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CLINICAL RESEARCH

Influence of Lisinopril and Losartan on Parameters of Cardiac Hemodynamics and Kidney Function in Patients with Congestive Heart Failure

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Abstract

The purpose of the present research was to study the comparative influence of lisinopril and losartan on the parameters of cardiac hemodynamics and kidney function state in CHF (Congestive Heart Failure) patients with NYHA Functional Class (FC) I-III.

Methods: The study included 92 CHF patients aged from 41 to 75 years (mean age 66.3±9.8 yrs) with FC I-III of ischemic genesis. The patients were divided into two groups. Group I consisted of 47 CHF patients with FC I-III who had been receiving losartan for 6 months in addition to standard therapy. Group II consisted of 45 CHF patients with FC I-III who had been receiving lisinopril for 6 months in addition to standard therapy. The dose of losartan was 50–100 mg/day, and lisinopril, 5–10 mg/day. The control group included 20 healthy volunteers. NYHA FC was determined by the 6-minute walk test (6MWT) and the Russian scale of evaluation of the clinical condition of the patients. All patients underwent clinical examination, ECG, and echocardiography. Estimated creatinine clearance rate (eC_{Cr}) was calculated using the Cockcroft-Gault formula; estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula.

Results: The results obtained show a clear association between maladaptive LV remodeling and kidney dysfunction at CHF. Our analysis revealed the significant direct correlation between EF and eGFR, as well as between 6MWT and eGFR. The 6-month therapy of CHF patients with NYHA FC I-III based on a combination of standard therapy with ACEi/ARB has resulted in a significant improvement in the cardiac hemodynamic, LV myocardial contractility, and renal function, with a more significant effect in the patients treated with losartan.

Keywords*:* congestive heart failure; *kidney dysfunction; losartan; lisinopril.*

Introduction

Congestive heart failure (CHF) will, as many authors believe, become the basic problem of cardiology in the next 50 years [1,2]. Already today, CHF causes more hospitalizations than do myocardial infarction and angina pectoris taken together [3]. The prevalence of kidney function disorders with CHF, according to the data of various studies has fluctuated from 25% to 60%. Similar to the left ventricular ejection fraction (LVEF)**,** the decreases in the glomerular filtration rate (GFR) and creatinine level are considered as independent signs of an unfavorable prognosis in CHF. An analysis of the results of 16 randomized clinical studies devoted to CHF established that 63% of the patients with CHF had a mild form and 20% had moderate and severe forms. In these cases, the reduction of GFR per every10 ml/min/m^2 was associated with an increase of cardiovascular mortality by 7% [4]. The main elements of the pathogenesis of kidney dysfunction (KD) in CHF are a reduction of cardiac output, activation of neurohumoral systems, inflammation, and oxidative stress [1,4]. The association of KD and CHF with the formation of cardiorenal syndrome (CRS) creates serious problems during the therapeutic treatment, requiring combination therapy, and as is known, the clearance of many drugs is significantly reduced in these cases [5,6].

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are recommended at the various stages of the cardiovascular continuum as well as at formation of CHF; these drugs help to protect the organs and

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improve clinical outcomes [7]. Their beneficial effect in relation to survival and risk of repeated hospitalizations connected with decompensation of CHF is an established fact. The results of multiple studies (SAVE, SOLVD, CONSENSUS, SMILE, and TRACE) have demonstrated the ACEi capacity to reduce the death risk, cardiovascular complications, and morbidity rate; to improve clinical symptoms; and to slow the progress of CHF and improve the outcome prognosis [8].

Likewise, a meta-analysis of a number of clinical research studies (SHARM, Val-HeFT, HEAAL) over the last 10 years has proved the efficacy and safety of ARBs, namely irbesartan, valsartan and losartan, in patients with CHF; significant decreases in mortality rate and hospitalization have been demonstrated that are comparable to the effects of ACEi [9]. The progressive increase in serum creatinine level has been observed rather frequently in CHF patients after using ACEi and spironolactone, the main groups of preparations for CHF treatment. KD limits the use of these classes of drugs in CHF patients, which always results in a significant reduction in the efficacy of the treatment, particularly in the improvement of the long-term prognosis. It should be noted that there is a high risk for further worsening of the kidney function in CHF when ACEi is prescribed in high doses without the appropriate control of creatinine and GFR monitoring. At the same time, research devoted specifically to the role of ACEi in CRS has not been carried out.

The purpose of the present research was to study the comparative influence of lisinopril and losartan on the parameters of cardiac hemodynamics and kidney function state in CHF patients with NYHA FC I-III.

Material and Methods

The study included 92 CHF patients aged from 41 to 75 years (mean age 66.3±9.8 yrs) with FC I-III of ischemic genesis. The patients were divided into two groups. Group I consisted of 47 CHF patients with FC I-III (FC I: n=13; FCII: n=23; FC III: n=11) who had been receiving losartan (Lozap, "ZENTIVA") for 6 months in addition to standard therapy (spiranolaton, bisoprolol, aspirin). Group II consisted of 45 CHF patients with FC I-III (FCI: n=13; FC II: n=22; FC III: n=10) who had been receiving lisinopril (Diroton, GEDEON RICHTER) for 6 months in addition to standard therapy. The dose of losartan was 50–100 mg/day, and lisinopril, 5–10 mg/day. The control group included 20 healthy volunteers. Written informed consent was obtained from each patient.

NYHA FC was determined by the 6-minute walk test (6MWT) and the Russian scale of evaluation of the clinical condition of the patients (V. Mareev, 2000). All patients underwent clinical examination, ECG, and echocardiography. Estimated creatinine clearance rate (eC_{Cr}) was calculated using the Cockcroft-Gault formula; estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula. Echocardiography was performed using the ultrasound system («Radison accuvix V20», «Samsung» Korea). Standard views and techniques were used according to guidelines of the American Society of Echocardiography [10]. Measurement of end-diastolic and end-systolic LV volumes (EDV and ESV of LV) was carried out using the modified Simpson's method in the apical 2-wire and 4-chamber view. LV dimension and LV relative wall thickness (LVRWT) were measured by echocardiography in M-mode according to the recommendations of the American Society of Echocardiography [11]. Then, using the standard formula, stroke volume (SV) and LV ejection fraction (LVEF) were calculated. LV mass and LVMI (LV mass standardized by body surface area) were measured by M-mode echocardiography with the use of the Devereux formula [12,13]. Finally, end-diastolic and end-systolic sphericity index (EDSI and ESSI) was measured.

Statistical analysis was performed using the statistical software «Statistica». For data with normal distribution, inter-group comparisons were performed using student's t-test. The mean (M) and standard error of the mean (SEM) were calculated. The difference was considered reliable when $P<0.05$.

Results and Discussion

Parameters of systolic meridional stress in patients with CHF FC II-III were significantly higher ($P<0.01$) compared with the control group (Table 1). A worsening of clinical signs of heart failure was associated with advanced LV remodeling,

Table 1. Initial LV geometric patterns and GFR in the patients with CHF FC I-III

Parameter	Control	Group I (n=47)			Group 2 CHF (n=45)		
		FC I	FC II	FC III	FC I	FC II	FC III
EDV, ml	98.2±12.7	148.1±17.,7	168.9±27.85	198.31±55.2	151.5±29.9	162.5±15.5	200.65±35.6
ESV, ml	42.4± 5.1	63.08±9.3	91.7±15.4	133.2±36.6	69.8±16.79	88.8±8.02	135.8±24.6
EF, %	56.4±2.11	56.8±1.48	45.7±0.95	36.31±1.65	56.4±2.91	45.4±1.58	35.73±2.24
LVPWT, cm	1.08±0.08	1.1±0.074	1.09±0.09	1.08±0.07	1.19±0.10	1.11±0.09	1.09±0.09
IVST, cm	1.01±0.03	1.23±0.14	1.17±0.19	1.1±0.108	1.26±0.137	1.14±0.08	1.07±0.08
LVMMI, g/cm^2	122.1±10.18	159.01±22.7	173.3±39.0	174.8±22.5	183.27±34.13	165.0±16.4	192.8±25.9
RTW	0.485±0.041	0.427±0.037	0.389±0.04	0.364±0.07	0.434±0.036	0.401±0.03	0.34±0.05
MS, din/ cm^2	114.57±19. 4	124.7±27.8	154.7±27.5	162.7±44.0	110.2±30.9	147.7±25.3	167.0±40.9
Ld, cm	8.0±0.046	8.04±0.051	8.11±0.057	8.08±0.14	7.99±0.083	8.1±0.047	8.25±0.13
Ls, cm	5.7±0.052	5.85±0.052	6.1±0.067	6.15±0.166	5.79±0.083	6.04±0.07	6.25±0.12
ISd	0.537±0.025	0.681±0.035	0.716±0.05	0.757±0.088	0.708±0.052	0.705±0.03	0.777±0.05
ISs	0.608±0.037	0.653±0.04	0.735±0.05	0.819±0.086	0.685±0.06	0.732±0.02	0.846±0.06
GFR ml/min/1.73	88.9±15.6	76.4±11.1	68.4±11.9	58.1±9.3	69.08±9.06	64.53±9.06	60.6±10.3

** - P<0.01 and ** - P<0.001 versus control group.*

an increase in the degree of LV dilatation, and the deterioration of LV myocardial contractility. The increase of LV wall tension in the process of remodeling in combination with activation of neurohumoral factors results in its contractility dysfunction progressing. The chronic increase in LV wall tension is capable of supporting a vicious circle, in which the high stress stimulates the process of maladaptive remodeling with transition to the more and more spherical form of the ventricle with consequent further increase of myocardial stress.

Renal function parameters are shown in Fig.1. In CHF patients, KD was revealed at the subclinical stage without clinical signs of kidney insufficiency. With CHF, it is considered that KD develops due to the decrease of cardiac output with the subsequent renal hypoperfusion, an increased resistance of the renal vessels, and a reduction of the renal blood flow. However, a number of studies have shown an absence of a clear connection between parameters of myocardial contractility and markers of KD with CHF. Our analysis revealed a significant direct correlation between EF and eGFR (r=0.953, *P<0.01*), as well as 6MWT and eGFR (r=0.985, *P<0.01*). eC_{Cr}<60 ml/min was found in 6 of 26 patients with CHF FC I, in 10 of the 45 patients with CHF FC II, and 10 of the 21 patients CHF FC III. eGFR≤60ml/min/1.73^2 was found in 6 of the 26 patients with CHF FC I, in 16 of the 45 patients with CHF FC II, and in 11 of the 21 patients with CHF FC III. eGFR<60ml/min/1.73^2 was revealed in 17 of the 47 patients in Group I and in 16 of the 45 patients in Group II.

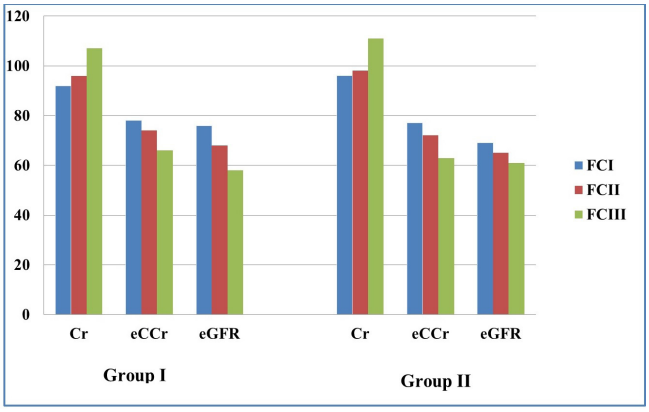

Figure 1. *Renal function parameters in patients with CHF FC I-II-III*

Patients with eGFR<60 ml/min/1.73^2 had the lowest rates of 6MWT; LVEF of these patients was 40.7±11.4% compared to 49.9±13.8% in patients with eGFR≥60 ml/min/1.73^2.

The data obtained show that the long-term therapy of CHF based on a combination of beta-blocker with ACEi/ARB has resulted in a significant improvement of the cardiac hemodynamic and renal function.

In CHF patients with FCI, during long-term standard therapy with inclusion of losartan and lisinopril, the significant decrease of EDV by 20.5% (*P<0.05*) and 17.8% (*P<0.01*), ESV by 20.6% (*P<0.01*) and 36.4% (*P<0.05*), respectively, was revealed in comparison with initial parameters. Though the initial parameters of the EF in these patients were normal, the significant increase in EF by 9.5% (*P<0.01*) and 12.6% (*P<0.001*) was found in Group I and Group II, respectively, after 6 months therapy in comparison with initial parameters.

In CHF FCII patients of Group I, there was also noted a significant reduction of ESV and EDV by 26.2% and 36.4% (*P<0.001*), respectively, with an increase of EF by 9.9% (*P<0.01*) after 6 months' therapy with losartan. In CHF FC II patients of Group II, after 6 months' therapy with lisinopril, the reduction of EDV and ESV was 19.9% and 26.9% (*P<0.001*), respectively, with an increase in EF by 9.8% (*P<0.01*) in comparison with initial data.

In CHF FC III patients of Group I, during long-term therapy with losartan, there was a significant reduction of EDV and ESV by 28.7% and 42.5% (*P<0.05*), respectively, and an increase in EF by 29.1% (*P<0.001*), in comparison with the initial data. In CHF FC III patients of Group II, after 6 months' therapy with lisinopril, the reduction of EDV and ESV was 20.3% (*P<0.02*) and 30.9% (*P<0.05*), respectively with an increase in EF by 17.1% (*P<0.05*), in comparison with the initial data.

Alongside these changes, in Group I patients with CHF FC I-II-III, there was found a significant reduction of LVMMI by 28%, 35.8% and 34.3% (*P<0.05*), respectively; in Group II patients with CHF FC I-II-III, the reduction of LVMMI was 39%, 22% and 30.6% (*P<0.05*), respectively, in comparison with initial data. In Group I patients with CHF FC I-II-III, SMS was reduced by 21.6% (*P<0.01*), 31.7% (*P<0.001*) and 29.2% (*P<0.05*), respectively; in Group II patients with CHF FC I-II-III, SMS was reduced by 20.6% (*P<0.05*), 27.5% (*P<0.05*) and 24.6% (*P<0.01*), respectively.

In Group I patients with CHF FC I-II-III, there was found a reduction of EDSI and ESSI by 5.6% and 7% (*P<0.05*), 10% and 14.6% (*P<0.05*), 10.2% and 11% (*P<0.05*), respectively, in comparison with initial parameters. In Group II patients with CHF FCI-II-III, there was also revealed the reduction of EDSI and ESSI by 11% and 12.4% (*P<0.05*), 7.1% and 8.2% (*P<0.05*), 10.4% and 8.3% (*P<0.05*), respectively, in comparison with initial parameters.

The 6-month treatment with inclusion of losartan and lisinopril resulted in an increase of GFR in comparison with initial values. In Group I patients with CHF FC I-II-III, there was found an increase in eGFR by 9.8%, 10.1% and 11.6%, respectively, in comparison with initial parameters. In Group II patients with CHF FC I-II-III, there was found an increase in eGFR by 8.7%, 8.8% and 10.9%, respectively, in comparison with initial parameters. A significant increase in eGFR was observed only in patients with CHF FCIII in both groups. The number of patients with eGFR<60 ml/min/1.73^2 was decreased by 4 (23.5%) in Group I and by 3 (18.8%) in Group II. A more positive dynamic of eGFR was found in the Group I patients.

Our results are confirmed by the results of several studies performed on CHF patients. The organ protective and anti-remodeling effects of ACEi are known from a number of studies (ELITE, ELITE II, ORACLE-RF, etc.). These positive properties of ARBs were the first subject of a special discussion after the publication of LIFE results, which included patients with essential hypertension, differentiated

by maximal cardiovascular risk. The renoprotective effects of ARB were more convincingly demonstrated in large controlled studies involving patients with d*iabetic kidney disease* and proteinuria >1g/day [14,15]. In these studies, the ARB demonstrated superiority over any other antihypertensive therapy (study RENAAL) in terms of ability to prevent irreversible deterioration of renal function. In an experimental model of CHF it was also shown that infusion of eprosartan leads to an increase in renal blood flow and a decrease of renal venous resistance [14,16].

Conclusion

The results obtained show a clear association between maladaptive LV remodeling and KD at CHF. Our analysis revealed the significant direct correlation between EF and eGFR, as well as between 6MWT and eGFR. The 6-month therapy of CHF patients with NYHA FCI-III based on a combination of standard therapy with ACEi/ARB has resulted in a significant improvement in the cardiac hemodynamic, LV myocardial contractility, and renal function, with a more significant effect in the patients treated with losartan.

Competing interests

The authors declare that they have no competing interests.

References

1. Belenkov Yu. Chronic heart failure. M.: GEOTAR-MEDIA; 2009.
2. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). Eur Heart J 2012; 33:1635-1701.
3. Van der Velde M, Matsushita K, Coresh J et al, Chronic Kidney Disease Prognosis Consortium. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int 2011; 79(12):1341-52.
4. Arutyunov G. Pathophysiological processes in kidneys at the patients with CHF. Serdechnaya nedostatochnost 2008; 5(49):234-249.
5. Damman K. Pathophysiological mechanisms contributing to renal dysfunction in chronic heart failure. J Renal Care 2010; 36:18–26.
6. Soni S, Fahuan Y, Ronco C, Cruz D. Cardiorenal syndrome: biomarkers linking kidney damage with heart failure. J Biomarkers Med 2009; 3(5):549-560.
7. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int (Suppl.) 2013; 3:1-150.
8. Keyhan G, Chen S, Pilote L. Angeotensin converting enzyme inhibitors and survival in women and men with heart failure. Eur J Heart Fail 2007; 9(67):594-601.
9. Jason P, Pharm D. Are all angiotensin receptor blockers created equal in themanagement of heart failure? PharmaNote 2012; 27(5):1-8.
10. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantification of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantification of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989; 2:358–367.
11. Sahn DJ, Demaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. Circulation 1978; 58:1072–1083.
12. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: anatomic validation of the method. Circulation 1979; 70: 1308–1316.
13. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N. Echocardiographic assessment of left ventricular hypertrophy: comparison with necropsy findings. Am J Cardiol 1986; 57: 450–458.
14. **Arutyunov AG.** ACE Inhibitors in CHF: Necessity despite the Change of Goals. Difficult patient 2014; 5:1-8; http://t-pacient.ru.
15. Ruggenenti P, Remuzzi G. Worsening kidney function in decompensated heart failure: treat the heart, don't mind the kidney. Eur Heart J 2011; 32(20): 2476–2478.
16. Meune C, Wahbi K, Duboc D, Weber S. Meta-analysis of Renin-Angiotensin-aldosterone blockade for heart failure in presence of preserved left ventricular function. J Cardiovasc Pharmacol Ther 2011; 16 (3-4):368-75.