

## **The Effect of a Fixed Combination of Perindopril and Amlodipine on Intrarenal Hemodynamics and the Functional State of the Kidneys in Patients with Essential Arterial Hypertension**

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### **ABSTRACT**

*In recent years, there has been an increase in the incidence of chronic kidney disease (CKD) and, according to the NHANES III study; the prevalence of kidney dysfunction is 11% [1]. In addition, it has been shown that the presence of CKD is accompanied by an almost 2-fold increase in the prevalence of coronary heart disease, cerebrovascular disease and diabetes mellitus [2, 3].*

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The kidneys play an important role in the pathogenesis and prognosis of arterial hypertension (AH), as well as in the choice of antihypertensive therapy tactics [4]. In essential hypertension (EAH), the renal vascular system undergoes structural and functional restructuring—remodeling of intrarenal vessels, especially at the level of the microvasculature, resulting in fibrosis and sclerosis [5]. In addition, damage to the vascular endothelium leads to functional depletion of the endothelium with increased apoptosis and decreased regeneration of endothelial cells, which contributes to ischemia of the renal tissue and becomes the pathophysiological basis for the formation of hypertensive nephropathy [6, 7]. In this regard, the question of the nature of changes in intrarenal hemodynamics in patients with EAH and its relationship with glomerular filtration, as well as the possibility of antihypertensive therapy to ensure nephroprotection, is of great importance [8]. According to the nephroprotective strategy, adequate control of blood pressure (BP) and the choice of a rational combination of antihypertensive drugs leads to a 30-50% reduction in the risk of developing end-stage renal failure, the need for renal replacement therapy and/or kidney transplantation, and also allows for huge financial savings. resources [4]. In modern recommendations for the diagnosis and treatment of hypertension, combinations of calcium antagonists and angiotensin-converting enzyme inhibitors are considered rational and recommended two-component treatment regimens, which is determined by their synergistic and complementary therapeutic effects, neutralization of unwanted side effects, as well as rapid and adequate reduction in blood pressure [9, 10]. Based on the generally accepted strategy for combination therapy of hypertension, the creation of fixed combinations of drugs is considered a priority, one of which is the fixed combination of perindopril arginine and amlodipine besilate - Prestance [11, 12]. The purpose of the study is to evaluate the impact of Prestance on indicators of intrarenal hemodynamics and the functional state of the kidneys, and also to study their correlations during 24-week therapy in patients with stage I-II EAH.

### **Materials and methods**

An open prospective clinical study included 120 patients (54 men and 66 women) aged 45 to 69 years suffering from grade I-II EAH. Depending on the glomerular filtration rate (GFR), 3 groups of patients

were identified: in group 1 (n=48) GFR was 90 ml/min/1.73 m<sup>2</sup> and higher (stage I CKD), in group 2 (n=42) - 89-60 ml/min/1.73 m<sup>2</sup> (stage II CKD) and in group 3 (n=30) - 59-30 ml/min/1.73 m<sup>2</sup> (stage III CKD). Prestance was prescribed depending on the achievement of target blood pressure levels at a dosage of 10/5 or 10/10 mg once a day. The criteria for inclusion in the study were also the absence of proteinuria and hyperuricemia in patients, satisfactory ultrasound visualization of the kidneys, heart and blood vessels. Exclusion criteria from the study were GFR <30 ml/min/1.73 m<sup>2</sup>; symptomatic hypertension; diabetes; myocardial infarction and cerebral stroke suffered within the last 6 months; chronic heart failure (CHF) above functional class II (FC); clinical and laboratory manifestations of chronic diseases liver and kidneys; diffuse connective tissue diseases and cancer. A comparative analysis of the examined patients revealed a relatively high incidence of metabolic disorders, microalbuminuria (MAU) and left ventricular hypertrophy (LVH) in patients with lower GFR (Table 1). The difference in GFR between groups was statistically significant (p<0.05). The average daily levels of systolic (SBP) and diastolic (DBP) blood pressure in the groups differed statistically insignificantly. CHF I-II FC in group 3 was detected 1.5 times more often than in other groups. The kidney examination included Doppler ultrasound, determination of daily urinary albumin excretion, blood creatinine and GFR. Ultrasound examinations of the heart and kidneys were performed using an Acuson Antares device (Siemens Medical Solutions, Germany—USA). Ultrasound of intrarenal hemodynamics determined the Doppler spectrum in the interlobar artery [13]. We calculated resistive characteristics of arterial blood flow—resistance index (RI) and pulsatility index (PI), as well as speed indicators of blood flow—peak (maximum) systolic blood flow velocity (V PS) and end-diastolic (minimum) blood flow velocity (V ED). RI was determined in the interlobar arteries of both kidneys, and on their basis the arithmetic mean of this indicator was calculated for each patient. Albumin content was determined by enzyme immunoassay method in the first morning portion of urine collected at night, and the level of albumin excretion in urine was expressed in milligrams per 1 liter of urine, which is normally 30-300 mg/l [14]. GFR, standardized by body surface area, was calculated using the MDRD formula, which in healthy adults is 90 ml/min/1.73 m<sup>2</sup> [9]. Daily blood pressure monitoring (DBPM) was carried out using the BPLab device in standard mode. The intervals between blood pressure measurements were 30 minutes during the day and 60 minutes at night. We calculated the average daily indicators of SBP, DBP, time index (TI) of pressure load (TI SBP, TI DBP), the degree of nocturnal decrease (SNS) of SBP and DBP, variability of SBP and DBP, the magnitude of the morning increase in SBP and DBP, the ratio of the residual hypotensive effect to the maximum effect (t/p index). Doppler echocardiography was used to calculate left ventricular (LV) end-systolic and end-diastolic dimensions, cardiac index (CI), LV ejection fraction, and total peripheral vascular resistance. LVH was diagnosed when the LV myocardial mass index was more than 110 g/m<sup>2</sup> for women and more than 125 g/m<sup>2</sup> for men [9]. The vasoregulatory function of the endothelium was studied by assessing endothelium-dependent vasodilation (EDVD) of the brachial artery (BA) according to the method of D. Celermajer et al. [15]. Statistical data processing was carried out using the Statistica 6.0 software package and Excel for Windows. Results are presented as means (M) ± standard deviation (SD). The Mann-Whitney test (U test) was used to compare mean scores between two independent samples. Correlation relationships were assessed using the Spearman correlation coefficient (r). Differences and correlations were considered statistically significant at p<0.05.

## Results and discussion

A comparative analysis of indicators of intrarenal hemodynamics and the functional state of the kidneys before treatment revealed statistically significantly high RI and PI, as well as the level of albumin excretion in the urine in patients of group 3. It has been shown that against the background of treatment Prestansome in all groups there is a decrease in V PS, which was statistically significant in groups 2 and 3 (on average by 20.2 and 24.4%, respectively; p<0.05) and, conversely, a tendency to increase indicator V ED. Indicators of vascular resistance - RI and PI - decreased in all groups, especially in patients of groups 2 and 3. In group 1, GFR tended to decrease during treatment (on average by 6.9%), which was probably due to initial hyperfiltration. However, in groups 2 and 3, GFR, on the contrary, increased statistically significantly: on average by 13.8% (p=0.034) and 31.5% (p<0.001), respectively. As a result, the ratio of patients depending on the degree of renal dysfunction has significantly improved. Thus, the number of patients with GFR above 90 ml/min/1.73 m<sup>2</sup> increased to 38 mainly due to patients with stage II CKD, and the number of patients with stage II CKD - from 28 to 41 due to a significant decrease in the number

of patients with stage III stage (from 23 to 3). The content of creatinine in the blood serum in the 1st and 2nd groups corresponded to the norm, and out of 23 patients, the 3rd. In 16 (69.6%) groups, its borderline value was revealed - 115-133  $\mu\text{mol/l}$  in men and 107-124  $\mu\text{mol/l}$  in women. Serum creatinine levels before treatment in patients of group 3 were statistically significantly higher than in groups 1 and 2: on average by 24% ( $p < 0.001$ ) and 15.9% ( $p < 0.01$ ), respectively. During treatment with Prestance in groups 1 and 2, changes in serum creatinine levels were not significant, but in group 3 it decreased statistically significantly by an average of 14.9% ( $p = 0.032$ ). In all groups after 24 non-effective therapy, urinary albumin excretion in patients who had MAU in the initial state decreased statistically significantly. At the same time, MAU disappeared in the 1st group in 5 (55.6%) of 9 patients, in the 2nd group - in 6 (60%) of 10 and in the 3rd group - in 5 (38.5%) out of 13. The study of VEDV in the initial state showed that especially in the 3rd group, endothelial dysfunction (ED) was expressed, which turned out to be statistically significantly lower than in patients of the 1st and 2nd groups: on average by 21.9 and 20 % respectively ( $p < 0.001$ ). During treatment with Prestance, a highly statistically significant increase in VEDV was noted in all groups ( $p < 0.001$ ). Despite this, in group 3 and after treatment, VEDV was statistically significantly inferior to that in other groups. In addition, in patients of group 3, who had severe renal dysfunction in the initial state, compared with the other groups, CI increased statistically significantly after treatment ( $p = 0.034$ ). According to ABPM data, a pronounced antihypertensive effect of treatment was revealed in all groups, but no statistically significant differences were noted between the groups. In particular, during treatment there was a highly statistically significant decrease in the average daily readings. SBP and DBP, IV SBP and IV DBP. Indicators of IV SBP and IV DBP below 20% per day, indicating normalization of blood pressure, were detected in 43 (74.2%) patients of the 1st group, in 40 (71.4%) of the 2nd group and in 37 (60, 9%) 3rd group. It should also be noted that in all groups and in all patients with stage I-II EAH, a positive "response" to Prestance therapy was achieved. The indicators of SNS SBP and SNS DBP increased statistically significantly, especially in patients of the 2nd and 3rd groups. As a result, the therapy also contributed to the normalization of the daily blood pressure profile. Thus, in the 1st group, the number of cases with pathological types of daily blood pressure profile decreased from 19 to 6 (by 68.4%), in the 2nd group - from 16 to 6 (by 62.5%) and in the 3rd group - from 17 to 9 (47.1%). The magnitude and rate of morning increase in blood pressure, associated with the incidence of myocardial infarction and cerebral stroke, also decreased statistically significantly. In addition, the criterion for the real duration of the antihypertensive effect of the drug - the t/p ratio during therapy in the compared groups - did not differ significantly and was about 70%, which indicates reliable control of normal blood pressure levels during the day, including in the early morning hours. In a univariate correlation analysis, statistically significant connections between RI and the functional state of the kidneys were revealed only in patients of group 3. Thus, RI had an inverse correlation with VEDP, SI and GFR and a direct correlation with MAU. Maximum systolic blood flow velocity (VPS) had an inverse correlation with GFR ( $r = -2.455$ ;  $p = 0.023$ ). Thus, the study once again demonstrated the important role of changes in intrarenal hemodynamics in assessing the severity of kidney damage and risk factors for the development of cardiovascular complications in EAH. It has been shown that a significant decrease in GFR (less than 60 ml/min/1.73 m<sup>2</sup>), in contrast to preserved renal function, is associated with a high incidence of metabolic factors, LVH and CHF; this is consistent with the results of the study by I.G. Fomina et al. [8]. It is important to note that in patients with GFR less than 60 ml/min/1.73 m<sup>2</sup>, a direct correlation was revealed between VERD of PA and the resistance of the interlobar renal arteries, indicating pronounced DE of the intrarenal arteries and their structural remodeling. We also showed the influence of the functional state of the kidneys on the circadian rhythm of blood pressure, in particular, it was noted that as GFR decreases, the frequency of detection of pathological types of circadian blood pressure profile increases, especially non-dipper and night-picker. Evaluation of the effectiveness of Prestance in patients with stage I-II EAH depending on the functional state of the kidneys and taking into account changes in intrarenal hemodynamics revealed a more pronounced decrease in the resistive indicators of the interlobar renal arteries - RI and PI, an increase in VEDV and SI with initially severe renal dysfunction. It is important to note that in patients with GFR less than 60 ml/min/1.73 m<sup>2</sup>, the structural and functional parameters of the kidneys statistically significantly improved. Thus, during treatment with Prestance, both urinary albumin excretion and the frequency of MAU episodes significantly decreased. As is known, MAU is an early sign of renal dysfunction and is a strong and independent predictor of the progression of renal failure and cardiovascular mortality [14]. The

appearance of MAU precedes GFR and an increase in intrarenal vascular resistance, and at the same time normocreatinemia persists for a long time [7]. It has been shown that in the early stages of development of hypertensive nephropathy, DE, primarily local renal DE, is manifested by an increase in albumin excretion in the urine. Therefore, along with an increase in GFR, a decrease in MAU levels indicates a pronounced nephroprotective effect of Prestance.

## Conclusion

Prestance, due to a decrease in intrarenal vascular resistance, improvement of endothelial function and a pronounced antihypertensive effect, causes a nephroprotective effect, manifested in a significant decrease in MAU and an increase in GFR. Therefore, diagnosis of the early stages of hypertensive nephropathy and adequate pharmacological nephroprotection are urgent tasks for the successful prevention of cardiovascular complications in patients with EAH.

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