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Clinical efficacy of treating chronic heart failure with a combination of spironolactone and trimetazidine

A. A. Upnitskiy

Klinische Effektivität der Therapie der chronischen Herzinsuffizienz mit Kombination von Spironolacton und Trimetazidin.
Kurzfassung: In vorliegender Arbeit sind die Ergebnisse der Untersuchung der klinischen Wirksamkeit der Therapie der chronischen Herzinsuffizienz bei Patienten, die sich in einer Risikogruppe gemäß dem Alterskriterium befinden, präsentiert. 90 Patienten mit chronischer Herzinsuffizienz bei einer erhaltenen linksventrikulären Ejektionsfraktion wurden in 3 Gruppen mit einer weiteren Beobachtung nach 6 und 12 Monaten eingeordnet. In Gruppe B (n = 30) erhielten die Patienten ausschließlich eine Basistherapie, in Gruppe S (n = 30) wurde zusätzlich Spironolacton verordnet, in Gruppe S+T (n = 30) wurden zusätzlich Spironolacton und Trimetazidin eingesetzt. In allen Gruppen wurde im Verlauf der Therapie ein positiver klinischer Effekt beobachtet: Verbesserung des Allgemeinbefindens, Reduktion der Dyspnoe, Beseitigung der Ödeme der unteren Extremitäten, Erhöhung der Belastungstoleranz nach den Ergebnissen des 6MGT (6-Minuten-Gehtest). Es wurde festgestellt, dass eine 12-monatige Therapie mit einem zusätzlichen Einsatz von Spironolacton in Kombination mit Trimetazidin im Vergleich zur Basistherapie effektiver ist. Dies äußerte sich in einer signifikant größeren Zunahme der Gehstrecke im Rahmen des 6-Minuten-Gehtests, in der Reduzierung der Punkte im Minnesota-Fragebogen zur Lebensqualität der Patienten mit chronischer Herzinsuffizienz, in einer häufigeren Erholung des zirkadianen Blutdruckrhythmus, in einer signifikanten Verkleinerung des linken Ventrikels, in der Reversion der Dilatation des linken Vorhofs und in der Senkung des systolischen Blutdrucks in der Pulmonalarterie aufgrund einer signifikanten Verbesserung der linksventrikulären diastolischen Funktion.

Schlüsselbegriffe: chronische Herzinsuffizienz, Pharmakotherapie, Morbiditätssenkung, klinische Studie, Spironolacton, Trimetazidin.

Abstract: This paper presents the results of a study of the clinical efficacy of treatment of chronic heart failure in patients who are at risk by age. 90 patients, who have chronic heart failure with preserved ejection fraction, were divided into three groups with further observation after 6 and 12 months. In group B (n = 30), patients received only basic therapy, in group S (n = 30), spironolactone was additionally prescribed, in group S+T (n = 30), additionally spironolactone and trimetazidine. A positive clinical effect was noted in all groups during treatment – improvement in general well-being, reduction of dyspnea, liquidation of lower limb swelling, and an increase in exercise tolerance according to T6X results. As it was found, 12-month treatment with the additional use of spironolactone in combination with trimetazidine is more effective compared with basic therapy. It was expressed in a significantly greater increase in the six-minute walk distance, a decrease scores in the Minnesota's questionnaire about quality of life for patients with chronic heart failure, a greater frequency of recovery of disturbed circadian rhythm of blood pressure, a significant reduction of the size of the left ventricle, reversion of dilatation of the left atrium, a decrease in systolic blood pressure in the pulmonary artery due to a significant improvement in left ventricular diastolic function. **Z Gefäßmed 2019; 16 (2): 10–22.**

Key words: chronic heart failure, pharmacotherapy, morbidity rate decrease, clinical trial, Spironolactone, Trimetazidine

Introduction

The causes of emergence of diastolic dysfunction, which is considered as the main component of the formation of chronic heart failure with the preserved ejection fraction (CHFpEF), are processes of impaired active relaxation of the left ventricle (LV) and growth of passive rigidity. Violation of active relaxation of the left ventricle is an energy-intensive process that can manifest itself as a result of ischemia of cardiomyocytes or impairment of their energy metabolism. Also, an increase of myocardial stiffness of LV leads to an increase in end-diastolic pressure and a decrease in cardiac output, which is described in studies of diastolic function at rest and under the influence of loads with the help of both invasive and non-invasive measurements. The excessive accumulation of collagen and sodium ions with the transition to erythrocytes, along with a deficiency in titin phosphorylation are the reason for the increase in the rigidity of the extracellular matrix. Other pathophysiological mechanisms were also studied: impaired left ventricular vascular compliance, reduced of peripheral vasodilation, chronotropic response, diastolic and systolic dyssynchrony, and dysfunction of autonomic nervous system [1].

It is a well-known fact that in CHFpEF, the disease progresses due to hyperactivation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Many recent studies have focused on molecular disorders, in particular, the study of reduction of the cascade activity of the nitrogen oxide cyclic bed of systemic vascular guanosine monophosphate (cGMP) – proteinkinase, which aggravates oxidative stress and leads to endothelial dysfunction and microvascular inflammation. Systemic inflammation is a trigger of endothelial (ED) and microvascular dysfunction, which can develop both in cardiovascular disease and in physiological aging. ED plays an important role in increasing the stiffness of the arterial vessels of the elastic type. In addition to changes in the vascular endothelium, one of the main factors in the formation of rigidity of the aorta as an important extracardiac factor in the development of CHFpEF during aging and arterial hypertension (AH) is the reduction in number of elastic fibers in the aortic wall, their depletion, splitting and fragmentation due to increased content of collagen fibers of basal substance and calcium deposits. In turn, an increase in rigidity of the aorta accelerates speed of propagation of pulse wave (SPPW), increase in amplitude and duration of the reflected wave contributes to an increase in systolic and pulse arterial pressure (AP) [2]. This mechanism is fundamentally important from point of view of the formation of left ventricular hypertrophy – the central morphological substrate of the development of CHFpEF [3].

Deceleration of relaxation of the myocardium occurs in case of pressure load. It should be noted that at the moment there is a noticeable lack of complex scientific works that would si-

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multaneously study the function of the vascular endothelium and the resilient-elastic properties of arteries in patients with arterial hypertension with CHFpEF.

Concomitant diseases have a significant effect on the pathophysiological features of chronic hematologic functional conditions, arterial hypertension, coronary heart disease, diabetes mellitus, atrial fibrillation (AF), obesity, obstructive apnea of sleep and chronic kidney disease (CKD). The presence of atrial fibrillation, pulmonary hypertension, anemia, vascular pathologies, and chronic renal failure affects prognosis of the course of the disease in patients suffering from CHFpEF [4]. With a serum creatinine level of more than 2 mg/dl, during inpatient treatment the risk of mortality increases, regardless of left ventricular ejection fraction (LVEF): 4.8% for CHFpEF, 8.4% for CHF with decreased LVEF, $p < 0.0001$. The increase in blood urea nitrogen is > 37 mg/dl (odds ratio: 2.53; 95% confidence interval [CI] 2.22–2.87) and the SAP level is ≤ 125 mmHg (odds ratio –2.58; 95% CI 2.33–2.86) are the most powerful predictors of stationary lethality in chronic CHFpEF and in CHF with reduced LVEF.

Literature Review

Arturi et al. [5] conducted a study in which the effect of the content of extracellular matrix on hemodynamic parameters, as well as forecasts of patients with CHF of non-ischemic etiology, was invasively measured. In patients in whom > 30.5% of the extracellular matrix was registered, regardless of values of left ventricular ejection fraction, the frequency of hospitalizations for decompensation or cardiovascular death during the 9-month observation period was statistically higher than in patients with area of extracellular matrix less than 30.5%. The authors noted direct correlations between LV end-diastolic pressure, the pressure of jamming of pulmonary capillaries, average arterial pressure in pulmonary artery, pressure in the right atrium, and extracellular matrix shares.

Among the Echo-CG parameters, the most stringent predictor of a poor prognosis is the volume of left atrium (VLA). Roth et al. [6] identified an VLA index of > 32 ml/m^2 as an independent predictor of cardiovascular events in a population over 65 years of age. This indicator predicted the occurrence of first cardiovascular complication at the same level with such Echo-CG-indicators such as IMM LV > 120 g/m^2, systolic and diastolic LV dysfunction. Similar data were obtained in the echocardiographic sub-study of Irbesartan in CHFpEF (I-PRESERVE), where the increase in left atrium (LA) was more significant in determining the prognosis than ultrasound doppler-sonography indicators DD. The importance of determining the size of the left atrium is due to the fact that its increase does not depend on overload volume of the heart and reflects presence of DD for a long period.

Constant relevance of CHFPEF is due to the uncertainty of its pathogenesis, diagnosis, lack of clear positive results of treatment. The issues of improving the diagnosis of CHFpEF in old age with high polymorbidity levels remain actual. Laboratory tests, first of all, plasma level of BNUP, and echocardiographic data that confirming the presence and severity of diastolic dysfunction [7] are mandatory stages of diagnosis.

Among clinical manifestations of CHF, the following typical symptoms are considered: dyspnea, peripheral edemas, pulmonary rales, tachycardia, hepatomegaly, increased pressure in jugular veins, general weakness, most of which are due to sodium and fluid retention. However, in elderly people, their sensitivity and specificity are insufficient for the diagnosis of CHF, due to influence of comorbid conditions. In general, patients with CHFpEF are characterized by a high level of polymorbidity. Among the diseases that are associated with CHFpEF, the most significant specific weight is AH, type 2 diabetes, obesity, CKD, COPD, AF and anemia. Recently, the influence of subclinical hypothyroidism on development of HSNSFV has been noted. A comparative analysis of 2429 patients with reduced and 2167 with preserved LV EF showed that, on average, in the group of patients with CHFpEF, obesity, AF and AH were more common, while with reduced EF – are the ischemic heart disease (CHD) and valve lesions [8].

In general, the elderly patients are characterized by the absence of typical symptoms in one third of patients and, conversely, the presence of atypical symptoms associated with comorbidities. In this regard, an analysis of specificity and sensitivity of symptoms in patients with suspected CHF syndrome with concomitant diseases was carried out. The main complaints were reduction of working capacity (40%), dyspnea (35%), cognitive impairment (31%) and disorders of musculoskeletal system (29%). Half of the patients had a combination of two or more symptoms. According to the results of the analysis, independent determinants of heart failure were identified: male gender, age, paroxysmal night dyspnea, lack of wheezing, loss of appetite, and low body mass index (BMI) [9]. Pulmonary rales and peripheral edema are often found in acute decompensation of heart failure, while in chronic course interstitial edema decreases due to increased lymphatic drainage from the lung tissue, which leads to an increase in pressure in the left atrium in absence of pulmonary congestion. Uncontrolled AH was more often found in CHFpEF, and pulmonary rales and increased pressure in the jugular veins were found in CHF with systolic dysfunction. In general, the presence of typical symptoms of CHF is more characteristic of CHF with systolic dysfunction. Among concomitant diseases that "mask" CHF, a special place is occupied by COPD. Dyspnea is observed in one third of patients with CHF; it is a factor in increased risk of cardiovascular mortality. Dyspnea is also a symptom of diseases such as anemia, obesity, and neurological diseases (myopathies, anxiety disorders). The sensitivity of this symptom in diagnosis of CHF is 66%, and the specificity is only 52%, while higher specificity is inherent in orthopnea – 85% and paroxysmal shortness of breath at night – 76%, with lower sensitivity [10].

In the geriatric population, relationship between CHF and cognitive impairment must be considered. Cognitive dysfunction affects the attitude of patients to their state of health and adherence to treatment, and also complicates the diagnostic search. In the group of patients with cognitive dysfunction, a higher rate of hospitalization and mortality was observed. Results of recent studies have shown that neuropsychological functions can improve, but not normalize, after treatment for CHF decompensation.

A more complete blockade of RAAS in patients with CHF is achieved with use of aldosterone antagonists in addition to an ACE inhibitor. Aldosterone, which is synthesized in the glomerular zone of adrenal cortex, is considered the most powerful of mineralocorticoids and one of the markers of CHF severity. Among the mechanisms of increased aldosterone synthesis in patients with CHF, there is an activation of the RAAS and angiotensin II, irritation of the volumo- and osmoreceptors of heart and blood vessels while reducing the minute volume of blood, increasing central venous pressure, which leads to irritation of the right atrial baroreceptors and hollow veins. Well-known effects of aldosterone are sodium and fluid retention with simultaneous release of potassium and magnesium ions. By activating the mineralocorticoid receptors in heart and vessels, circulating and tissue aldosterone promotes the activation of fibroblasts, enhancing the formation of collagen and the formation of interstitial myocardial and perivascular fibrosis. And this, in turn, leads to an increase in the stiffness of left ventricle, an increase in DD myocardium, and the occurrence of CHFpEF [11].

The blockade of mineralocorticoid receptors (MR) is considered as a promising way of treating HSNSF in connection with pleiotropic effects – inhibition of inflammation and production of free radicals, LVH regression, improvement of vascular elasticity and myocardial perfusion. The antagonist of MKR spironolactone improves quality of life, LV diastolic function, as evidenced by the results of the Aldo-DHF, TORCAT study. In particular, the study ALDO-DHF (ALDOsterone receptor blockade in Diastolic Heart Failure) studied the effect of 25 mg of spironolactone during 12 months compared with placebo in 422 patients with CHFpEF on E/E‘ and portability of physical exercise with peak oxygen use during bicycle ergometry time. After 12 months of treatment in the group of patients who received spironolactone, diastolic function was significantly improved (decrease in E/E‘). It was accompanied by a simultaneous decrease in LV and Nt-pro-MNUP with a moderate decrease in blood pressure by an average of 8.3 mmHg. However, these significant structural and functional changes in the heart did not lead to an improvement in exercise tolerance, FC according to NYHA and quality of life. Among the side effects of using spironolactone, kidney function deterioration was recorded in 36% of patients compared to the placebo group, where these changes were recorded in 21%, a higher incidence of hyperkalemia, anemia (16% vs 9%) and gynecomastia (4% vs 1%) [12].

In a study using spironolactone at a daily dose of 50 mg for 6 months, 92 patients with CHFpEF improved diastolic function, which was reflected in a change in transmitral blood flow (increase in the velocity of wave E, time of slowing down wave E and the ratio E/A while reducing the velocity of wave A and the time of isovolumic relaxation of LV). These changes were accompanied by an improvement in clinical symptoms, a decrease in the level of Nt-pro MNUP, which correlated with a decrease in FC on the NYHA. However, the assessment of DD LV was performed only with use of the transmitral blood flow assessment, which to some extent limits the significance and interpretation of the obtained results [13].

The results of the TOPCAT study (Treatment of Preserved Cardiac function heart failure with an Aldosterone anTagonist) with participation of 3445 patients showed a significant decrease in the frequency of hospitalizations for CHFpEF in the group of patients who took spironolactone, however, reduction of mortality level was not achieved. When analysing subgroups depending on the region, in patients from countries such as USA, Canada, Argentina and Brazil, primary endpoints (cardiovascular death, sudden cardiac arrest with successful resuscitation) were recorded 3 times more often in placebo group than in patients treated with spironolactone, in contrast to patients from Slovakia and Poland, where these differences have not been identified. However, additional decrease in blood pressure and high frequency of hyperkalemia in this group were also not recorded, which casts doubt on the correctness of inclusion of Eastern European patients in the study and with observation of the spironolactone reception mode [14].

It is known that contraction and active relaxation of the ventricles are energy-dependent processes. Violations of energy metabolism help to slow down contraction and relaxation of the myocardium. In early stages of heart failure, myocardial function may not suffer. However, as CHF progresses, oxidative processes in mitochondria are inhibited. On the one hand, oxidation of glucose and fatty acids slows down, and on the other, glycolysis is enhanced. Izadi et al. [15] showed that in heart failure, switching of myocardial metabolism with trimetazidine, with predominant utilization of fatty acids towards glucose oxidation, improves myocardial contractility and improves prognosis of patients with CHF and LV systolic dysfunction. Revealed positive effects of trimetazidine, which consist in maintaining the level of cellular phosphocreatine and adenosine triphosphate, reducing cellular apoptosis, improving endothelial function and reducing calcium overload of cells, were associated exclusively with CHF of ischemic genesis. According to a meta-analysis conducted by Benz [16], which included 955 patients from 17 randomized controlled clinical trials, the use of trimetazidine in patients with CHF led to a significant improvement in both clinical status (increase in the duration of exercise tests and the improvement of FC) and systolic myocardial function. In case of long-term use, these effects were accompanied by a decrease in total mortality, frequency of cardiovascular complications and hospitalizations. According to Bektas et al. [17], in addition to the above positive effects of using trimetazidine in patients with CHF, there was also a decrease in the levels of BNUP – a laboratory marker of CHF severity. Against the background of declining hospitalization, trimetazidine did not affect overall mortality rate. At the same time, in a multicenter retrospective study [18], conducted in patients who received trimetazidine compared with placebo, there was a decrease in hospitalization rates, general and cardiovascular mortality.

In few studies, the positive effects of trimetazidine in elderly patients with HSNSFV have been demonstrated – improving not only the morphofunctional state of the heart, but also main arteries and kidneys [19].

Lack of data on possible positive effects of a combination of the antagonist of the mineralocorticoid receptor spironolactone and the cardiocytoprotector trimetazidine in elderly patients with chronic hepatic hapticatomial neuritis determined one of the objectives of our study.

Materials and Methods

In the course of the experiment, 90 patients with CHFpEF were divided into three groups, 30 people each (B, S, S+T), with different methods of treatment. Further observation was carried out after 6 and 12 months. The pathogenetic treatment of the same type was the basis for all patients, which corresponded to the recommendations for the diagnosis and treatment of chronic heart failure. The main treatment included prescribing drugs from groups of an ACE inhibitor (perindopril, an average dose of 6.8 ± 0.2 mg/day) – 70%, or ARBA-II for intolerance to an ACE inhibitor (valsartan, an average dose of 189.0 ± 24.6 mg/day) – 30.0%, betablocker (bisoprolol/nebivolol in the most tolerant dose) – 67.8%, diuretic (indapamide 1.3 mg ± 0.1 mg/day) – 79.5%, calcium antagonist (amlodipine 4.2 ± 0.1 mg/day) – 45.5%. In the first group (B), only the main treatment was prescribed to patients, it was constant for at least 3 months prior to the study and remained unchanged during the experiment, the second group (S) was additionally prescribed spironolactone (25 mg/day), and the third group (S+T), in addition to basic therapy, received spironolactone (25 mg/day) and trimetazidine (35 mg twice a day). To achieve the target values of blood pressure in studied groups, an extended range of spironolactone was created, and if necessary, dosages of other antihypertensive drugs, except for spironolactone, were selectively reduced (Tab. 1). The measure of confidence, taking into account the coefficient p, was 99.9% for all calculations.

Table 1. Comparative characteristics of antihypertensive drugs indicated to patients with CHFpEF, %.

Drugs	Group B (n = 30)	Group S (n = 30)	Group S+T (n = 30)
ACE inhibitor (Perindopril)	66.7	73.3	70.0
ARB-II (Valsartan)	33.3	26.7	30.0
β-blocker (Nebivolol/Bisoprolol)	66.7	70.0	66.7
Diuretic (Indapamide)	83.3	76.7	80.0
Calcium antagonist (Amlodipine)	46.6	46.6	43.3
Spironolactone 25 mg	0	100	100
Trimetazidine 35 mg BID	0	0	100

Results and Discussion

The prescribed treatment had a positive clinical effect for all studied groups: general well-being of the patients improved, dyspnea decreased, edema of the lower extremities disappeared, and also, according to the results of T6X, the tolerance to physical exertion improved. So, it was found that the range of the 6-minute walk significantly increased in all groups 6 months after starting of therapy. The most noticeable increase in the walking distance was observed in group S (10%) and S+T (by 9.5%), in group B this figure was much lower (by 5.7%). After 12 months of treatment, an increase in the 6-minute walk distance was also observed (in group S by 13.4% compared with initial values, in group S+T by 15.1%). Presented figures are significantly higher than in group B, which received only main treatment (an increase of 6.8%) (Fig. 1).

Alleviating symptoms and improving general well-being of patients are the most important therapeutic tasks in treatment of patients with chronic heart failure. This largely refers to older patients, as with respect to the geriatric contingent, treatment priorities change in favor of improving quality of life. Proposed therapy significantly improved quality of life of patients in all studied groups. The number of points on medical parameters of quality of life (MPQL) compared with initial values decreased after 6 months of treatment: group B – by 15.4%, group S – by 27.7%, group S+T – by 24.2%. When spironolactone and spironolactone were added in combination with trimetazidine, this improvement was more pronounced (Tab. 2). Similar dynamics was also noted as a result of 12-month control, the value of MIQL decreased in group B by 25.0%, in group S by 36.8% and in group S+T by 33.2%.

Throughout the experiment, a steady positive dynamics of growth in walking distance was observed when performing T6X in the observed S and S+T groups, and in group B, an increase in distance was observed only after 6 months, but then sharply reduced. In a number of studies, during therapy with spironolactone, the results of T6X did not change significantly. However, when performing a cardiorespiratory exercise test to assess the effect of spironolactone on the functional state of subjects with CHFpEF, a significant improvement was noted, which correlated with a decrease in the severity of diastolic dysfunction in terms of E/E‘ and an increase in maximum oxygen consumption during the continuation of treatment.

A real decrease in the functional class (FC), which is the basis for assessing the severity of chronic heart failure, was detected only with addition of trimetazidine – by 40%, and contributed to the transfer of 66.7% of the studied patients (S+T group) to a smaller FC according to NYNA (Tab. 2). In group S, there was only a tendency to decrease in FC by NYNA by 10% from the initial level. Positive changes in functional state and quality of life of patients can be partially attributed to a decrease in blood pressure.

As it is shown in Table 2, a decrease in both office systolic blood pressure (SBP) and diastolic blood pressure (DBP) was observed in all control groups. At a 6-month control examination was recorded the reduction in SBP by 7.7% in group B,

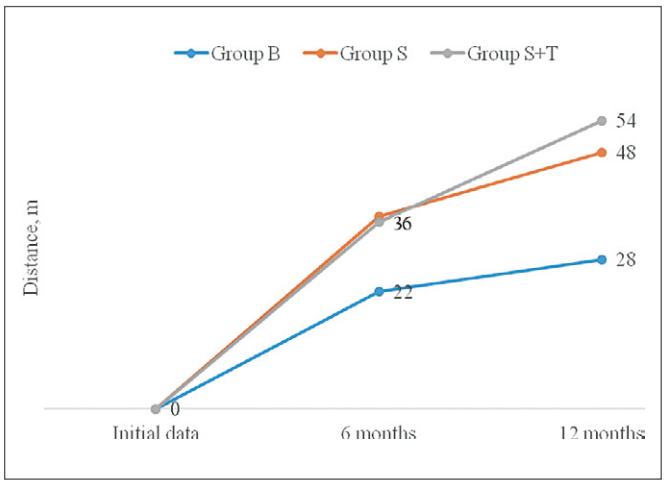

Figure 1. Increase of 6-minute walk distance length in different treatment groups.

Table 2. Dynamics of blood pressure, functional status and quality of life in patients who received basic therapy (group B) and basic therapy in combination with spironolactone (group S) and with spironolactone and trimetazidine (S +T)

Parameter	Group B			Group S			Group S +T		
	Initial data	Δ_{0-6}	Δ_{0-12}	Initial data	Δ_{0-6}	Δ_{0-12}	Initial data	Δ_{0-6}	Δ_{0-12}
SPB, mmHg	155.4 ± 2.8	–12.0 ± 1.9*	–14.6 ± 2.0*	154.1 ± 2.4	–16.5 ± 2.0*	–21.5 ± 2.8*#	152.7 ± 2.6	–14.5 ± 2.0*	–18.1 ± 2.5*#
DBP, mmHg	89.3±1.7	–5.7 ± 1.6*	–7.9 ± 1.2*	90.3 ± 1.8	–9.0 ± 1.5*	–11.0 ± 1.4*	88.0 ± 1.9	–7.5 ± 1.4*	–9.3 ± 1.8*
SMWT, m	380.7 ± 13.5	21.7 ± 8.3*	26.0 ± 8.7*	363.1 ± 13.5	36.4 ± 9.2*	48.8 ± 3.9*#	361.0 ± 12.9	34.3 ± 6.2*	54.6 ± 8.0*#
FC, units	1.9 ± 0.1	–0.1 ± 0.1	–0.1 ± 0.1	2.0 ± 0.1	–0.2 ± 0.1	–0.2 ± 0.1	2.1 ± 0.1	–0.3 ± 0.1*	–0.4 ± 0.1*
MPQOL, score	39.6 ± 3.0	–6.1 ± 1.9*	–9.9 ± 2.4*	46.5 ± 2.7	–12.9 ± 1.9*#	–17.1 ± 2.6*#	38.8 ± 3.1	–9.4 ± 1.9*#	–12.9 ± 2.3*#

*p < 0.05 in comparison with the initial data of the respective group; #p < 0.05 in comparison with the respective parameters in group B

by 10.7% in group S and by 9.5% in group S+T. As a result of therapy with spironolactone and its combination with trimetazidine, a more pronounced decrease in SBP was observed after 12 months of treatment (group S – by 4.6% and group S+T – by 2.5% compared with group B, all p < 0.05), which may be due to pleiotropic effects of spironolactone. DBP values had similar changes in all three groups when compared after 6 and 12 months of follow-up.

Also, the result of the proposed therapy was a regression of left ventricular hypertrophy (LVH) in all studied groups, but statistically true values could be detected only 12 months after start of treatment. In group B, which received the main treatment, decrease in mass of the left ventricular myocardium (MLM), 6 months after hospitalization, was insignificant and did not reach a statistically significant level (Tab. 3). There was a regression of LVH, which was about 4.0% and achieved a significant decrease (p < 0.05) while evaluating effectiveness of basic therapy after 12 months.

Table 3. Dynamics of structural and functional heart status parameters in the course of basic therapy after 6 and 12 months of therapy (group B)

Parameter	Initial data	Δ_{0-6}	Δ_{0-12}
LVM, g	261.5 ± 8.1	–9.3 ± 7.6	–10.4 ± 4.4*
LVMi, g/m²	130.1 ± 4.9	–4.5 ± 3.4	–5.0 ± 2.1*
IST, mm	12.6 ± 0.3	–0.4 ± 0.3	–0.7 ± 0.3*
LVPW, mm	11.4 ± 0.3	0.2 ± 0.3	–0.1 ± 0.3
LVIWT	0.46 ± 0.01	–0.01 ± 0.01	–0.02 ± 0.01
EDD, mm	49.9 ± 0.9	0.4 ± 1.0	0.6 ± 0.8
ESD, mm	30.1 ± 1.3	0.9 ± 1.4	–1.3 ± 1.4
EDV, ml	96.0 ± 5.6	–0.7 ± 3.7	6.1 ± 3.4
ESV, ml	38.5 ± 3.1	0.8 ± 2.3	0.2 ± 2.3
LVEF, %	60.3 ± 1.5	2.2 ± 1.4	1.5 ± 1.5
LAV, ml	56.6 ± 3.4	–1.0 ± 2.5	–1.3 ± 2.8
LAVi, ml/m²	27.7 ± 1.5	–0.5 ± 1.3	–0.8 ± 1.4
E/A, CU	0.84 ± 0.05	0.01 ± 0.04	0.08 ± 0.05
DT, ms	226.1 ± 11.1	–5.8 ± 4.1	–10.3 ± 5.0*
IVRT, ms	109.0 ± 4.6	–7.0 ± 6.0	–5.0 ± 5.3
E/E', units	10.5 ± 0.6	–1.3 ± 0.7	–1.2 ± 0.7
RA, mm	31.2 ± 0.6	–0.8 ± 0.6	–0.3 ± 0.5
mPAP, mmHg	25.8 ± 1.4	2.0 ± 1.6	1.6 ± 1.5

*p < 0.05 in comparison with initial data; LVM: left ventricular mass; LVMi: left ventricular mass index; IST: interventricular septum thickness; LVPW: left ventricle posterior wall thickness; EDD: end-diastolic dimension; ESD: end-systolic dimension; EDV: end-diastolic volume; ESV: end-systolic volume; LVEF: left ventricular ejection fraction; LVIWT: left ventricle interior wall thickness; LAV: left atrial volume; LAVi: left atrial volume index; DT: deceleration time; IVRT: isovolumic relaxation time; mPAP: mean pulmonary arterial pressure

With addition of basic therapy with spironolactone for 12 months, as the study showed, there is a decrease in the mass of the left ventricular myocardium and the left ventricular myocardial mass index (LVMI) by 8.9% (p < 0.001), which is significantly different compared to group B (Tab. 4). The most pronounced positive dynamics was observed during the examination after 12 months of treatment of the S+T group patients. Changes in MMLV and IMM LV were 11.0% (p < 0.001) in this group and were much higher compared with dynamics of the corresponding indicators in group B (Tab. 5). The authors found no differences in the reverse development of LVH when comparing groups S and S+T.

Regression of LVH for the most part was due to a decrease in thickness of the interventricular septum of left ventricle (TISLV), which in the additional groups of spironolactone (S and S+T) was observed after 6 months (all p < 0.05), while in group B only after 12 months.

Initial values of thickness of the posterior wall of left ventricle (PWLV) and indicators of the relative thickness of the wall of left ventricle (RTWLV), calculated on the basis of PW LV and of a finite-diastolic size (FDS), were in all test groups. However, with additional effect of spironolactone and its combination with trimetazidine, a decrease in RTWLV was observed (p < 0.05), which was not observed in the basic therapy group.

A comparative analysis of indicators describing the linear dimensions of LV (end-diastolic size [EDS], end-systolic size [ESS]) and volumetric parameters (end-diastolic volume [EDV], end-systolic volume [ESV]), obvious differences between different groups at all stages of the observation were not found, which is considered to be a typical manifestation of cardiac remodeling in CHFpEF (Tab. 3–5). The coefficient of global contractility, LV EF under the influence of the applied therapeutic approaches did not change. Table 3 shows that in

Table 4. Dynamics of structural and functional heart status parameters in the course of additional therapy with spironolactone after 6 and 12 months of therapy (group S)

Parameter	Initial data	Δ_{0-6}	Δ_{0-12}
LVM, g	249.1 ± 16.9	–10.0 ± 8.2	–22.1 ± 7.9$^{**\#}$
LVMi, g/m^2	126.8 ± 7.4	–5.0 ± 3.8	–11.2 ± 3.7$^{**\#}$
IST, mm	13.1 ± 0.5	–1.4 ± 0.6*	–1.6 ± 0.5*
LVPW, mm	10.8 ± 0.4	–0.5 ± 0.4	–0.4 ± 0.3
LVIWT	0.46 ± 0.03	–0.03 ± 0.01*	–0.03 ± 0.01*
EDD, mm	46.6 ± 1.8	1.2 ± 2.0	1.2 ± 1.8
ESD, mm	28.0 ± 1.6	–0.5 ± 1.5	0.6 ± 2.0
EDV, ml	83.4 ± 6.7	5.2 ± 7.8	3.1 ± 4.4
ESV, ml	35.7 ± 3.0	–1.0 ± 2.5	–3.0 ± 1.7
LVEF, %	60.8 ± 1.6	1.5 ± 1.6	2.2 ± 1.8
LAV, ml	68.0 ± 4.1	–7.6 ± 2.1*	–9.3 ± 2.4$^{**\#}$
LAVi, ml/m^2	34.6 ± 1.7	–3.9 ± 1.2**	–4.7 ± 1.2$^{**\#}$
E/A, CU	0.82 ± 0.08	0.03 ± 0.04	0.04 ± 0.05
DT, ms	245.7 ± 10.9	–42.8 ± 10.6$^{*\#}$	–24.9 ± 8.5$^{*\#}$
IVRT, ms	122.1 ± 7.4	–18.5 ± 8.0*	–7.8 ± 10.5
E/E', units	10.7 ± 0.6	–1.9 ± 1.0	–2.3 ± 0.8$^{*\#}$
RA, mm	30.1 ± 0.7	–0.4 ± 0.9	–0.8 ± 0.5
mPAP, mmHg	29.7 ± 1.9	–1.8 ± 2.6	–4.6 ± 2.1$^{*\#}$

$^{*}p < 0.05$, $^{**}p < 0.001$ in comparison with initial data; $^{\#}p < 0.05$ in comparison with the respective parameters in group B

Table 5. Dynamics of structural and functional heart status parameters in the course of additional therapy with spironolactone and trimetazidine after 6 and 12 months of therapy (group S +T)

Parameter	Initial data	Δ_{0-6}	Δ_{0-12}
LVM, g	259.9 ± 13.1	–13.0 ± 7.3	**–28.6 ± 7.7$^{**\#}$**
LVMi, g/m^2	133.7 ± 6.0	–6.5 ± 3.8	**–14.7 ± 4.1$^{**\#}$**
IST, mm	12.7 ± 0.5	–0.8 ± 0.4*	–1.4 ± 0.4*
LVPW, mm	11.8 ± 0.5	–0.4 ± 0.3	–0.7 ± 0.5
LVIWT	0.47 ± 0.02	–0.01 ± 0.01	–0.02 ± 0.01*
EDD, mm	49.3 ± 1.0	–0.1 ± 1.0	0.3 ± 0.9
ESD, mm	28.1 ± 1.0	0.7 ± 0.8	1.8 ± 1.0
EDV, ml	88.9 ± 5.3	–0.1 ± 3.8	1.4 ± 5.0
ESV, ml	34.8 ± 3.2	–2.2 ± 2.3	–2.4 ± 3.1
LVEF, %	62.2 ± 1.5	1.4 ± 1.6	1.9 ± 1.6
LAV, ml	56.5 ± 3.1	–7.6 ± 2.2**	**–8.8 ± 2.3$^{**\#}$**
LAVi, ml/m^2	29.3 ± 1.6	–2.9 ± 1.0**	**–4.4 ± 1.1$^{**\#}$**
E/A, CU	0.96 ± 0.06	–0.06 ± 0.05	**–0.12 ± 0.05$^{*\#}$**
DT, ms	222.2 ± 11.5	**–16.8 ± 5.2$^{**\#}$**	**–20.9 ± 6.8$^{**\#}$**
IVRT, ms	111.1 ± 4.6	–3.5 ± 5.9	–5.9 ± 0.9**
E/E', units	10.9 ± 0.5	–2.0 ± 0.7*	**–2.8 ± 0.5$^{**\#}$**
RA, mm	30.5 ± 0.5	–0.1 ± 0.6	–0.3 ± 0.5
mPAP, mmHg	28.6 ± 1.3	–1.4 ± 1.1	**–4.2 ± 1.8$^{*\#}$**

$^{*}p < 0.05$ and $^{**}p < 0.001$ in comparison with initial data; $^{\#}p < 0.05$ in comparison with respective parameters in group B.

group B, there was a slight decrease in the volume of the left atrium in indexed parameters (IPLA) by 1.7% after 6 months and by 2.3% after 12 months of treatment compared with initial values ($p > 0.05$). A statistically significant decrease in IOLP was recorded exclusively for groups S and S+T: after 6 months of observation, the dynamics of changes was reliable compared with baseline values and amounted to 11.3% in group S (Tab. 4) and 9.9% in group S+T (Tab. 5).

A decrease in IPLA by 13.6% and 15.0% in comparison with baseline values in respective groups was also observed after 12 months of therapy (Tab. 4, 5). A comparative analysis of differences between the groups showed that decrease in PLA and its indexed of indicator in groups S and S+T after 12 months of treatment was significantly different from indicators of group B who received main treatment. When analyzing the effect of different treatment methods on the regression of increased drug exposure (IPLA > 34 ml/m^2), the quantitative changes in patients in each of the studied groups were determined, their changes in quantitative ratio at all stages of control were noted. Thus, during the initial examination in baseline treatment group, the designated parameter was noted in 20% of patients; at 6th and 12th month of control no changes were detected. In patients with group S, where spironolactone was used, there was a decrease in the proportion of patients with an increased IPLA from 66.7% to 40.0% after 6 months of treatment ($\chi^2 = 4.28$; $p < 0.05$) and 26.7% after 12 months of treatment ($\chi^2 = 9.64$; $p < 0.001$). Dynamically similar changes were noted in the S+T group, where a combination of spironolactone and trimetazidine was prescribed: IPLA > 34 ml/m^2 was recorded in 33.3% of patients during the initial examination and manifested only in 16.7% of patients after 6 months of treatment ($\chi^2 = 2.22$; $p > 0.05$), decreasing to 6.7% after 12 months of treatment ($\chi^2 = 6.67$; $p < 0.001$).

When studying the effect of various treatment approaches on diastolic function of the LV, no significant changes in the E/A index were found, except for its decrease in the S+T group at 12-month control stage ($p < 0.001$) [20–22].

When analyzing temporal parameters of diastolic function (DF) in control groups, an increase in the initial IVRT averages and the absence of a significant effect on this treatment indicator in groups B and S was found. In the S+T group, a statistically significant decrease in isovolumetric relaxation time was found by 5.3 % at stage of 12-month control ($p < 0.001$). There was a significant reduction in temporal index of LV DF-DT interval in groups S and S+T after 6 and 12 months of treatment, differences with group B were noted. Similarly, a significant decrease in E/E‘ was observed only in groups, to which, in addition to basic treatment appointed spironolactone. It should be noted that statistically significant dynamics of E/E’ parameter changes were registered after 6 months of therapy in group S+T and after 12 months of therapy in groups S and S+T ($p < 0.05$) with lack of significant differences between the specified treatment plans and the basic therapy. In 80.0% of examined patients I type DD was registered; II type DD was registered only in 20.0% of patients. Hence, reduction of E/A value in group S+T patients after 12 months of treatment was not a sign of DD progression, but was associated with transformation of patients share with more severe DD by the type of pseudonormalization into a milder degree of DD-delayed relaxation. According to analysis results, the most sensitive DD parameter, which changed significantly in the course of additional spironolactone therapy and spironolactone and trimetazidine combination therapy, was E’. In group B the share of patients with E’ > 9 cm/s was equal to 86.7% during initial testing and did not change significantly in the course of therapy. However, in group S significant reduction of patients

Table 6. Dynamics of BP and ABMP parameters in the course of basic therapy

Parameter	Initial data	After 6 months of therapy	After 12 months of therapy
SBPof, mmHg	155.4 ± 2.8	143.4 ± 2.2*	140.8 ± 1.8*
SBPad, mmHg	143.0 ± 3.0	135.4 ± 2.4*	130.2 ± 2.0*
SBPd, mmHg	146.6 ± 3.1	138.3 ± 2.6*	136.1 ± 2.0*
SBPn, mmHg	136.2 ± 3.6	124.4 ± 2.2*	121.4 ± 2.1*
DBPof, mmHg.	89.3 ± 1.7	83.6 ± 1.4*	81.5 ± 1.3*
DBPad, mmHg	76.9 ± 2.0	75.0 ± 1.4	72.5 ± 1.2*
DBPd, mmHg	81.3 ± 1.8	79.4 ± 1.3	78.3 ± 1.2
DBPn, mmHg	71.5 ± 2.2	69.0 ± 1.3	66.6 ± 1.0*
PBPad, mmHg	64.9 ± 2.1	57.9 ± 1.8*	56.7 ± 1.6*
HRd, bpm	65.9 ± 1.8	71.4 ± 1.4	72.1 ± 1.2
HRn, bpm	58.8 ± 1.5	61.9 ± 1.8	59.4 ± 1.1
TI SBPd, %	57.8 ± 4.9	49.9 ± 4.0*	40.1 ± 6.1*
TI SBPn, %	67.0 ± 5.0	46.7 ± 4.1*	46.7 ± 7.1*
TI DBPd, %	27.4 ± 4.7	20.6 ± 2.7	18.4 ± 2.1*
TI DBPn, %	37.1 ± 6.0	28.1 ± 4.6	15.3 ± 2.2*

*$p < 0.05$ in comparison with initial data; SBPof: office systolic blood pressure; SBPad: average daily systolic blood pressure; SBPd: daytime systolic blood pressure; SBPn: nighttime systolic blood pressure; DBPof: office diastolic blood pressure; DBPad: average daily diastolic blood pressure; DBPd: daytime diastolic blood pressure; DBPn: nighttime diastolic blood pressure; PBPad: average daily pulse blood pressure; HRd: daytime heart rate; HRn: nighttime heart rate; TI SBPd: time index of daytime systolic blood pressure; TI SBPn: time index of nighttime systolic blood pressure; TI DBPd: time index of daytime diastolic blood pressure; TI DBPn: time index of nighttime diastolic blood pressure.

share with the specified DD parameter by 66.7% was observed in comparison with initial data ($\chi^2 = 26.8$; $p < 0.01$), and in group S+T – by 63.4% ($\chi^2 = 26.4$; $p < 0.01$) after 12 months of treatment.

In each of the studied groups the authors registered a share of patients with signs of moderate pulmonary hypertension, which was equal to 36.6% (11 patients), 46.6% (14 patients) and 60.0% (18 patients) in groups B, S and S+T, respectively. In the course of basic therapy there were no significant changes in mPAP observed, while in groups with additional spironolactone and additional spironolactone and trimetazidine combination therapy, a significant decrease in this parameter was registered (by 15.5% and by 14.7%) after 12 months of therapy.

The importance of influence on enlarged LA, which is considered to be a marker for DD severity, is confirmed by observation studies data, where LAVi > 34 ml/m^2 acted as an independent predictor of both cardiovascular and overall mortality, manifested heart failure development, atrial fibrillation and ischemic stroke, regardless of associated LV hypertrophy. Thus, decrease of LAVi in the course of treatment with spironolactone and its combination with trimetazidine requires further detailed investigation in order to determine the probable prognosis modified influence of spironolactone in patients with CHFpEF.

The improvement of diastolic function (by the dynamics of E/E', E' and DT parameters) resulted in mPAP decrease only in groups S and S+T by 4.6 ± 2.3 mmHg and 4.2±1.8 mmHg, respectively, after 12 months of therapy. RV dimensions, measured from parasternal access by the heart long axis, were similar in all the comparison groups and did not change under treatment. However, in 60.0% of patients from group B the authors registered insignificant excess of RV > 30.0 mm, which was identified in 33.3% of patients in group S and in 20.0% of patients in group S+T.

The importance of this parameter positive dynamics, associated with pulmonary hemodynamics, was confirmed by the conducted studies that demonstrated the role of pulmonary hypertension and enlargement of RV as survival limiting factors in patients with CHFpEF.

Geriatric patients diurnal blood pressure profile is characterized by circadian rhythms disorders, increase of morning rising rate and variability of blood pressure. One of the prospective observation studies, which enrolled 516 patients with CHF, was focused on evaluation of overall mortality and rate of cardiovascular events development (median of observation was 20.9 months) in relation to diurnal blood pressure profile. It was determined that in patients with CHFpEF, circadian rhythm of "non-dipper" BP type increased the possibility of unfavorable events by 2.3 times in comparison to patients with CHFpEF.

According to the data obtained by Japanese researchers, patients with CHFpEF had higher rates of BP and higher rates of "night-peaker" blood pressure circadian rhythms disturbances in comparison with patients with CHFpEF.

After 6 months of basic therapy, a significant decrease of office blood pressure variables was registered (Tab. 6). Along with it, SBP levels did not reach target values (< 140 mmHg) in 63.3% of patients that received basic therapy, and DBP levels (< 90 mmHg) in 40.0% of patients. Similar trending changes were observed during evaluation of 24-hour blood pressure parameters monitoring (ABPM): SBPad significantly decreased after 6 months of therapy, while DBPad significantly changed only after 12 months of therapy. Mean pulse blood pressure (PBPad) values significantly decreased at all stages of treatment control.

The most significant office SBP and DBP decrease (by 16.5 ± 2.0 and 9.0 ± 1.5 mmHg, respectively) was registered in the group with additional spironolactone therapy after 6 months of treatment, while only in 6 (20.0%) patients SBP values exceeded the target ones, and in 2 (6.7%) patients' threshold values of DBP were registered, which showed significant tendency towards decreasing in the course of further therapy (Tab. 7).

Target BP levels were not achieved in patients, who had additional combination therapy with spironolactone and trimetazidine, with the rate similar to the patients, who had additional spironolactone therapy: by SBP level in 5 (16.6%) patients after 6 and 12 months of therapy and by the level of DBP in 6 (20.0%) patients after 6 months of therapy, i.e. decreased by 2 times after 12 months of therapy (Tab. 7). Target level based BP analysis in geriatric patients with BP < 150/90 mmHg showed that in each of the studied groups a share of patients remained, whose

Table 7. Dynamics of BP and ABMP parameters in the course of additional spironolactone therapy

Parameter	Initial data	After 6 months of therapy	After 12 months of therapy
SBPof, mmHg	154.1 ± 2.4	137.6 ± 1.8*	132.6 ± 1.5*#
SBPad, mmHg	141.0 ± 3.5	130.2 ± 2.4*	129.9 ± 2.0*
SBPd, mmHg	144.3 ± 3.7	135.7 ± 2.5*	134.7 ± 2.3*
SBPn, mmHg	137.1 ± 3.9	123.8 ± 2.8*	117.0 ± 2.7*
DBPof, mmHg	90.3 ± 1.8	81.3 ± 1.2*	79.3 ± 1.0*
DBPad, mmHg	78.0 ± 1.6	74.5 ± 2.4	70.5 ± 1.5*
DBPd, mmHg	81.2 ± 3.4	80.5 ± 2.7	75.0 ± 1.7*
DBPn, mmHg	73.8 ± 2.2	68.9 ± 2.2	65.9 ± 1.4*
PBPad, mmHg	62.6 ± 1.7	57.2 ± 1.2*	56.2 ± 1.8*
HRd, bpm	68.2 ± 3.1	71.3 ± 3.2	67.3 ± 1.9
HRn, bpm	60.5 ± 2.3	62.0 ± 1.6	60.6 ± 1.7
TI SBPd, %	58.7 ± 4.8	45.7 ± 3.8	39.8 ± 4.9*
TI SBPn, %	68.1 ± 5.9	43.0 ± 4.0*	36.3 ± 5.4*
TI DBPd, %	31.4 ± 8.2	25.6 ± 6.4	13.3 ± 1.9*
TI DBPn, %	38.2 ± 7.9	33.0 ± 6.9	14.5 ± 2.4*

*$p < 0.05$ in comparison with initial data; #$p < 0.05$ in comparison with respective parameters from group B

Table 8. Dynamics of office BP and ABMP parameters in the course of additional spironolactone and trimetazidine therapy

Parameter	Initial data	After 6 months of therapy	After 12 months of therapy
SBPof, mmHg	152.7 ± 2.6	138.2 ± 1.6*	134.6 ± 1.7*#
SBPad, mmHg	138.2 ± 2.8	128.3 ± 2.3*	123.8 ± 2.0*
SBPd, mmHg	141.2 ± 2.5	135.6 ± 1.8*	132.6 ± 1.8*
SBPn, mmHg	130.2 ± 3.1	121.5 ± 2.2*	115.7 ± 2.1*
DBPof, mmHg	88.0 ± 1.9	80.5 ± 1.4*	78.7 ± 1.4*
DBPad, mmHg	76.2 ± 2.0	71.2 ± 1.4	69.8 ± 1.4*
DBPd, mmHg	79.7 ± 1.8	76.6 ± 1.3	76.0 ± 1.5
DBPn, mmHg	70.1 ± 2.1	65.8 ± 1.3*	63.6 ± 1.1*
PBPad, mmHg	61.1 ± 1.6	56.7 ± 1.3*	55.6 ± 1.5*
HRd, bpm	68.8 ± 1.5	71.0 ± 1.5	70.5 ± 1.9
HRn, bpm	61.4 ± 1.5	61.2 ± 1.2	58.8 ± 1.3
TI SBPd, %	49.2 ± 5.1	40.6 ± 4.4*	33.4 ± 4.0*
TI SBPn, %	60.7 ± 6.8	40.5 ± 3.9*	29.5 ± 4.8*
TI DBPd, %	23.1 ± 4.2	16.7 ± 2.5	13.1 ± 1.8*
TI DBPn, %	30.1 ± 6.0	17.0 ± 3.8*	12.1 ± 2.2*

*$p < 0.05$ in comparison with initial data; #$p < 0.05$ in comparison with respective parameters in the control group

BP did not meet target levels. There were 9 (30%) patients in group B with only basic therapy, while there were only 2 (6.7%) patients in group S and 1 (3.3%) patient in group S+T.

It is known that in patients with arterial hypertension, who do not receive therapy, average diurnal level of SBP is by 4–15 mmHg lower and level of DBP is by 3–9 mmHg lower than the values, obtained after single BP measurements in the clinics. In geriatric patients more significant differences are observed, which can be different by 22 mmHg for SBP and 10 mmHg for DBP from average diurnal levels. Average night time SBP and DBP levels were lower by 14 mmHg and 13 mmHg than the respective average daytime levels. This data indicates on complementarity of these methods and the necessity to measure office BP and to conduct ABPM.

The results of ABPM data analysis in patients with CHFpEF revealed similar above mentioned clinical picture in comparison with office BP values. In all the studied groups increase of average diurnal, daytime and night time values of SBP was registered, which was especially significant in the course of 6 months of additional spironolactone and spironolactone and trimetazidine combination therapies (Tab. 7, 8). However, these levels did not meet the recommended threshold values. Only after 12 months of therapy average diurnal values of SBP significantly changed in patients, who received spironolactone and spironolactone in combination with trimetazidine in addition to the basic therapy for CHF: SBPad was < 135 mmHg, SBPd was < 135 mmHg and SBPn was < 120 mmHg. It should be noted that in all patients, regardless of the received therapy, decrease of SBP after 6 and 12 months of treatment was statistically significant. The analysis of the respective parameters of DBP showed that its average diurnal levels did not exceed the recommended 80 mmHg in one of the studied groups and significantly decreased in all groups only after 12 months of therapy ($p < 0.05$). At the same time, the authors registered insignificant excess of average diurnal (> 80 mmHg) and average night time (> 70 mmHg) output DBP values. It should be noted that significant decrease of DBPd was registered only after 12 months of therapy in all three groups. However, additional indication of trimetazidine led to statistically significant decrease of average night time DBP values after 6 months of monitoring (Tab. 8).

The target BP level for general population of patients with AHT is determined considering age-related BP increase. There are higher BP threshold values for geriatric patients, while for ABMP parameters evaluation there is no differentiated approach. According to the data, reported by Sega et al., average daytime BP values were registered in 800 ambulatory and hospitalized patients with AHT older than 65 years old. They ranged from 128/77 mmHg to 140/78 mmHg. According to other researchers' data, average diurnal BP values were equal to 138/82 mmHg in older patients and 147/83 mmHg in elderly patients (> 80 years old). Exclusion of age-related peculiarities during ABMP parameters analysis leads to a certain inconsistency and increase of patients share, whose BP did not achieve target levels, which requires higher reference values than in middle age patients.

Level of average diurnal PBP, which is > 55 mmHg, is an important predictor of cardiovascular complications, especially, in elderly patients. Despite the fact that BP control was significant for target values achievement in the majority of patients, the values of PBP remained quite high at the stages of control, although significantly after 6 and 12 months of therapy.

HR values during daytime and night monitoring remained within the norm in all patients from all groups and did not change significantly in the course of treatment.

For quantitative evaluation of increased BP events, the parameters of "pressure load" are used. The authors in the pre-

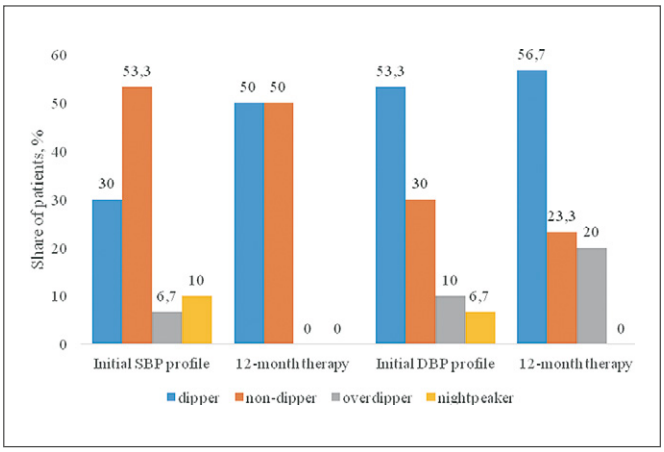

Figure 2. Changes of diurnal BP profile in the course of basic therapy.

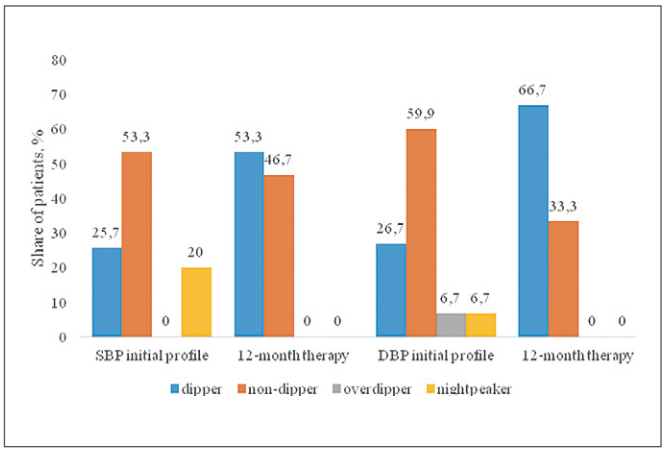

Figure 3. Changes of diurnal BP profile in the course of additional spironolactone therapy.

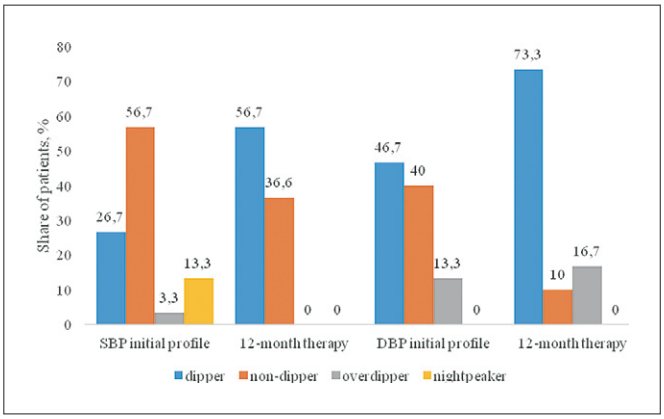

Figure 4. Changes of diurnal BP profile in the course of additional spironolactone and trimetazidine combination therapy.

sent study used time index (TI) of both BP variables in different time of the day. This parameter characterizes hyperbaric load on target organs more precisely than average BP values, and it is considered "normal" at excessive BP threshold values during daytime and night < 15% and "increased" at > 30%. As it is shown in Tables 6–8, TI SBP value exceeded the specified thresholds in all the study groups during primary examination and further at all stages of control. After treatment this parameter significantly decreased in each group. The most significant dynamics of TI DBP (by 13.0%) was registered after 6 months of treatment in group S (Tab. 7). The analysis of IT PBP showed that its decrease did not reach significant values after 6 months of therapy in group B and in group S. However, additional trimetazidine therapy led to more significant decrease of TI DBP during night after 6 months of therapy ($p = 0.04$). TI DBP daytime and night target values were registered after 12 months of treatment in groups with additional spironolactone and trimetazidine therapy (for all $p < 0.05$).

It is known that physiological profile of BP circadian rhythm is expressed as a two-phase curve with decrease of SBP and DBP values by 10–20% at night in comparison with daytime. Overall, patients with CHFpEF often had insufficient decrease of both BP variables (in 21.1% of cases). Along with this, a phenomenon of SBP or DBP "isolated non-dipping" was registered in the studied groups. Diurnal profiles of SBP and DBP in patients with CHFpEF are presented on three diagrams, depending on the treatment plan (Fig. 2–4). Daily index (DI) SBP was reduced in all the groups and was equal to 7.1 ± 1.5% in group B, 5.0 ± 2.3% in group S and 7.7 ± 1.3% in group S+T, which is explained by the share of patients with diurnal "nondipper" BP profile. Initial values of DI DBP were higher and were equal to 12.2 ± 1.5, 10.4 ± 1.8 and 13.0 ± 1.5%.

As it is shown in Figure 2, in the course of 12-month therapy the share of patients with normal diurnal SBP profile increased. However, the specified changes were statistically significant ($\chi^2 = 2.5$; $p > 0.05$). At the same time, in group S (Fig. 3) the share of patients with diurnal "dipper" BP profile significantly increased and the share of patients with "non-dipper" profile ($\chi^2 = 4.44$; $p < 0.05$) decreased. In group S+T (Fig. 4) more significant changes were observed, which influenced on DI SBP rise, which on average exceeded 10.0% in the group and after 12-month therapy was equal to 11.9±1.2%, which was explained by the increase of "dipper" patients share ($\chi^2 = 5.55$; $p < 0.05$) and insignificant increase of "over-dipper" patients share.

Under the influence of basic therapy diurnal DBP profiles did not change significantly, except for 2 patients with the most unfavorable "night-peaker" profile, whose profile changed to "non-dipper", and the share of "overdippers" patients increased by 2 times in comparison with initial data (Fig. 2).

Changes of diurnal DBP profile were mostly significant in group S (Fig. 3). Additional indication of spironolactone decreased the share of "non-dipper" patients almost by 2 times (χ^2=4.29; $p < 0.05$) and increased the share of "dippers" by 2.5 times ($p < 0.01$). At the same time, pathologic profiles with excessive increase or decrease of DBP disappeared.

As it is shown in Figure 4, therapy with additional indication of spironolactone and trimetazidine normalized the circadian DBP profile almost in ⅔ of patients at the final stage of control ($p < 0.05$). However, there were no intergroup differences identified in comparison with basic therapy.

In the course of therapy significant rate decrease of morning SBP rise was registered in all the groups: from 33.6 ± 5.9 to 18.5 ± 1.1 mmHg/h in group B, from 28.4 ± 4.2 to 18.4 ± 1.6 mmHg/h in group S and from 33.1 ± 3.7 to 19.3 ± 2.6 mmHg/h in group S+T. At the same time, morning SBP rise values did not significantly change under therapy.

Output characteristics of central aortal pressure (CASP, CADP and CPP) were similar in the three study groups in patients with CHFpEF (Tables 9–11). Basic therapy did not change these parameters statistically significant at the stages of control in 6 and 12 months (Tab. 9).

CASP decreased by 6.1 ± 0.7 mmHg in comparison with initial data ($p = 0.05$) after 12 months of spironolactone therapy, CAP decreased by 6.1 ± 0.6 mmHg after 6 month of therapy ($p < 0.05$) and by 6.9 ± 0.8 mmHg after 12 of therapy ($p < 0.05$) (Tab. 10). Similar dynamics with significant decrease of SBP and PBP was registered in group S+T (Tab. 11). However, intergroup analysis did not reveal any differences based on the treatment plan.

PWV, which is the key parameter in regional aorta stiffness evaluation, was similar in all the study groups during evaluation of initial data. In the group with basic therapy the dynamics of PWV changes did not reach statistically significant level. At the same time, in groups with additional spironolactone and trimetazidine combination therapy significant and similar decrease of PWV by 0.30 ± 0.05 m/s was registered after 6 months of therapy with further decrease by 0.50 ± 0.07 m/s after 12 months of therapy in comparison with initial data ($p < 0.05$).

AoSI, that characterized local aorta stiffness, significantly decreased in all the study groups after 6 and 12 months of monitoring. The most significant decrease of AoSI parameter was observed in group S, by 2.5 times ($p < 0.001$), and in group S+T, by 3.5 times ($p < 0.0001$), in comparison with the group with basic therapy, where AoSI decrease by 2.2 times was quantitatively the lowest in comparison with initial data ($p < 0.05$).

Evaluation of IMC in groups S and S+T showed statistically significant decrease after 6 and 12 months of monitoring. In group with basic therapy the decrease of IMC by 0.05 ± 0.01 mm was registered only after 12 months.

Endothelium vasomotor function, which was evaluated by the rate of EDVD, after primary examination was similar in the groups of comparison and ranged within 2.7% – 3.1% – 3.1% per 60 seconds of reactive hyperemia, increasing to 6.6% – 7.3% – 78% in 120 seconds (Fig. 5–7).

The most significant positive changes in EDVD were observed at early stages of reactive hyperemia: after 6 months of basic therapy EDVD rate rose by 4% in comparison with initial data when evaluated during first 60 seconds, i.e. by 2.5 times, and remained stable by the 12th months of therapy (Fig. 5). EDVD increase rate per 120 seconds during the basic therapy was lower; it was equal to 3.8% in comparison with initial level after 6 months of therapy and did not change significantly after 12 months of monitoring.

In group S EDVD increase by > 10% per 120 seconds of reactive hyperemia was registered after 6 and 12 months of therapy. It increased by 4.8% and 5.9%, respectively, in comparison with initial data, which was equal to 7.3% (Fig. 6).

Additional spironolactone and trimetazidine combination therapy had the same influence on EDVD as additional spironolactone therapy (Fig. 7).

Table 9. Changes in central hemodynamics parameters and arteries elasticity and stiffness status in the course of basic therapy, (M ± m).

Parameter	Initial data	6 months of therapy	12 months of therapy
CASP, mmHg	142.6 ± 2.4	144.5 ± 2.9	139.3 ± 3.2
CADP, mmHg	82.9 ± 2.3	84.9 ± 1.6	81.3 ± 2.1
CPP, mmHg	59.7 ± 3.0	59.4 ± 3.0	58.1 ± 2.4
PWV, m/s	9.5 ± 0.2	9.4 ± 0.2	9.4 ± 0.2
AoSI	26.3 ± 4.1	12.1 ± 1.9*	12.2 ± 2.7*
IMC, cm	1.06 ± 0.02	1.04 ± 0.03	1.02 ± 0.02*

* $p < 0.05$ in comparison with initial data; CASP: central aortal systolic pressure; CADP: central aortal diastolic pressure; CPP: central pulse pressure; PWV: pulse wave velocity; AoSI: aortic stiffness index; IMC: intima-media complex of the common carotid artery.

Table 10. Changes in central hemodynamics parameters and arteries elasticity and stiffness status in the course of additional spironolactone therapy, (M ± m).

Parameter	Initial data	6 months of therapy	12 months of therapy
CASP, mmHg	140.6 ± 3.0	136.8 ± 3.2	134.5 ± 2.9*
CADP, mmHg	80.3 ± 2.2	82.5 ± 2.3	80.9 ± 1.6
CPP, mmHg	60.4 ± 2.4	54.3 ± 2.0*	53.5 ± 2.2*
PWV, m/s	9.4 ± 0.2	9.1 ± 0.1*	8.9 ± 0.2*
AoSI	23.2 ± 3.1	17.5 ± 2.9*	9.3 ± 2.2**
IMC, cm	1.10 ± 0.01	1.07 ± 0.02*	1.05 ± 0.02*

*$p < 0.05$, **$p < 0.001$ in comparison with initial data

Table 11. Changes in central hemodynamics parameters and arteries elasticity and stiffness status in the course of additional spironolactone and trimetazidine therapy, (M ± m).

Parameter	Initial data	6 months of therapy	12 months of therapy
CASP, mmHg	136.2 ± 2.6	132.8 ± 2.5	130.1 ± 2.0*
CADP, mmHg	77.3 ± 1.8	79.9 ± 1.6	78.5 ± 1.9
CPP, mmHg	58.5 ± 1.9	53.3 ± 1.8*	52.5 ± 2.2*
PWV, m/s	9.5 ± 0.2	9.2 ± 0.1*	9.0 ± 0.2*
AoSI	28.0 ± 4.4	17.4 ± 3.9*	7.9 ± 1.4**
IMC, cm	1.10 ± 0.02	1.00 ± 0.02*	1.00 ± 0.01*

*$p < 0.05$, **$p < 0.001$ in comparison with initial data

The analysis of therapy impact on EDVD increase rate after 12 months of monitoring showed significant increase of patients share, whose EDVD rate exceeded 10%: in the group of additional spironolactone therapy in 80% (24 patients) in comparison with 20% (6 patients) after primary examination ($\chi^2 = 21.60$; $p < 0.01$) and in 70% (21 patients) in comparison with 20% (6 patients) after primary examination in the group of additional spironolactone and trimetazidine combination therapy ($\chi^2 = 15.15$; $p < 0.01$). At the same time, significant increase of patients share with EDVD rate >10% was not registered in group with basic therapy ($\chi^2=0.00$; $p > 0.05$). Thus, the proposed treatment plans, that included additional indi-

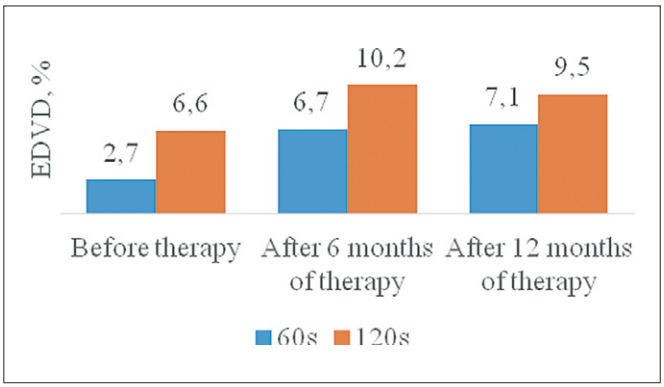

Figure 5. Influence of basic therapy on endothelium vasomotor function in patients with CHFpEF.

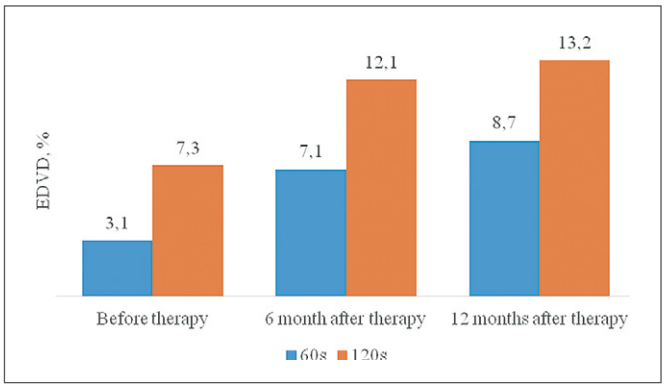

Figure 6. Influence of additional spironolactone therapy on endothelium vasomotor function in patients with CHFpEF.

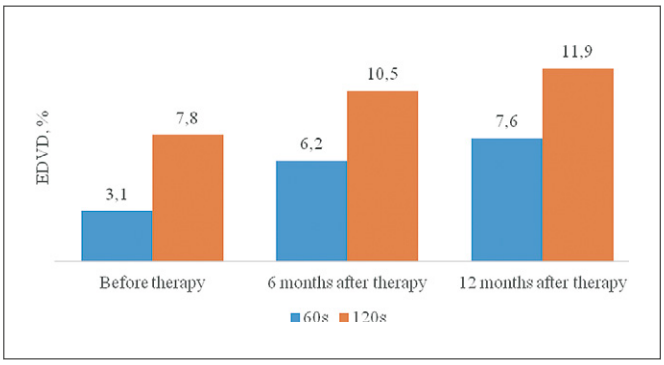

Figure 7. Influence of additional spironolactone and trimetazidine therapy on endothelium vasomotor function in patients with CHFpEF.

cation of spironolactone, had more significant impact on endothelium vasomotor function in comparison with the basic therapy.

Initial average creatinine levels did not exceed the norm in the examined patients and were equal to 88.0 ± 2.7 μmol/L in group B, 78.1 ± 3.1 μmol/L in group S and 86.2 ± 3.2 μmol/L in group S+T. However, initial values of GFR were reduced in patients in all study groups (Tab. 12). CHF class I, characterized by GFR > 90 ml/min/1.73m^2 identified at primary examination, was registered in 3 patients (10.0%) in group B and in around 7% of patients in groups S and S+T.

In groups B and S the examined patients had CHF class II with GFR values from 60 to 89 ml/min/1.73 m^2 registered more often: in 18 patients (60.6%) in group B and in 22 patients (73.0%) in group S. At the same time, in group S+T the equal shares of patients had CHF class II and III registered (in 14 patients – 46.5%, respectively). GFR was within the range of 30 – 59 ml/min/1.73m^2 in patients in group B (30%) and group S (20%).

Freedman ANOVA test was used for evaluation of different treatment plans on kidneys functional status, in particular, on GFR parameter, which was calculated by the formula CKD-EPI. Certain differences were registered in the dynamics of the GFR parameter in the course of treatment (Fig. 8–10). No significant changes in GFR were registered in group B after 12 months of therapy, which influenced on the distribution of patients by CHF classes: class I – in 5 patients (16.5%), class II – in 20 patients (67.0%) and class III – in 5 patients (16.5%), which did not differ significantly from initial distribution (Fig. 8).

In group S average creatinine levels and GFR did not reach statistically significant changes and, thus, the distribution of patients by CHF classes did not change after 6 and 12 months of (Fig. 9, 10).

At the same time, in group S+T the increase of GFR from 62.1 ± 2.4 to 68.7 ± 2.1 ml/min/m^2 was registered after 6 months of therapy and to 77.0 ± 2.6 ml/min/m^2 after 12 months of therapy, which was significantly different ($p < 0.001$). These positive dynamics in GFR contributed to the increase of patients share with CHF class I and II ($\chi^2 = 5.71$; $p < 0.05$) and to the respective change of patients share with CHF class III after 12 months of therapy ($\chi^2 = 12.27$; $p < 0.01$).

Table 12. Alternations in kidneys functional status in the course of therapy.

Parameter	Group B		Group S		Group S +T	
	Initial data	After 12 months	Initial data	After 12 months	Initial data	After 12 months
Creatinine, μmol/L	88.0 ± 2.7	85.2 ± 3.4	78.1 ± 3.1	76.3 ± 2.2	86.2 ± 3.2	83.4 ± 2.9
GFR, ml/min/1.73m^2	69.2 ± 2.9	72.0 ± 2.8	69.5 ± 2.8	68.2 ± 2.8	62.1 ± 2.4	77.0 ± 2.6*
CHF class I, number of patients	3	5	2	2	2	5
CHF class II, number of patients	18	20	22	22	14	23
CHF class III, number of patients	9	5	6	6	14	2

*$p < 0.001$ in comparison with initial values of the parameter in the respective group

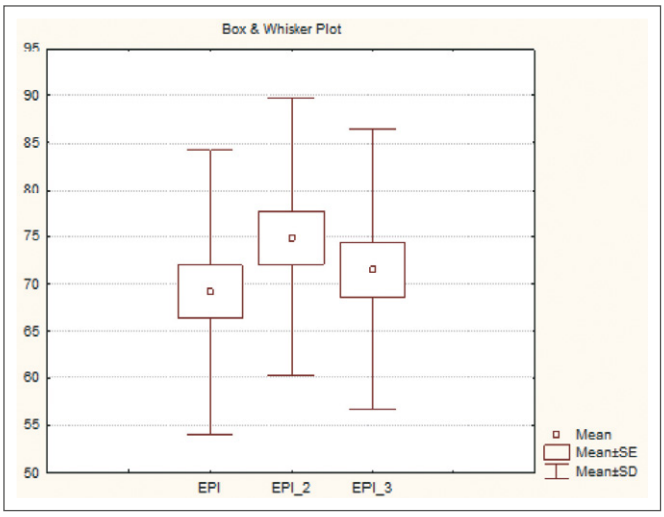

Figure 8. Evaluation of changes in GFR by CKD-EPI after 6 (EPI_2) and 12 (EPI_3) months of basic therapy.

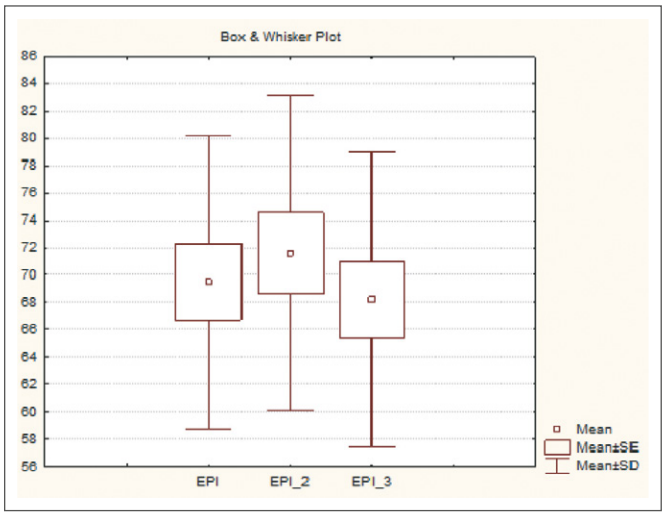

Figure 9. Evaluation of changes in GFR by CKD-EPI after 6 (EPI_2) and 12 (EPI_3) months of additional 25 mg spironolactone therapy.

Thus, Freedman ANOVA test revealed the differences in different treatment plans impact on kidneys functional status. It is possible that increase of GFR (by 14.9 ± 0.8 ml/min/1.73m^2), observed only during spironolactone and trimetazidine combination therapy, confirms positive influence of trimetazidine on kidneys functional status.

Conclusions

The clinical efficacy of a 12-month treatment with the additional use of spironolactone and the combination of spironolactone with trimetazidine compared with basic treatment manifested itself in a twofold increase in the six-minute walk, a decrease in the Minnesota quality of life score for patients with chronic heart failure (by 11.8% and 8,2% respectively). Also, there was a decrease in office and average daily blood pressure, restoration of the circadian rhythm of blood pressure, a decrease in the rate of morning increase in systolic blood pressure.

The additional use of spironolactone and its combination with trimetazidine influenced a significant decrease in the left ventricular myocardium mass index by 11.2 ± 3.7 and 14.7 ± 4.1 g/m^2, respectively, and compared to baseline therapy – by 5.0 ± 2.1 g/m^2 ($p < 0.05$). Therapy with spironolactone and its combination with trimetazidine, unlike the main therapy, was marked by a large regression of left ventricular hypertrophy and was accompanied by a noticeable reduction in the left atrial volume index (by 4.7 ± 1.2 ml/m^2 and 4.4 ± 1.1 ml/m^2), improvement of left ventricular diastolic function (decrease of E/E‘ by 2.3 ± 0.8 and 2.8 ± 0.5), decrease of systolic pressure of the pulmonary artery (by 4.6 ± 2.1 and 4.2 ± 1.8 mmHg).

It was found that the additional prescription of spironolactone and its combination with trimetazidine accompanies a significant decrease in aortic systolic and pulse arterial pressure, as well as a positive effect on the functional state of the aorta: the calculated flow rate decreased equally (by 0.50 ± 0.07 m/s), the aortic stiffness index decreased (by 59.9% and 71.7%).

An increase in the degree of endothelium-dependent vasolidation, with the appointment of spironolactone and its combination with trimetazidine in addition to the basic therapy,

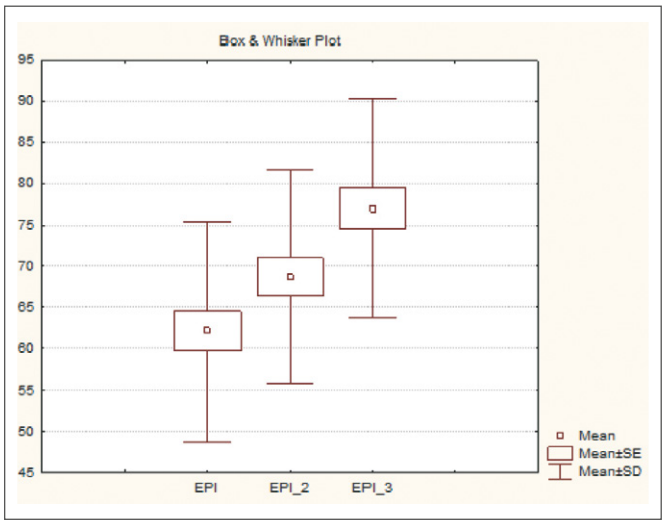

Figure 10. Evaluation of changes in GFR by CKD-EPI after 6 (EPI_2) and 12 (EPI_3) months of additional spironolactone and trimetazidine combination therapy.

was more significant and was accompanied by its normalization in 80% and in 70% of patients ($\chi^2 = 21.60$; $p < 0.01$; $\chi^2 = 15.15$; $p < 0.01$), and in the main treatment, normalization of endothelium-dependent vasolidation was detected only in 23.3% of patients ($\chi^2 = 1.00$; $p > 0.05$ compared with baseline).

A combination of trimetazidine and spironolactone led to a marked improvement in the course of chronic heart failure, affecting the change in the functional class according to NYHA by 0.40 ± 0.01 standard units with transition of 66.7% of patients to a smaller functional class according to NYHA. It was also stated that trimetazidine has a beneficial effect on the functional state of the kidneys, as evidenced by the fact that a significant increase in glomerular filtration rate (by 14.9 ± 0.8 ml/min/1.73m^2) occurs only when co-administered with spironolactone and trimetazidine.

Conflict of Interest

The author declares that there is no conflict of interest.

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