesser extent of organprotective claims of used hypotensive drug assessment, which is very important in long-term hypotensive therapy [*Mischenko L et al., 2012*]. Taking this into account, it's important to assess therapeutic action of hypotensive treatment not only in terms of studying antihypertensive claims but also from the position of organ protection.

In our work we analyzed the nephroprotective activity of various therapy schemes. The indicant is the uncertain dynamics of GFR rate, calculated using both Cockroft-Gault and MDRD formula. The tendency to glomerular filtration according MDRD level reduction occurred more expressed in first 2 groups (by 22.99% and 18,04 % respectively) that is explained either by pharmacological effects of renin-angiotensin-aldosterone system (RAAS) at the beginning of the therapy (the pressure relieve in nephron glomerulus with perfusion pressure reduction) and absence of patients with renal failure or by the fact that in these subgroups there is recorded about 40% of patients with initial increased GFR or hyperfiltration (early nonspecific marker of kidney failure) [*Levey A et al., 2011*]. The reduction of initially increased GFR is a positive fact that is indicative of levelling of the main nonspecific nephrosclerosis developvent factor. It should be noted that the positive renotrophicy of the therapy including RAAS inhibitors is also approved by the fact that under receiving ACE inhibitor and ARB there was various-directional GFR dynamics, particularly in patients with EH with increased GFR rates they contribute to its normalization, and in reduced they restore the level of glomerular filtration. The tendency to GFR reduction also was noted under receiving BAB and IRA. Since patients with chronic kidney disease weren't included into the research, the plasma creatinine level in all patients was within normal rates either initially or after the therapy, however there was noted the tendency to the increase within I and II groups and within a range of up to 10% in relation to initial level.

Another thing that draws attention is a deep and certain increase of renal filtration reserve, which is evident in all 5 groups. The biggest differences were achieved in patients of groups of ACE inhibitor and ARB, where the increase amounted to 3.4 and 2.9 times respectively. The differences for III and V groups occurred 48.54% and 48.82% respectively. In group BAB there were no certain differences recorded. It should be noted that in addition to cumulative GFR increase within the group there is noted statistically significant reduction of number of patients with exhausted (with negative rates) renal reserve for I ($\chi2=6.02$, $p=0.014$) and II groups ($\chi2=4.82$, $p=0.028$).

At the same time in I and II groups in patients along with reduction of glomerular filtration index (by 50% and 35.29%) there was noted a certain reduction of the level of albumin excretion with urine by 48.91% and 53.49%. Yet, the rate of urinary albumin to creatinine ratio also showed similar dynamics (-56.88% and -64.94% in comparison to initial values), reaching the rates of practically healthy persons. The incidence of microalbuminuria also certainly increased till the end of 12 week treatment for I ($\chi2=3.91$, $p=0.041$) and II groups ($\chi2=4.02$, $p=0.014$), demonstrating class drug differences under the reduction of urine protein losses.

There is also a clear tendency to reduction of albuminuria and rate of urinary albumin to creatinine ratio in III and V groups (differences in comparison with initial level were 19.29%, -30.7% and -38.84% and -19.57% respectively $p<0.05$). Yet, the glomerular filtration index dynamics also occurred less evident only for group CCB (-21.74%), in patients under IRA it was recorded certainly, by 47.62% the reduction of mentioned rate. In contrast, in IV group under the therapy the reduction of urinal albumin excretion in patients wasn't much significant, and the reduction of glomerular filtration index wasn't much expressed.

The analysis data of excretion of another uroprotein – MG – are interesting. The data analysis of the research showed that the biggest its reduction is noted exactly in patients of I, II, IV and V groups, where as a result of the therapy there was a statistically certain reduction of microgloburia by 64.46%, 61.11%, 51.01% and 55.01% respectively. Yet, the frequency of hyper- β2-MGU was mostly reduced in patients in I ($\chi2=11.36$, $p<0.01$), II ($\chi2=13.86$, $p<0.01$) and V groups ($\chi2=5.29$, $p=0.022$).

It's notably, that the adequate nephroprotection assessed according to original patented method is registered in major number of cases (more than 90% of patients) in patients from subgroups 1, 2 and 5. It should be noted, that in patients with evident NP the biggest renoprotective effect is noted for subgroup 1 and 2, the least – for BAB, under the equitable initial renal status within therapy groups.

The analysis of received data of the influence of treatment on the state of renal blood flow in pa-

tients with different types of therapy showed that indices of vascular resistance of vascular bed of kidneys in patients with EH of all groups changed unidirectionally. In 84% of patients in I group and 79% patients in III group there was a reduction of initially increased rates of circumferential blood flow resistance (RI and PI MPA, SBRA and ILBRA and their systolodiastolic correlations) up to values of practically healthy persons. The depression of both rates (RI and PI of dopplerographic spectrum on the level of interlobar branches of renal arteries) was best expressed in II group (by 45.9% and 65.69%) and III group (by 49.15% and 67.01%). The therapy CCB and ARB mostly had a positive impact on the dynamics of rather important rate of renal blood flow – linear velocity gradient on the level of segmental-interlobar branches, which is statistically significantly, mostly expressed reduced in mentioned groups, which was accompanied by levelling out the velocity gradient on the SBRA and ILBRA levels (by 48.49% and 5.22%) with the establishment of physiological, more homogenous renal blood flow. Systolodiastolic correlation also most essentially clinically positively changed in group under Amlodipine (-41.15%).

According to covariance analysis, antihypertensive activity and the possibility of reaching the target AP level ($F=4.73$, $p<0.05$) are not the main clinical predictors, which determine the regress of the ratio of urine albumin-to-creatinine and accordingly the adequate renoprotection, but the recovery of functional state of vascular endothelium ($F=14.37$, $p<0.05$) and normalization of intrarenal haemodynamics with reduction of cases of intraglomerular hyperfiltration/hypertension ($F=7.5$, $p<0.05$) is the main key determinants, stipulating the reduction of excretion of urinal albumin.

The dysfunction of vascular endothelium and intraglomerular hypertension is the main "target" of nephroprotective strategy in EH, the expressiveness of pathological abnormalities of which is important and more significant in comparison to changes in systemic heamodynamics, predictors of increased albuminuria level reverse, integral nephropathy marker [*Félétou M et al., 2010*]. It is shown that the most expressive certain positive effect of combined split-level modulation of RAAS activity (Indapamid+ACE inhibitor or +ARB) on the rates, which characterize the severity of intraglomerular haemodynamics offence, moreover one of the pathogenic aspects of nephroprotective effect of modulators of neurohumoral activity RAAS is their endotheliumprotective effect, which statistically significantly stipulate the improvement of intraglomerular haemodynamics and perfusion [*Ivanov D, 2016*].

Thus, assigning an antihypertensive therapy, under the optimization of treatment, the development of nephroprotective strategy and differentiation in choice of the therapy, the initial functional state of kidneys must be taken into account. In case of significant changes in kidneys with account of contra indications and restrictions to prescription for regression of NP in EH and reversion of endothelin, it's preferable to use low-dose combination of Indapamide+ACE inhibitor or +ARB). As possible alternative therapy in early pathological changes as a treatment of choice is recommended the combination of Indapamide with either ACE inhibitor (in severe damage of endothelium of mediated vasoregulative function of brachial artery and/or expressed intraglomerular hypertension) or with CCB (in a case of severe systematic AH) or with IRA (in case of tubular dysfunction (according to the β2-MGU level) and/or manifestations of intraglomerular hyperfiltration/hypertension, particularly with overweight and carbohydrate intolerance), and also taking into account individually the clinical situation, accompanying pathology and drug tolerance. Yet, according to the results of present study according to nephroprotective effect (under 1.5 *mg* Indapamide) in EH it's possible to put groups in order of decrease of activity this way: ACE inhibitor>ARB>CCB>BAB.

Possibly, the lack of effect of CCB is connected with the fact that in accordance to recommendations of National Kidney Foundation USA [*KDOQI, 2007*] dihydropyridine calcium antagonists are the most effective and safe in patients with kidney leisure without proteinuria [*Gavriliuk V, 2011*], and in our case in CCB group the excessive excretion of urinal albumin was 21.74%, yet, the rates of urinary albumin to creatinine ratio, according to 4 centile corridor were maximal, 23.74 (3.98; 207.05) *mg/g*. In this subgroup 3 the biggest values of glomerular filtration index were also noted, reflecting average floating albumin in urine ultrafiltrate [*Chuba L, Vinnichenko L, 2008*].

Conclusion

Despite the equitable antihypertensive effect of therapy (both under analysis of AP office measurements data and ambulatory AP monitoring), treatment groups were different in renoprotective features. Thus, if the biggest positive dynamics of AP under the therapy was in group Indapamide + CCB, the maximum reduction of microprotein excretion levels (albumin by 85.24% and 85.72% and MG by 67.13% and 67.18% respectively), and also normalization of intrarenal haemodynamics (increase of renal functional reserve in 2.9 and 2.8 times and reduction of PI ILBRA by 65.69% and 64.7% respectively) was recorded in group Indapamide + ACE inhibitor or + ARB.

The prevalence of microalbuminuria also certainly reduced till the end of 12 week treatment for the group Indapamide + ACE inhibitor ($\chi 2=3.91$, $p=0.041$) and for Indapamide + ARB ($\chi 2=4.02$, $p=0.014$). The frequency of hyper- β2-MGU detection mostly reduced in patients of groups Indapamide + ACE inhibitor and Indapamide + ARB ($\chi 2=13.16$ and ($\chi 2=12.86$, $p<0.01$) and for Moxonidine ($\chi 2=5.29$, $p=0.022$).

Adequate nephroprotection, recorded in a big number of cases (in more than 90% of patients) receiving therapy ACE inhibitor, ARB and IRA under Indapamide. Moreover, in patients with evident NP the biggest renoprotective effect is noted for subgroups 1 and 2, the least – for BAB, in initial equitable functional status of kidneys within therapy groups.

Positive renotrophicy of treatment including modulators RAAS is proved by the same fact as under receiving ACE inhibitor or ARB there was divergent GFR dynamics, particularly in patients with EH in increased values of GFR the mentioned therapy contributes to its normalization, in reduced – reactivated the glomerular filtration level.

The main clinical predictors, which determine the regress of the ratio of urine albumin-to-creatinine, integral nephropathy marker are not only the antihypertensive activity and the possibility of reaching the target AP level ($F=4.73$, $p<0.05$), but also normalization of intrarenal haemodynamics with reduction of cases of intraglomerular hyperfiltration/hypertension ($F=7.5$, $p<0.05$) with the recovery of functional state of vascular endothelium ($F=14.37$, $p<0.05$), which are the main key determinants, stipulating the reduction of excretion of urinal albumin and the main "target" of nephroprotective strategy in hypertensive disease.

It's logical that conclusive and statistically reasonable argument of renoprotective superiority in EH of one group of antihypertensive medication, long-term, wide-ranging, multicentral comparable clinical studies are needed. The assessment of reversion of exactly hypertensive NP sings in EH unlike kidney damage in diabetes is also very difficult, because the mentioned pathology is rather rare and progresses rather slowly in nonspecifical, but clinically effective antihypertensive treatment. The study of pathogenic aspects of nephroprotective potential of studied medication groups is perspective.

REFERENCES

1. *2013 ESH/ESC Guidelines* for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013; 34(28): 2159-2219.
2. *Bakris GL, Serafidis PA, Weir MR.* ACCOMPLISH Trial Investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of randomised controlled trial. Lancet. 2010; 375(9721): 1173-1181.
3. *Balakhonova TV, Soboleva GN, Atkov OIu, Karpov IuA.* [Determination of sensitivity of brachial artery to shear stress on endothelium as a method of assessment of the state of endothelium-dependent vasodilatation with the help of high resolution ultrasound in patients with arterial hypertension] [Published in Russian]. Zhurnal kardiologiya, 1998; 38(3): 37.
4. *Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI., et al.* Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992; 340(8828): 1111-1115.

5. *Chikhladze NM, Chazova IE.* [Arterial hypertension and renal] [Published in Russian]. Consilium medicum. 2015; 17(10): 8-12.
6. *Chuba LI, Vinnichenko LB.* [Use of schemes of combination therapy in patients with high-risk and enough high-risk arterial hypertension] [Published in Ukrainian]. Vestnik Sumskogo Gosudarstvennogo Universiteta. 2008; 2(2): 37-40.
7. *Dudar IA.* [Neuroprotection by blockers of renin-angiotensin system] [Published in Ukrainian]. News of Medicine and Pharmacy. 2013; 444(3): 27-35.
8. *Dziak GV, Khaniukov AA, Liulka IuP, Pisarevskaya OV.* [Relevant issues on antihypertensive therapy. Rational choice of drugs: ACE inhibitor, diuretics, combination drugs] [Published in Ukrainian]. Meditsinskiy zhurnal. 2009; 69(1): 17-25.
9. *Dziak GV, Kolesnik TV, Pogoretskiy IuI.* [Holter monitor of arterial pressure] [Published in Ukrainian]. Ukraine: Dnepropetrovsk. 2005. 200p.
10. *Félétou M, Köhler R, Vanhoutte PM.* Endothelium-derived vasoactive factors and hypertension: possible roles in pathogenesis and astreatment targets. Curr Hypertens Rep. 2010; 12(4): 267-275.
11. *Gavriliuk VA.* [Functional renal condition in patients with essential arterial hypertension with obesity] [Published in Ukrainian]. Eksperimentalna i klinichna meditsina. 2011; 51(2): 67-70.
12. *Ivanov DD.* [Next step in chronic kidney disease therapy] [Published in Ukrainian]. Zhurnal Pochki. 2016; 16(2): 10-13.
13. *Karpov RS, Koshelskaya OA, Efimova EV, Vrublevskiy AV.* [Dopplerographic assessment of the dynamics of renal blood flow under the influence of cilazapril in combined arterial hypertension and Diabetes mellitus type 2 at an early stage of nephropathy] [Published in Russian]. Zhurnal kardiologiya. 1999; 4: 16-20.
14. *KDOQI.* Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. AJKD. 2007; 49: 1-179.
15. *Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC., et al.* The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011; 80(1): 17-28.
16. *Mankovskiy BN, Ivanov DD.* [Influence of antihypertensive therapy on renal function of patients with Diabetes mellitus type 2: results of prospective research "SKIF-2"] [Published in Ukrainian]. Liki Ukrayini. 2010; 144(8): 28-32.
17. *Mischenko LA, Svischenko EP, Bezrodnyy VB.* [Predictors of deterioration of renal functional state in patients with hypertension disease with hypertensive nephropathy] [Published in Ukrainian]. Ukrayinskiy kardiologichniy zhurnal. 2012; 87 (1): 8-11.
18. *Noble VE, Brown DF.* Renal ultrasonography. Emerg Med Clin North Am. 2004; 22(3): 641-659.
19. S*chmierder RE*. End organ damage in hypertension. Dtz. Arztebl. Int. 2010; 107(49): 866-873.
20. *Sirenko IuN, Rekovets OL.* [Morning increase of arterial pressure in patients with mild and moderate arterial hypertension and method for correcting using metoprolol retard] [Published in Ukrainian]. Arterial hypertension. 2017a; 55(5): 55.
21. *Sirenko IuN, Rekovets OL.* [Ramipril in patients with arterial hypertension as monotherapy or in combination with hydrochlorothiazide] [Published in Ukrainian]. Arterialnaya gipertenziya. 2017b; 51(1): 81-91.
22. *Sirenko IuN.* [Hypertension disease and renal: how to treat more effectively] [Published in Ukrainian]. Arterialnaya gipertenziya. 2008; 1(1): 34-41.
23. *Spinara J, Vitovec J, Soucek M.* Anti-hypertensive strategies in patients with metabolic parameters, diabetes mellitus and/or Nephrop-Athy (the MEDINA study). Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub. 2014; 158(3): 412-421.
24. *Svischenko EP.* [Arterial hypertension and renal pathology] [Published in Ukrainian]. Zdorov'ya Ukrayini. 2015; 13-14: 146-147.
25. *Svischenko EP.* [Recommendations on differential diagnosis of arterial hypertensions] [Published in Ukrainian]. Ukraine: Kiev. 2014. 50p.
26. *Vander A.* [Renal physiology] [Published in Russian]. Russia: Saint-Petersburg. 2000. 256p.
27. *Zagorodnyi MI.* [Clinical basis of arterial hypertension; pharmacotherapeutic aspect] [Published in Ukrainian]. Ratsionalna farmakoterapiya. 2017; 43(2): 2: 29-34.