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REVIEW ARTICLES

The Influence of the Losartan, Enalapril and their Combination on the Functioning of the Heart

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Abstract

The effects of the drugs Losartan, Enalapril and their combination on the hemodynamics and morphofunctional parameters of the heart were studied in 80 patients with chronic heart failure (CHF) of II-IV functional class and the ejection fraction of the left ventricle less then 45% which worsened the ischemic cardiopathia. It was established that after a 24-week therapy with each drug and their combination, there was a decrease in symptoms in every group, but more so in the group that took the combined therapy. Along with the symptoms, there was also a decrease in the functional class of the chronic heart insufficiency by 16.4% of those who took Losartan, by 15.5% of those who took Enalapril and by 19.9% of those who took the combined therapy. The treatment with Losartan increased the fraction of ejection of the left ventricle by 14.9%, with Enalapril by 8.9% and with both drugs by 21.4%. It was established that the combined therapy, which included Losartan and Enalapril, had a better impact on the parameters of the myocardium remodeling then these drugs taken seperately.

Key words: chronic heart failure, ischemic cardiopathy, Losartan, Enalapril, myocardium remodeling.

Влияние лозартана, эналаприла и их комбинации на функцию сердца

У 80 пациентов с хронической сердечной недостаточностью II-IV функциональных классов и фракцией выброса левого желудочка менее 45% с осложнением ишемической болезни сердца изучали влияние препаратов лозартан, эналаприл и их сочетание на гемодинамические и морфофункциональные параметры сердца. Было установлено, что после 24-недельного курса лечения, все схемы терапии привели к улучшению симптоматической картины в каждой группе, но больше в группе, которая принимала комбинированную терапию. Произошло уменьшение функционального класса хронической сердечной недостаточности на 16,4% под влиянием Лозартана, на 15,5% – Эналаприла и 19,9% – комбинированной терапии. Лечение лозартаном увеличило долю выброса левого желудочка на 14,9%, Эналаприлом – на 8,9%, а обоими препаратами – на 21,4%. Было установлено, что комбинированная терапия, которая включала Лозартан и Эналаприл, имела более эффективное воздействие на параметры ремоделирования миокарда.

Ключевые слова: хроническая сердечная недостаточность, ишемическая болезнь сердца, Лозартан, Эналаприл, ремоделирование миокарда.

Introduction

Chronic heart failure (CHF) is a syndrome caused by disorders of neurohumoral regulation of the circulatory system, accompanied by systolic and/or diastolic function disorders manifested by blood stagnancy in the large and small circulatory systems [1]. Chronic heart failure is a complication of almost all cardiovascular diseases, coronary heart disease being the most frequent [3]. CHF is one of the most frequent causes of hospitalization in developed countries, especially in patients of older age groups. Patients hospitalized for decompensated heart failure are at high risk of repeated hospital admissions, the frequency of which reaches 50% within 6 months after discharge and within one year re-hospitalization reaches 68% of patients with chronic heart failure [3, 4]. According to the modern neurohumoral concepts of the pathogenesis, the primary role in the development of CHF is given to the sympathetic-adrenal (NAC) and its opposing system of the atrial natriuretic factor (PNF). This fact justifies the use of different neurohormonal modulators (NGM), including ACE inhibitors and AT receptor antagonists I in the treatment of patients with CHF [3, 4]. ACE inhibitors were the first group of drugs acting directly on the RAAS and used in a broad clinical practice [2]. By reducing the activity of RAAS and activating the system of bradykinin, ACE inhibitors have important anti-remodeling, vasodilating, diuretic and antiproliferative effects [3]. The harmonious combination of efficacy and safety has allowed this class of drugs to gain a worthy place in the treatment of patients with CHF. However, numerous clinical studies have shown that monotherapy can effectively control the symptoms of CHF in a small number of patients. This is due to the many factors of CHF and the multiple pathogenetic components involved in its development.

The period of formation and progression of CHF and its severity is defined in the majority of patients by well-timed and adequately matched pharmacotherapy. Detailed analysis of the pathogenetic model of formation and development of CHF may help in developing differentiated approaches to pharmacotherapy of this disease adapted to the pathogenic and clinical course of CHF in each specific patient. In the literature, the impact of individual drugs on various parameters and cardiac function of patients with CHF is covered pretty adequately [1, 2], but few studies have examined the possibility of combined therapy between ACE inhibitors and antagonists of AT I - receptors of the CHF.

Aim of the study - to evaluate the influence of AT I receptor antagonist Losartan, ACE inhibitor Enalapril and their combination on the clinical manifestations, hemodynamics and morphofunctional parameters of the heart in patients with chronic heart failure as a complication of chronic heart disease.

Materials and methods

The study included 80 patients with stable symptomatic CHF II-IV FC (classification of New York Association of Cardiologists - NYHA) and LV EF ≤ 45% as complication of CHF. Among the examined patients 77.5% were male and 22.5% - women aged 48 to 72 years (average age being 62.2 ± 8.4 years). 42 patients were diagnosed with CHF II FC, 21 - III FC, 17 patients - CHF IV FC. All patients have suffered an acute myocardial infarction (AMI) no earlier than 6 months before the study and had a clinically expressed angina pectoris I-III FC. Angina of I FC was diagnosed in 20 patients, II FC - in 47 patients, III FC - in 13 patients, the average angina pectoris CF value was 1.88 ± 0.2. The average duration of CHF was 8.83 ± 2.42 years. Presence of old MI was confirmed by ECG and echocardiography data. CHF duration ranged from 6 months to several years and averaged 54.8 ± 13.2 months. All patients with CHF showed a decrease of contractile function of LV myocardium, left ventricular ejection fraction averaged 42.7 ± 1.89%. CHD developed on the background of arterial hypertension (AH) in 39 patients (48.7%). All patients with CHF were divided into 3 groups: group 1 (26 patients) received Losartan at a dose of 50-100 mg once a day, group 2 (27 patients) - Enalapril 5-10 mg twice a day and group 3 (27 patients) - a combination consisting of Losartan and Enalapril. Duration of treatment was 24 weeks. All the patients were administered the standard therapy for CHF consisting in diuretics, antiagregants and, if necessary, cardiac glycosides and peripheral vasodilator - nitrates. 37.5% of patients received digoxin in a dose of 0.125 – 0.5 mg/day, 29 (36.2%) patients received hypothiazide 12.5 - 50 mg 1 time per day, 10 (12.5%) patients - Furosemide 1 mg/day 2-3 times a week. Evaluation of the effectiveness of the drugs and their combination included the examination of the dynamics of clinical manifestations of CHF, the tolerance to everyday physical activities, hemodynamic parameters - heart rate, systolic and diastolic blood pressure (mm Hg). Systolic function was assessed according to the value of LV EF and the degree of shortening of the anteroposterior size of the left ventricle in systole, diastolic function - highest peak velocity of early filling (PVEF), peak velocity of late filling (PVLF), modulus of elasticity (ME) and stiffness (MS). Morphological and functional cardiac parameters were assessed using echocardiography: by determining the size of the left atrium (LA, cm), end diastolic (EDD, cm) and end systolic (ESD cm) dimensions, LV ejection fraction (EF) in %. The tolerance to physical exertion in patients with CHF was assessed by bicycle stress test with the determination of the total performed work (TPW, W) and duration of load. Clinical and instrumental examinations were performed before treatment and after 12 and 24 weeks of therapy with Losartan, Enalapril and their combination. To assess the safety of the treatment, it was carried out a laboratory exam with an analysis of blood potassium and creatinine before treatment and after 12 and 24 weeks of treatment.

Statistical data analysis was carried out using standard methods of statistics, including the calculation of the unpaired Student-t criteria. All data are presented as mean standard deviation (M ± m). The difference was considered statistically significant at $p < 0.05$.

Table 1

The dynamics of clinical manifestations of CHF under the influence of Losartan therapy, Enalapril and their combination

Clinical symptoms	Group I (n = 26)			Group II (n = 27)			Group III (n = 27)		
	Initial values	12 weeks later	24 weeks later	Initial values	12 weeks later	24 weeks later	Initial values	12 weeks later	24 weeks later
Dyspnea in physical effort	26 100%	15 57.7%	10 38.5%	27 100 %	18 66.6%	12 44.4%	27 100%	15 55.5%	8 29.6%
Dyspnea at rest	3 11.5%	2 7.7%	1 3.8%	2 7.4%	2 7.4%	0 0%	2 7.4%	1 3.7%	0 0%
Weakness	22 84.6%	13 50.0%	10 38.5%	23 85.2%	14 51.8%	13 48.1%	21 77.7%	13 48.1%	8 29.6%
Palpitations	17 65.4%	12 46.2%	9 34.6%	17 63.0%	16 59.3%	12 44.4%	17 62.9%	10 37.0%	5 18.5%
Acrocyanosis	6 23.1%	3 11.5%	1 3.8%	6 22.2%	3 11.1%	0 0%	8 29.6%	7 25.9%	1 3.7%
Peripheral swelling	20 76.9%	13 50.0%	11 42.3%	22 81.5%	15 55.5%	13 48.1%	25 92.6%	17 62.9%	829.6%

Results and discussion

Analysis of clinical manifestations of the disease showed that after 24 weeks of treatment in all patients with CHF, there was a decrease of dyspnea and weakness, an increase in tolerance to daily stress, but it should be noted that in the group of patients treated with the drug combination consisting of losartan and enalapril, the positive dynamics of clinical symptoms of CHF was more pronounced than in case of monotherapy (tab. 1).

The data presented in table 1 reveals that after 24 weeks of treatment with Losartan the dyspea diminished by 2.6 times, with Lisinopril – 2.2 times, with the combined therapy – by 3.4 times. In all three groups the administered therapy contributed to a diminishing or disappearance of peripheral edemas: in the patients of the I and II groups this manifestation diminished by 1.8 and 1.7 times, while in the III group – by 3.1 times in comparison with the original data.

The results of the study confirmed that the positive dynamics of clinical symptoms of CHF reduced the FC, but the significance of the decrease of FC was different in every surveyed group. Thus, after 12 weeks of treatment with Losartan the FC decreased by 9.1% ($p < 0.05$), with Enalapril - by 7.2% ($p > 0.1$) and the treatment with the combination of drugs – by 13.9% ($p < 0.01$), by the end of 24 weeks the FC decreased by 16.4%, 13.5% and 19.9% respectively ($p < 0.001$, $p < 0.05$, $p < 0.001$). The dynamics of the FC under the influence of various schemes of pharmacotherapy is shown in pic. 1.

The influence of both drugs and their combination on heart rate and blood pressure in patients with chronic heart failure as a complication of CHD was approximately the same. Thus, heart rate before treatment with Losartan was 78.1 ± 12.5 bpm, with Enalapril – 79.5 ± 11.2 and with the combination of drugs – 78.3 ± 12.4 bpm. After 24 weeks of treatment significant changes in the heart rate were not observed in either group 78.7 ± 11.2; 74.4 ± 9.0 and 76.3 ± 12.1 bpm, respectively.

Receiving Losartan contributed to a reducing of SBP and decreasing of DBP from 92.4 ± 4.2 to 78.5 ± 4.0 mm Hg, while

Table 2

The evolution of the LV systolic function (M ± m)

Indices	Examined groups					
	I (n = 26)		II (n = 27)		III (n = 27)	
	Initial values	24 weeks later	Initial values	24 weeks later	Initial values	24 weeks later
LV EF, %	44.2 ± 0.92	50.8 ± 0.87***	44.5 ± 0.94	46.4 ± 0.95	42.4 ± 0.87	51.5 ± 0.71***
% DS	28.1 ± 0.73	31.5 ± 0.74**	28.3 ± 0.87	30.1 ± 0.73	27.9 ± 0.54	23.8 ± 0.68***

Note: ** - $p < 0.01$; *** - $p < 0.001$ - statistically significant differences in performance between the initial and 24 weeks later values.

Table 3

The evolution of the LV diastolic function (M ± m)

Indices	Examined groups					
	I (n = 26)		II (n = 27)		III (n = 27)	
	Initial values	24 weeks later	Initial values	24 weeks later	Initial values	24 weeks later
PVEF, cm x sec	57.8 ± 1.14	63.1 ± 1.15**	58.1 ± 1.13	61.4 ± 1.17*	57.2 ± 0.84	65.1 ± 0.95***
PVLF, cm x sec	54.4 ± 1.31	51.3 ± 1.14	54.7 ± 1.21	53.2 ± 1.30	55.4 ± 0.91	50.4 ± 0.88**
ME, c.u.	4.21 ± 0.18	3.90 ± 0.16	4.09 ± 0.19	3.93 ± 0.21	4.20 ± 0.15	3.70 ± 0.14*
MS, c.u.	3.30 ± 0.23	2.91 ± 0.12	3.20 ± 0.24	3.01 ± 0.28	3.20 ± 0.14	2.70 ± 0.13*

Note: * - $p < 0.05$; ** - $p < 0.001$; *** - $p < 0.001$ - statistically significant differences in performance between the initial and 24 weeks later values.

Table 4

Indicators of cardiac remodeling in patients with CHF before and after treatment

Indicator	Examined groups					
	I (n = 26)		II (n = 27)		III (n = 27)	
	Initial values	24 weeks later	Initial values	Initial values	24 weeks later	Initial values
LVMMI, g/m^2	135.2 ± 6.8	118.2 ± 7.2	141.1 ± 9.7	120.1 ± 9.7	137.5 ± 5.6	116.0 ± 5.3**
RTW, %	47.0 ± 1.3	43.0 ± 1.2*	46.9 ± 3.0	45.0 ± 3.0	47.1 ± 1.2	40.8 ± 0.9***
TPVR,din*s*cm-5	2187.7 ± 86.2	1862.0 ± 109.0*	2063.6 ± 80.5	2009.1 ± 106.3	2103.9 ± 84.9	1683.1 ± 107.2**
EDPLV, mm Hg	12.4 ± 0.9	11.0 ± 1.1	11.9 ± 1.1	13.0 ± 0.9	12.2 ± 0.8	9.1 ± 1.0*

Note: LVMMI - left ventricular myocardium mass index; RWT - relative wall thickness; TPVR - total peripheral vascular resistance; EDPLV - end diastolic pressure in the left ventricle.

* - $p < 0.05$;

** - $p < 0.01$ - statistically significant differences in performance between the initial data and after 24 weeks of treatment.

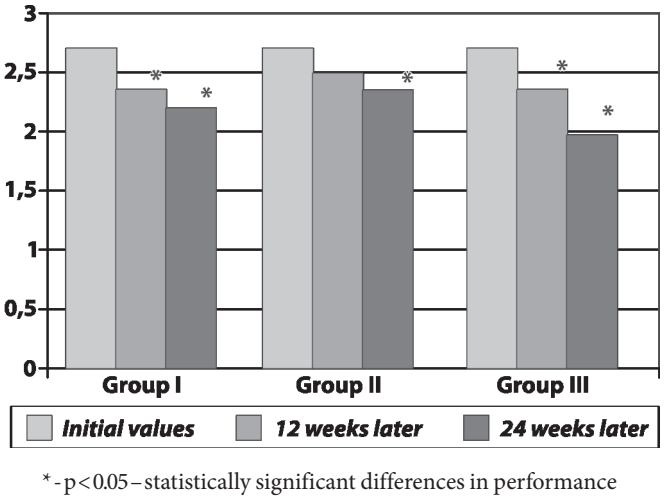
a more significant reduction in blood pressure was found in patients with concomitant hypertension. During the treatment with Enalapril SBP decreased by 6.6% from 135.8 ± 5.2 to 126.8 ± 3.9 mmHg ($p > 0.1$) and DBP by 5.4% from 85.2 ± 9.3 to 80.6 ± 8.7 mm Hg ($p > 0.1$). The medium arterial pressure decreased from 102.3 ± 10.8 to 96.0 ± 10.2 mm Hg or by 8.9% ($p > 0.1$). When treating with the combination of drugs including Losartan and Enalapril after 24 weeks there is was a significant decrease in SBP from 136.2 ± 4.2 to 123.5 ± 4.1 mm Hg by 9.3%, ($p < 0.05$), DBP – by 7.9% from 96.3 ± 3.7 down to 79.5 ± 3.5 ($p < 0.01$).

Ejection fraction of LV in patients with CHF before treatment was approximately the same in either group (tab. 2).

Treatment with Losartan during 24 weeks led to an increase in LV EF by 14.9% ($p < 0.001$), with Enalapril - by 4.3% ($p > 0.1$), with the combined therapy - by 21.4% ($p < 0.001$).

The evolution of the LV diastolic function during the applied therapy in the examined groups is presented in tab. 3.

Data from tab. 3 shows that monotherapy with Losartan and Enalapril contributed to an increase in peak velocity of early filling (PVEF) by 9.2% and 5.6% respectively, whereas their combination resulted in an increase of the same parameter by 13.8%. In patients treated with Losartan and Enalapril



* - $p < 0.05$ – statistically significant differences in performance between the initial and 24 weeks later values.

Fig. 1. The dynamics of the FC under the influence of various schemes of pharmacotherapy.

the peak velocity of late filling (PVLF) was reduced by 5.7% and 2.7% respectively, in patients receiving the combined therapy - by 9.0%. Modulus of elasticity (ME) and modulus of stiffness (MS) of the left ventricle decreased in group I by 7.3% and by 11.8% respectively, in the II-nd - by 3.9% and 5.9% respectively, in the III-rd - by 11.9% and 15.6% respectively.

The effect of Losartan, Enalapril and their combination on morphofunctional parameters of the heart expressed in decreasing the size of the left heart chambers. End systolic dimension (ESD) of the left ventricle before treatment with Losartan was 5.24 ± 0.67 cm, after 24 weeks of treatment – 5.10 ± 0.71 cm ($p > 0.1$), with Enalapril – 5.47 ± 0.43 and 5.25 ± 0.48 cm before and after treatment, respectively ($p > 0.1$), with the combination of drugs – 5.16 ± 0.24 and 4.98 ± 0.25 cm, respectively ($p > 0.1$). End diastolic dimension (EDD) before treatment with losartan was 6.4 ± 0.7 cm, with Enalapril – 6.52 ± 0.5 and 6.32 ± 0.7 cm with combination of drugs, after 24 weeks of treatment being 6.38 ± 0.8 cm, 6.56 ± 0.7 cm and 6.18 ± 0.5 cm, respectively ($p < 0.05$; $p < 0.05$; $p < 0.05$ respectively).

Indicators of cardiac remodeling in patients with CHF before and after treatment are presented in tab. 4.

The data in tab. 4 show that the use of combined therapy, which consisted of Losartan and Enalapril, provides a more favorable effect on the remodeling of the heart than their use in monotherapy. We found significant positive dynamics of parameters reflecting LV remodeling: LVMMI decrease by 15.6% with a 13.3% decrease RWT (tab. 4).

According to the bicycle stress test, the total amount of work performed by patients with CHF increased by 36.2% under the influence of Losartan, by 31.8% - of Enalapril and by 38.4% under treatment with both drugs.

The tolerance to drugs in all 3 groups was good. In patients from group I, transient hypotension was observed in 7.7% of cases, which required short-term reduction of the dose, but not cancellation of the administration. In patients from group II, side effects such as dry cough and transient hypotension were encountered during the observation period. This required a reduction in the dose of Enalapril in 11.1% of cases. Side effects were observed in 7.4% cases of the III group. Discontinuation of the drug was not required in any case.

Treatment measurements had a positive impact on the dynamics of basic indicators of quality of life in patients of all 3 groups. Thus, in patients treated with Losartan, physical activity and load and overall health have increased on average by 21.5%, 28.7% and 15.4% respectively, while in patients treated with Lisinopril these have improved only by 6.2%, 11.1% and 6.3%, respectively. Patients treated with the combined therapy had a better increase of physical activity and load and overall health – by 28.7%, 35.4% and 27.3%, respectively.

Conclusions

Angiotensin receptor antagonist Losartan is an effective drug in the treatment of CHF, providing cardioprotective effect and good tolerability.

The use of combination therapy, including Losartan and Enalapril, leads to a more pronounced reduction of clinical symptoms of CHF compared with losartan or Enalapril monotherapy.

Effects of Losartan, Enalapril and their combination on the functional parameters of the heart expressed in a decrease in the size of the left heart chambers and an increase in contractile function of the left ventricle, which were more pronounced when using combined therapy.

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Rolul pivotal al macrofagelor în progresia tumorală

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The Pivotal Role of Macrophages in Tumoral Progression

Clinical and experimental evidence have shown that macrophages (TAM) are the main component of the leukocyte infiltrate supporting tumor growth. Over the years the mechanisms that support the tumor growth have become increasingly clear and in several experimental tumor models, the activation of an inflammatory response mediated by macrophages has been shown to play an essential role for full neoplastic transformation and progression. TAMs are derived from peripheral blood monocytes recruited into the tumor. Upon being activated by cancer cells, TAMs can release a vast diversity of growth factors, proteolytic enzymes, cytokines and inflammatory mediators. Many of these agents are key factors in cancer progression. The presence of extensive TAM infiltration has been shown to correlate with poor prognosis in a variety of human carcinomas. TAMs promote cancer progression through several mechanisms including the growth of tumor cells, tumor angiogenesis and lymphangiogenesis, matrix remodeling, tumor cell migration and invasion. There are complex paracrine-signaling networks between TAMs and cancer cells to activate each other. This evidence strongly supports the idea that TAMs are one of the most important players in the inflammatory networks expressed in the tumor microenvironment, and it suggests these cells as possible targets of anticancer therapies.

Key words: macrophages, tumor growth, tumoral microenvironment, metastasis, angiogenesis, lymphangiogenesis.

Главенствующая роль макрофагов в прогрессии опухолевого процесса

Результаты многочисленных клинических и экспериментальных исследований доказали что макрофаги являются самой многочисленной клеточной популяцией лейкоцитарного инфильтрата, поддерживающего опухолевый рост. Со временем, различные механизмы через которые реализуется эта поддержка, стали хорошо изучены. В экспериментальных опухолевых моделях было доказано, что воспалительная реакция, опосредованная макрофагами, играет огромную роль в полной неопластической трансформации и прогрессировании опухолевого процесса. Макрофаги являются производными клетками моноцитов крови. Под воздействием активации опухолевыми клетками, макрофаги способны синтезировать широкую гамму факторов роста, протеолитических ферментов, цитокинов и медиаторов воспаления. Многие из этих веществ свидетельствуют об опухолевой прогрессии. Было доказано, что высокая