

**HYPERTENSION TO NORMALIZE HEMODYNAMICS OF PERINDOPRIL AND  
IVABRADINE**

**Yarmatov Suvon Tatlibayevich**

Assistant of the Department of Propaedeutics of Internal Diseases,

Samarkand State Medical University

**Muzaffarova Malika Sho'hratovna**

Assistant at the ABU ALI IBN SINO SIAB COLLEGE OF PUBLIC HEALTH (Samarkand)

**Ollaev Ilhom Bahriddinovich**

Samarkand State Medical University Faculty of treatment student group 511

**Axtamova Shirin Xayrulloevna**

Samarkand State Medical University Faculty of treatment student group 511

**Kattabekov Ozodbek Oybekovich**

Samarkand State Medical University Faculty of treatment student group 511

**Xushvaqtova Zuhraoy Berdiqulovna**

Samarkand State Medical University Faculty of treatment student group 511

**ABSTRACT:** Evaluation of the diastolic properties of the left ventricular myocardium (LV) in patients with hypertensive heart is relevant due to the fact that they, forming against the background of an increase in LV myocardial mass, are able to progress, manifesting clinical syndrome of chronic heart failure mainly in old age. The aim is to determine the effectiveness of perindopril and ivabradine in correcting blood pressure and heart rate, as well as functional parameters of LV myocardium, vasoregulatory function of peripheral arterial endothelium in patients with hypertension. Object and methods. The study included 43 men aged 52 to 64 years with a diagnosis of hypertension without systematic use of antihypertensive drugs in the past, who did not have clinical signs of chronic heart failure, with a sinus rhythm at rest of more than 75 per minute. The control group consisted of 21 men, comparable in age, without abnormalities on electrocardiography and physical signs of heart disease. All patients included in the study underwent an echocardiographic examination, which determined the main parameters at rest. Pulse-wave Dopplerography of the LV inflow pathway was also used, and in the tissue dopplerography mode, the speed of movement of the lateral part of the mitral valve ring and the LV myocardial productivity index were evaluated. Load testing was carried out on a bicycle ergometer for 2 minutes with a power of 25, 50 and 75 watts. Endothelial function and stiffness systemic arteries were assessed by finger computed photoplethysmography. The study was divided into 3 visits: on the 1st, patients were prescribed perindopril at a dose of 10 mg / day; on the 2nd,

ivabradine was added at a dose of 7.5 mg 2 times a day for a month; the 3rd visit was the final stage of the study. Results. According to blood pressure measurements at the last visit, the group of patients with hypertension did not differ from the control group in systolic and diastolic pressure while lying, sitting, and at a load of 25 watts. The addition of ivabradine to perindopril increased the bradycardic effect significantly equalized the group of patients with the control heart rate in the entire range of physiological conditions. The index of peripheral arterial endothelial function completely returned to normal during the follow-up. When studying the LV myocardial performance index, we have shown that performing physical activity and changing body position can significantly influence its increase in both healthy and hypertensive heart patients. Conclusion. A significant hypotensive effect of perindopril at rest, under dynamic load, and the effectiveness of ivabradine in normalizing heart rate have been demonstrated. The high sensitivity of the LV phase myocardial index as a marker of left ventricular dysfunction, dynamic changes in the index in response to normalization of blood pressure and pulse regardless of LV myocardial mass, as well as the possibility of normalization of the vasomotor function of the vascular endothelium of peripheral arteries, which creates the basis for improving the parameters of vascular rigidity in the future.

**Key words:** diastolic dysfunction, phase myocardial index, chronic heart failure, perindopril, ivabradine.

## INTRODUCTION

The clinical significance of left ventricular (LV) diastolic myocardial dysfunction is determined by the participation of this phenomenon in the formation of chronic heart failure (CHF) with a preserved ejection fraction (LV). The pathogenetic features of this current type of CHF are still poorly understood, although it is known that age and arterial hypertension (AH) are the main predisposing factors. The morphological basis of diastolic dysfunction is LV myocardial hypertrophy, which can be effectively reduced with proper hypotensive therapy. The parameters of the diastole themselves, measured echocardiographically, are difficult to interpret due to their dependence on the parameters of filling pressure, heart rate and LV afterload. It is of interest to study their dynamics under the influence of drugs that reduce blood pressure (BP) and heart rate (HR) both at rest and under the influence of physical activity (PA). Normalization of the chronotropic function of the sinus node under the influence of ivabradine, a drug that does not affect the contractile function of the myocardium, as well as blood pressure in these physiological conditions It provides an opportunity to evaluate the myocardium's own global properties characterizing its lusitropic and contractile function. The aim is to determine the effectiveness of perindopril and ivabradine in correcting blood pressure and heart rate, as well as functional parameters of the LV myocardium, vasoregulatory function of the peripheral artery endothelium in patients with hypertension (AH).

## MATERIALS AND METHODS OF RESEARCH

The study included 43 men aged 52 to 64 years with a diagnosis of AH without systematic use of antihypertensive drugs in the past, who did not have clinical signs of CHF, underwent clinical examination, with a sinus rhythm at rest of more than 75 per minute. The exclusion criteria were blood pressure <140 and 90 mmHg, resting heart rate less than 75 per minute,

non-sinus rhythm, frequent extrasystoles. The control group consisted of 21 men of comparable age, without complaints about their health status, abnormalities in electrocardiography and physical signs of heart disease. The study was divided into three stages: at the 1st visit, the initial echocardiographic parameters in the supine position were determined - the end-diastolic LV size (CDR), the end-systolic LV size, the thickness of the interventricular septum (IVS), the thickness of the posterior LV wall (TCS), the diameter of the left atrium (LA). The following parameters were calculated: LV myocardial mass index (LVMI),  $\text{g/m}^2$ ; LV hypertrophy index (IG):  $\text{IG} = (\text{TKC} + \text{TMJP}) / \text{CDR}$ , the index of the atrioventricular ratio is  $\text{LP} / \text{CDR}$ . All patients included in the study had LV hypertrophy (LVH),  $\text{LVH} > 115 \text{ g/m}^2$ . Because everyone has an IG the patient of the main group was above 0.42, with  $\text{LJ} > 115 \text{ g/m}^2$ , this corresponded to a concentric GLJ. We also used methods of pulse-wave Dopplerography of the LV inflow pathway, as well as in the mode of tissue dopplerography, the velocity of movement of the lateral part of the mitral valve ring was estimated. Despite LVH detected in each patient of the main group, signs of diastolic dysfunction, assessed in accordance with modern recommendations, were not observed in all. An increase in the anterior size of LP  $> 42 \text{ mm}$  was detected in 18 (43%) of them, the rate of displacement of the lateral part of the mitral valve ring into the rapid filling phase is less than  $10 \text{ cm/s}$  in 16 (37%), the ratio of the speeds of the transmittal flow and movement of the mitral valve ring  $\text{E}/\text{Em} > 14$  was only in 1 patient, although in 15 (35%) people this ratio was greater than 8, i.e. above the norm. The myocardial performance index (IPM) was evaluated using pulsed tissue Dopplerography of the lateral part of the mitral valve ring on a Vivid 7 (GE Healthcare) device LV as the sum of the phases of isovolumic contraction and isovolumic relaxation, related to the duration of the period of LV expulsion. Dopplerography with the determination of this parameter was also performed while sitting and performing a stepwise FN on a bicycle ergometer 2 minutes with a power of 25, 50 and 75 watts. Further, all patients were prescribed perindopril at a dose of  $10 \text{ mg} / \text{day}$  for 1 month in order to normalize blood pressure. On the 2<sup>nd</sup> visit, the examination was carried out in the same volume. Further, treatment with perindopril continued at the same dose of  $10 \text{ mg} / \text{day}$  with the addition of ivabradine in a dose of  $7.5 \text{ mg}$  2 times a day for a month. The third visit was the final stage of the study, the volume of which corresponded to the 1st and 2nd visits. Endothelial function and stiffness of systemic arteries were assessed by finger computed photoplethysmography (FPG). Registration and processing of the volumetric pulse wave was performed using a certified Eldar photoplethysmograph. The reflected wave was detected automatically, and the time of its appearance on the volumetric curve was determined. pulse rate. The stiffness index (SI) was defined as the ratio of the growth of the subject to the time of reflection of the pulse wave.

## THE RESULTS AND THEIR DISCUSSION

The average age in the control group was  $59.10 \pm 0.93$  years, not significantly different from the age in the main group –  $58.18 \pm 0.64$ . The body mass index in the control group was lower:  $26.12 \pm 0.66 \text{ kg/m}^2$  versus  $28.98 \pm 0.61 \text{ kg/m}^2$ ,  $p < 0.01$ , as well as waist circumference:  $87.29 \pm 0.84$  and  $93.04 \pm 1.33 \text{ cm}$ ,  $p < 0.01$ , reflecting the prevalence of well-known metabolic disorders in patients with AH. Echocardiographic parameters in the main group, determined at the 1st visit, they also revealed predictable differences in LVH, IG, and an increase in the atrioventricular ratio associated with an increase in LP size, which obviously reflects increased diastolic blood pressure (DBP). It is also typical that there are no changes in the linear dimensions of the LV, both in the diastole and in the systole in comparison with the

control, which provided a comparable expulsion fraction. This is also confirmed by the absence of any changes in the Sm parameter characterizing the rate of displacement of the mitral valve ring into the systole. The average age in the control group was  $59.10 \pm 0.93$  years, not significantly different from the age in the main group –  $58.18 \pm 0.64$ . The body mass index in the control group was lower:  $26.12 \pm 0.66$  kg/m<sup>2</sup> versus  $28.98 \pm 0.61$  kg/m<sup>2</sup>  $p < 0.01$ , as well as waist circumference:  $87.29 \pm 0.84$  and  $93.04 \pm 1.33$  cm,  $p < 0.01$ , reflecting the prevalence of well-known metabolic disorders in patients with AH. Echocardiographic parameters in the main group, determined at the 1st visit, they also revealed predictable differences in LVH, IG, and an increase in the atrioventricular ratio associated with an increase in LP size, which obviously reflects increased diastolic blood pressure (DAD). It is also typical that there are no changes in the linear dimensions of the LV, both in the diastole and in systole versus control, which provided a comparable exile fraction. This is also confirmed by the absence of any changes in the Sm parameter characterizing the rate of displacement of the mitral valve ring into the systole. echocardiographic parameters that distinguished the main group from the control group at the beginning of the study, although they had some tendency to improve, changed unreliably both under the influence of perindopril therapy (2nd visit) and after its combination with ivabradine. Since the total duration of therapy did not exceed 2 months, the tendency to decrease LVMI did not It was possible to achieve significant differences, despite the significant hypotensive effect on systolic BP – SAD and DAD. In terms of normalization of the heart rate, there was also a consistent positive trend, and as a result of monotherapy with perindopril (2<sup>nd</sup> visit). Interestingly, the decrease in heart rate was noted not only at rest, but also when performing PH. This highlights the pleotropicity of the blockade of the renin-angiotensin system and its indirect effect on sympathetic tone. As a result the load on the myocardium and the need for oxygen during physical exertion decreases not only due to the hypotensive effect, but also due to a decrease in excessive chronotropic activity. Heart rate values at the end of each stage of the load are 25, 50, Although 75 watts were higher than the corresponding healthy indicators, they did not differ in the degree of increase. So, in patients of the main group, initially (1st visit) Heart rate in the entire range of measurements performed at rest and during bicycle ergometry was higher than the corresponding values of the control group ( $p < 0.01$ ). Adding ivabradine to Perindopril enhanced the bradycardic effect, significantly aligning the group of patients with the control heart rate in the entire range of physiological conditions. In the supine position, the heart rate in the patient group remained significantly slightly higher (3<sup>rd</sup> visit). It should be noted that the pronounced bradycardic effect of ivabradine, expressed in a significant absolute decrease in heart rate at a power of 25, 50 and 75 Watts on the 3rd visit relative to the 2<sup>nd</sup> visit, was not accompanied by a change in the degree of its increase with each load stage. According to the DChS parameter 25 W (%), DCH 50 W (%), DCH 75 W (%) during the whole during the study period, the main group did not differ from the control group, which indicates the physiological normalization of heart rate and the safety of using ivabradine at a daily dose of 15 mg, which does not cause chronotropic insufficiency according to stress testing. The vascular stiffness parameter in the main group was significantly higher than the control group and, despite the significant hypotensive effect, did not undergo significant dynamic changes, detecting a positive trend. As shown in a number of studies, changes in the structure of the aortic wall require significant However, the reverse development is not obvious during the 2 months of the present observation. The interpretation of IL is also complicated by its dependence on the value of blood pressure, i.e., with a decrease in blood pressure, its value decreases. The PFE of the peripheral arteries, which was significantly reduced initially in the main group,

completely returned to normal during follow-up. These data are quite consistent with the possibility of perindopril to improve vascular endothelial function and are partly able to explain the decrease in blood pressure both at rest and with FN. Given the numerous data on the relationship of the properties of the vascular endothelium of peripheral arteries with the properties of the endothelium of the arteries of the brain and heart, this effect is the basis of cardio- and cerebroprotection. A special feature of our work was the study of this parameter while sitting, lying down and performing FN. We have shown that performing FN and changing the position of the body they can significantly influence its increase in both healthy and hypertensive heart patients. This means that with the increase in the work of this body there is an increase in the total phases of contraction and relaxation relative to the duration of expulsion of blood from the LV. It is also very important that a healthy heart has a significant reserve, and at rest this parameter is only 34%, and under load it increases 2.5 times, reaching 87% of the duration of exile. It should be noted that the reserve of increase in this indicator in patients with GB is reduced initially and does not increase either with an effective decrease in blood pressure or with an effective slowdown in the rate of heart contractions, being at a surprisingly stable level of 35-33% at a load of 25 watts and 64-63% when performing a load of 75 Watts against an increase of 100 and 150%, respectively, in the control group. This phenomenon has been identified by us for the first time and requires an explanation. From our point of view, this parameter characterizes the intrinsic properties of the LV myocardium, mainly lusitropic, without denying the contribution of insufficient growth contractility due to increased heart rate. In the early stages of a hypertensive heart, disorders of myocardial relaxation and stiffness are unlikely to lead to a significant increase in DBP in the LV cavity, but when performing LV, accelerating heart rate, these changes become pronounced. Obviously, hemodynamic unloading can improve phase parameters at rest, but does not have a decisive effect on the processes of myocardial relaxation under stress, which may indicate the absence of changes in the kinetics of calcium ions that determine the rate of relaxation of the LV myocardium.

## CONCLUSIONS

1. The use of the drug perindopril is effective in correcting hypertension both at rest and during AF in patients with AH. The effectiveness of hemodynamic relief under the influence of perindopril is also associated with its ability to maintain the rate of heart contractions both at rest and throughout the Ph range.
2. The addition of ivabradine to perindopril therapy is characterized by an effective bradycardic effect without disruption of chronotropic activity in FN in patients with AH.
3. IPM is a highly sensitive parameter characterizing the global properties of LV myocardium, regardless of the presence of diastolic dysfunction in patients with GB who do not have clinical manifestations of CHF. In a sitting position and with and patients with AH.

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