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THE LEFT VENTRICLE DIASTOLIC FUNCTION IN PATIENTS WITH HYPERTENSION UNDER THE USE OF DIFFERENT DRUG GROUPS

Abstract

The objective: To assess the prevalence of diastolic dysfunction in patients with hypertension and preserved left ventricular ejection fraction under pharmacological correction (monotherapy) with angiotensin converting enzyme inhibitors, angiotensin receptor blockers and β -blockers. **Materials and methods:** 82 patients (58 women and 24 men) with stage 2 hypertension were examined. The diastolic function was assessed via echocardiography in accordance with the European Association of Cardiovascular Imaging guidelines (2017). Echocardiography was performed before the onset of the treatment and 6 months after its onset. The treatment onset was considered to start after a 2-week period of elimination of previously used pharmacological substance and 2 weeks of assessing tolerability, dose and regimen adjustment. **Results:** For all selected drugs, target values of blood pressure were achieved, and no adverse effects were identified. The average values of the left atrial volume index before and after the treatment course did not show significant differences. In the majority of the examined patients, this parameter did not exceed the threshold value of 34 ml/m². Values exceeding the specified threshold were observed in Group 1 in 4 patients, in Group 2 in 3 patients and in Group 3 in 8 patients. According to the tissue Doppler ultrasound results on the velocity of myocardial motion at the early diastolic filling of the left ventricle, which was measured at the level of the lateral segments of mitral valve and the interventricular septum, positive, but unreliable, changes were observed in the groups of bisoprolol and valsartan, and no changes — in the group of perindopril. According to the traditional criteria, diastolic dysfunction was observed in 80 % of patients, while according to the criteria of the European Association of Cardiovascular Imaging (2017) — in 21 % of patients. **Conclusion:** The same efficacy of all three drugs is observed in terms of achieving target blood pressure values. The most pronounced effect on the morphometric parameters of the left atrium and intracardiac hemodynamics is shown in the groups of bisoprolol and valsartan.

Key words: hypertension, diastolic dysfunction, echocardiography, tissue Doppler ultrasound, valsartan, perindopril, bisoprolol

Conflict of interests

The authors declare no conflict of interests.

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BP — blood pressure; ARBs — angiotensin receptor blockers; EH — essential hypertension; DBP — diastolic blood pressure; DD — diastolic dysfunction; ACEI — angiotensin converting enzyme inhibitors; LV — left ventricle; LA — left

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atrium; SBP — systolic blood pressure; HF — heart failure; CVD — cardiovascular diseases; LVEF — left ventricular ejection fraction; ECHO-CG — echocardiography

Introduction

Hypertension is one of the biggest problems facing modern medicine. This is due to the polyetiology of increased blood pressure (BP), discovering multifaceted capabilities for therapeutic interventions in this condition, depending on its causes and concomitant diseases, as well as on the formation of pathophysiological vicious circles contributing to the deterioration of the patient's condition [1]. Multiple target organ damage is an additional factor, which exacerbates the progression of hypertensive conditions and is important for mortality rate development. Vascular accidents appearing against the background of elevated BP are known to be among the top three causes of death worldwide [2–4].

Changes in systemic and intracardiac hemodynamics in various hypertensive conditions are widely known. Currently, there is a wide range of diagnostic methods to identify said abnormalities on time. These include noninvasive assessment of the heart using echocardiography (ECHO-CG) [4, 5, 6]. This method allows to study morphometric parameters (wall thickness, sizes of the cardiac chambers and the main vessels), state of heart valves, and to assess intracardiac flows using Doppler methods. Investigations of changes in myocardial thickness, their temporal characteristics, reflecting the dynamics of heart muscle contraction and relaxation, are traditionally used to study the mechanics of heart contraction. Today, said possibilities are supplemented with widespread introduction of the tissue Doppler ultrasound, which significantly expanded the diagnostic capabilities of the method, in particular, relating to assessment of the diastolic state of myocardium [5–8].

Quite often, cardiac damage in hypertension is accompanied by the development of left ventricle (LV) diastolic dysfunction (DD) [8]. This condition includes changes in diastolic filling of the ventricle, accompanied by a decrease in ventricular distensibility and impairment in its relaxation. DD is of particular interest as a specific point connecting

hypertension and the development of heart failure (HF), especially in patients with normal parameters of the LV systolic function, namely with normal or slightly reduced ejection fraction (EF). Numerous studies have shown that DD is very common among patients with cardiac diseases, and it can be both isolated and combined with systolic function impairment. Of particular interest is that the occurrence of symptomatic HF and sudden cardiac death is a specific consequence of DD, even with intact EF [4, 2, 8].

Also, elevated BP contributes greatly to the causes of mortality from cardiovascular diseases (CVD) due to the fact that it leads to system, structural and functional remodeling involving multiple body organs and systems: changes in vessel wall stiffness, progressing nephropathy, and cardiac changes including diastolic and systolic dysfunction, as well as LV myocardial hypertrophy. According to the latest research, heart failure with normal EF is a socially significant health problem, because more than half of patients with early HF are known to have no changes in EF. Moreover, in recent decades there has been a tendency towards an increase in frequency of this condition with simultaneous increase in mortality from it [4, 2, 9].

Investigation of the incidence and manifestations of HF with intact EF is even more important due to the fact that to date, approaches to its pharmacological correction are underdeveloped, despite the common use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in decreased EF, which increase survival in patients with heart failure [1, 6, 10–13]. The above data indicate the social significance of studying diagnostic methods for HF with an intact EF and approaches to its drug correction in the presence of a combination of hypertension and LV diastolic dysfunction.

The aim of the study was to assess the frequency of diastolic dysfunction in patients with hypertension and an intact EF under conditions of pharmacological correction (monotherapy) with ACEI, ARB, and β -blockers.

Study objectives:

- assess the frequency of DD in patients with essential hypertension (EH), 2nd degree, 2nd and 3rd stage (according to the Russian classification), based on echocardiography data
- identify the most common DD markers
- assess changes in intracardiac hemodynamics parameters with pharmacological correction by antihypertensive agents of various groups

Materials and methods

The study had an open, non-randomized, prospective design.

Inclusion criteria: voluntary informed consent of the patient to participate in the study, diagnosis of 2nd–3rd stage and 2nd degree EH, blood glucose below 5.5 mmol/L, waist circumference less than 102 cm in men and 88 cm in women, sinus rhythm on ECG, type 1 DD.

Exclusion criteria: thyroid disease, chronic liver disease, secondary hypertension, history of use of 3 or more antihypertensive agents, exceeding the threshold values of lipid spectrum parameters, acquired or congenital cardiac abnormalities.

The clinical group consisted of 82 patients, of whom 58 were women and 24 were men, who underwent examination and treatment at the medical center

“MedExpert”. The mean age of the patients was 58.6 ± 7.4 years. The patients were divided into three groups. Bisoprolol as monotherapy was used in the first group, which consisted of 25 patients. The second group included 23 patients who were treated with perindopril. The third group consisted of 32 patients who were treated with valsartan. The distribution of patients by age is shown in Figure 1.

The patient examination included examination by a general practitioner and a cardiologist, complete blood count, urinalysis, biochemical blood test — glucose, lipid spectrum, urea, creatinine, 24-hour ECG monitoring, and chest X-ray. All patients underwent an echocardiographic study (ECHO-CG) immediately after prescription of drug therapy and 6 months from its start. ECHO-CG was performed on Logiq S8, manufactured by General Electric (USA). The study was conducted by the standard method with morphometric assessment of cardiac chamber sizes, thickness of the left and right ventricle myocardium, diameters of the aorta and pulmonary trunk at the level of the valve ring, EF calculation (in case of LV cavity remodeling, by Simpson and Teichholz method), and assessment of local myocardial contractility. The left atrium (LA) volume and LA volume index were calculated from apical four- and two-chamber views. The study of

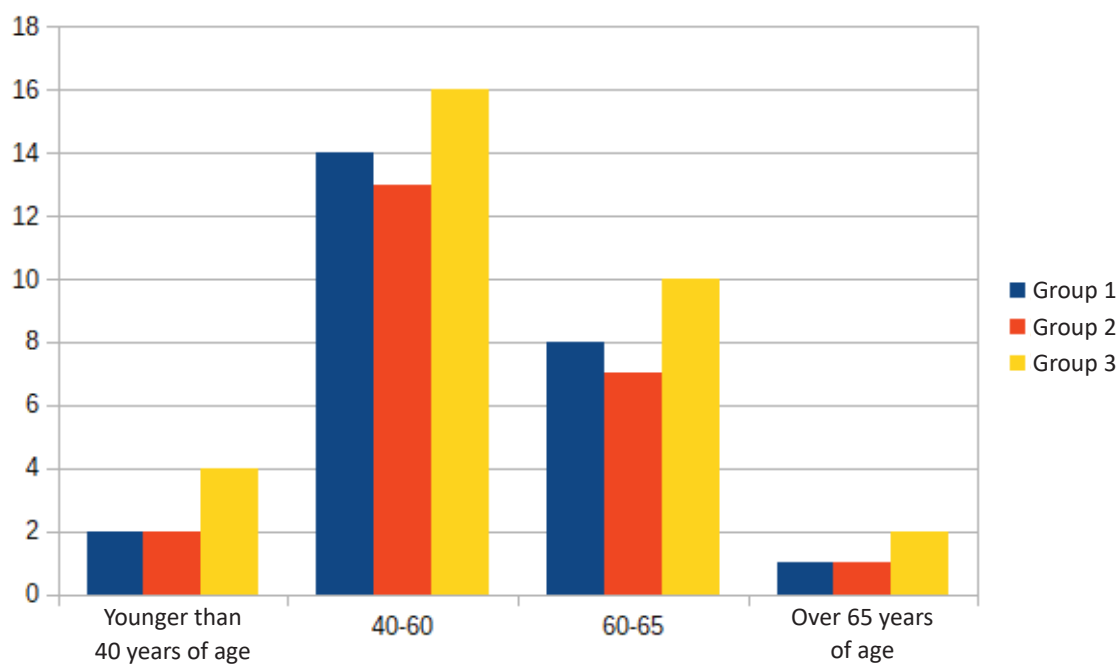


Figure 1. The distribution of patients in the study groups by age

DD parameters included the use of the tissue Doppler ultrasound with detection of LV myocardial velocity parameters at the level of the valve ring in septal and lateral parts with evaluation of e' lateral and septal, e'_{lat} and e'_{sept} . The intracardiac hemodynamics parameters were assessed using continuous-wave pulsed Doppler ultrasound, and values of early diastolic filling of the ventricles (E) and ventricular filling in atrial systole (A) were detected to assess blood flow through atrioventricular valves. In case of regurgitant flows, their velocity parameters were detected using continuous-wave Doppler ultrasound. Blood flow at the level of pulmonary veins ostia was evaluated by pulsed Doppler ultrasound in apical four-chamber view. Said additions to the standard protocol comply with the European Association of Cardiovascular Imaging guidelines of 2017 [13]. The results obtained were entered into a Microsoft Excel spreadsheet and processed using Statistica 10.0 software (Dell). The mean sample values were analyzed and compared using nonparametric Wilcoxon-Mann-Whitney tests and Friedman test. The top 2.5 % part of Friedman's F distribution was used as test statistics. Numerical values in the article are presented by median and interquartile range, as well as mean \pm standard deviation. After a 2-week period of elimination of the pharmacological substance of previously used agents, the compared drugs were prescribed for 14 days to assess tolerability, to select the dose and dosage regimen. Dose selection was performed by titration method starting with minimum doses. Bisoprolol, starting from 1.25 mg, with a gradual increase to achieve clinical effect presented as HR decrease to the selected threshold values and BP values near to the target ones (below 140 and 90 mm Hg). Valsartan, starting from 20 mg, the maximum dose did not exceed 80 mg per day (once daily).

Perindopril was prescribed at the initial dose of 2 mg until achieving said target HR and BP values (once daily). During the study, no cases of adverse effects of said treatment were observed.

Results and discussion

Significant decrease of BP measured at brachial artery was observed in all patients when using all of the selected agents. The values for BP parameters are provided in Table 1. When assessing the efficacy of the provided therapy 6 months after its start, BP was shown to have decreased to the target values in 23 of 25 patients (or 92 %) in the first group, in 21 of 23 patients (91.3 %) in the second group, and in 30 of 32 patients (93.8 %) in the third group. Thus, sufficiently high efficiency was shown for all drugs used. Investigation of morphofunctional cardiac parameters by means of ECHO-CG is of great interest in terms of evaluation of treatment efficacy and in terms of possible development of CHF with intact EF. Parameters of myocardial DD in patients without EF decrease are provided in Table 2. As shown in Table 2, mean values of the LA volume index before and after the selected course of treatment did not show significant differences. This parameter did not exceed the threshold values of 34 mL/m² in the vast majority of patients examined. Values that exceeded the threshold were observed in 4 patients in the first group, in 3 patients in the second group, and in 8 patients in the third group. The velocity ratio of early diastolic LV filling and blood flow in LA systole (E/A) is widely used in local and international practice as a classic parameter of DD of LV myocardium. At the same time, a tendency to the decrease in this parameter with age is shown.

Table 1. The values of blood pressure at brachial artery in patients before therapy and after 6 months of selected therapy (indicated median, interquartile range)

	Group 1		Group 2		Group 3	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
SBP, mm Hg	166.5	135.5	163.2	133.6	165.8	135.2
	161–169	128–139	160–169	125–137	161–171	130–138
DBP, mm Hg	105.1	83.1	107.1	80.1	107.8	82.2
	99–112	75–89	99–113	72–88	98–114	73–88

Table 2. Echocardiographic parameters in patients before treatment and after 6 months of selected therapy (median, interquartile range)

	Group 1		Group 2		Group 3	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
LA volume index, mL/m ²	30.5 25.2–33.9	29.2 25.2–33.9	30.7 25.6–33.8	28.5 24.9–33.9	31.2 25.3–34.8	28.8 25.1–33.8
EF, %	58.2 52.2–61.3	62.2±7.5 53.5–68.3	58.6 52.5–62.0	63.2 54.8–69.3	59.1 53.2–62.2	61.5 56.7–67.8
E/A	0.76 0.46–0.88	0.94* ^{**} 0.56–1.15	0.75 0.41–0.90	0.79 0.51–1.05	0.75 0.43–0.87	0.92* ^{***} 0.60–1.10
e' _{septal}	7.3 7.0–9.9	8.2 7.1–10.3	7.2 7.0–9.5	7.3 7.5–9.6	7.3 7.0–9.3	8.2 7.0–10.2
e' _{lateral}	10.8 10.0–15.8	12.9 10.2–13.6	10.5 10.0–12.1	10.6 10.1–12.1	10.5 10.0–12.3	12.8 10.2–14.6
E/e' _{mean}	11.8 6.2–16.8	11.2 8.2–13.2	11.2 6.1–16.2	11.4 6.3–16.2	11.5 6.3–16.4	10.2 7.2–13.2

Note: * — presence of significant differences for $p < 0.05$ before and after treatment
** — presence of significant differences for $p < 0.05$ between Group 1 and Group 2
*** — presence of significant differences for $p < 0.05$ between Group 2 and Group 3

However, according to guidelines, the threshold interval of its values is between 0.8 and 2.0. Thus, the mean values obtained demonstrate a decrease in this parameter below the threshold in all three groups before treatment. When studying the structure of groups, it was revealed that in some patients, the specified parameter, however, was in the range of standard values (5, 5, and 9 patients, respectively). Along with provided therapy, the patients treated with bisoprolol and valsartan were noted to have a significant increase in this parameter ($p < 0.05$). No significant changes were revealed in patients treated with perindopril.

The analysis of myocardial velocity parameters by the tissue Doppler ultrasound in the period of early diastolic LV filling when measured at the level of the mitral valve ring in its lateral parts and interventricular septum, showed positive, but statistically unreliable, changes in the groups treated with bisoprolol and valsartan, and practically no changes when perindopril was used. It should be noted that there was no decrease in these parameters (threshold value $e'_{\text{septal}} > 7$ cm/sec and $e'_{\text{lateral}} > 10$ cm/sec) in most patients examined before and after treatment. However, these parameters were decreased in 4, 4, and 7 patients (by groups), and they were restored to the normal values during treatment in 3, 3, and 5 from those.

The study of the E/e'_{mean} mean ratio demonstrated no significant change in all groups.

Conclusion

The results of advanced analysis of morphometric and functional echocardiogram parameters, which are DD markers, using criteria proposed by Euro-Filling Group (2017), showed presence of DD and increase in final flowing pressure (FFP) in the LV cavity only in 4, 4, and 7 patients, which was 16 %, 17.4 %, and 21.2 %, respectively by groups. At the same time, this pathological condition was observed in 20 (80 %), 18 (78.3 %), and 23 (71.9 %) patients, respectively, when using the E/A ratio, which is common in local practice. Analysis of the efficacy of the treatment revealed that in general, the positive impact was due to the change in decreased parameters in the group with the presence of DD or in the intermediate group in terms of the risk of its development (more than 50 %, or 50 % of criteria specified, respectively). DD prevalence in patients with EH significantly differs when using the most common traditional E/A criteria (up to 80 %) compared with using modern test panel (21.1 %). There is generally the same efficacy of all three drugs in terms of achieving target BP values. It has been shown that bisoprolol and

valsartan have the most pronounced effect on the morphometric parameters of the LA and intracardiac hemodynamics.

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