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Angiotensin-II Receptor Antagonist Losartan Dose-Dependently Improves the Left Ventricular Remodelling in Patients With Congestive Heart Failure

A. E. Berezin

This study examined the influence of the AT₁-receptor antagonist losartan on myocardial remodelling in patients with congestive heart failure. 240 patients with congestive heart failure functional class 2–4 aged 31–68 years were investigated. The inclusion criteria were left ventricular end-diastolic volume < 160 ml, ejection fraction < 35 %, sinus rhythm and the patient's consent to the study. All patients were randomised into three groups with 80 subjects in each one and all of them received conventional therapy with angiotensin-converting enzyme inhibitor. Placebo was added to conventional therapy in the first group of patients. The second group received losartan 25 mg/d along with conventional therapy. The third group of patients received losartan 50 mg/d. The course of treatment was 48 weeks. Cardiodynamic performances were examined by B-mode and Doppler echocardiography.

The analysis of outcomes showed that the decrease of ventricular end-diastolic volume and end-systolic volume, peripheral vessel resistance, Doppler index, myocardial stress index, associated with the increase of cardiac volume and left ventricular ejection fraction was more significant in the third group. Losartan 50 mg/d demonstrated an increased improvement of cardiodynamic status than losartan 25 mg/d and placebo. In conclusion, a dose of 50 mg daily produces a more significant improvement of left ventricular function and myocardial remodelling than 25 mg of losartan. *J Clin Basic Cardiol* 2002; 5: 83–86.

Key words: congestive heart failure, myocardial remodelling, losartan, treatment

At the moment, excessive activation of the renin-angiotensin (RAS) and the adrenergic system are considered as independent risk factors for sudden death, acute coronary syndromes, and also as a factor causing congestive heart failure (CHF) and provoking deterioration [1]. The origin of neurohumoral activation in patients with left ventricular dysfunction is associated with evolution of circulating and local plasma levels of catecholamines, vasopressin, endothelin, atrial natriuretic peptide, renin and angiotensin-II [2] remodelling of heart and vessels [3].

This process leads to growth and expansion of the collagen matrix, hypertrophy of cardiomyocytes, cytoarchitectonic violations of the myocardium and vessels and reduction of kinetic parameters of the cardiac wall [3].

The majority of contributors consider that limiting of influence of circulating and locally active components of RAS and the adrenergic system in the myocardium and vessels by the administration of angiotensin-II receptor antagonist₁ is directly connected with prevention of remodelling, improving the quality of life and survival in heart failure patients [4]. On the other hand, AT₁-antagonists did not dramatically influence survival in patients with CHF and were not better than ACE-inhibitors [5]. However, the role of AT₁-antagonists in real clinical practice is not completely defined [6].

The aim of the study was to examine the influence of the AT₁-receptor antagonist losartan on myocardial remodelling in patients with congestive heart failure.

Methods

240 patients with CHF functional class (FC) 2–4 due to ischaemic heart disease aged 31–68 years were included. Inclusion criteria: left ventricular (LV) end-diastolic volume > 160 ml; LV ejection fraction (EF) < 35 %; sinus rhythm; patient's consent to the study. Exclusion criteria: atrial fibrillation; sick sinus syndrome; atrioventricular blockade grade II–III; stroke; uncontrolled arterial hypertension; hepatic

dysfunction, renal dysfunction with elevation of plasma creatinine level above 140 μ mol/l; modification in conventional therapy of CHF within 3 weeks before randomisation; administration of beta-blockers before randomisation; myocardial infarction within 6 weeks before randomisation; administration of AT₁-antagonist prior to randomisation as a contraindication to AT₁-antagonist treatment.

The study protocol included the possibility of adding beta-blockers if necessary for improvement of clinical status. However, the aim of the study was the examination of efficacy of the AT₁-antagonist losartan added to an ACE inhibitor, but not to beta-blockers.

All patients were stabilised by conventional therapy (CT), which included isosorbide dinitrate (40–80 mg/d oral), aspirin (125–250 mg/d oral), digoxin (0.25–0.5 mg/d oral), furosemide (280–740 mg/week oral) and angiotensin-converting enzyme (ACE) inhibitor enalapril (mean dose 10 mg/d). Enalapril was up-titrated by 2.5 mg/d to 10–20 mg/d (run-in period). During the run-in period (1–3 weeks) the tolerance to the ACE inhibitor was examined.

The patients not tolerant to the ACE inhibitor were excluded from the study. 3 weeks after the start of the run-in period all remaining patients were randomised into three groups with up to 80 subjects in each one. Placebo was added to CT in the first group of patients. The second group of patients received losartan in a dose of 25 mg/d orally (low dose) in addition to CT. The third group of patients received losartan in a dose of 50 mg/d orally (high dose).

The course of treatment was 48 weeks. All patients underwent physical examination. Systolic, diastolic, and mean blood pressure as well as ECG-recording and echocardiography were performed at baseline and after every 3 weeks.

Evaluation of Cardiohaemodynamics

M- and B-mode echocardiography was carried out according to the Recommendations of the American Society of Echocardiography in 4-chamber apical view and parasternal view

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every 3 weeks [7] by a SONOLINE VERSA Plus (SIEMENS, Germany) using a transducer with a frequency of 5 MHz. The LV wall thickness, LV short axis dimensions in diastole and systole were serially measured by M-mode echocardiography. The LV long axis dimensions in diastole and systole were measured by B-mode echocardiography. The LV end-diastolic (LVEDV) and end-systolic volumes (LVESV) were obtained using a two-dimensional reference sector according to Simpson's method [8].

Two-dimensional and Doppler tracings were recorded over 8 cardiac cycles and stored on videotape for further analysis.

The following cardiohaemodynamic indices were calculated: stroke volume (SV), ejection fraction (EF) (according to conventional method), and peripheral vascular resistance, diastolic LV sphere index (LVSI_d) and myocardial stress index according to the formulae given below.

Peripheral vascular resistance (PVR):

$$PVR = \{MBP \times BM\} / \{CO \times HR\} \quad (1)$$

(MBP = mean blood pressure; BM = body mass; CO = cardiac output; HR = heart-rate)

Myocardial stress index (MSI):

$$MSI = SBP \times Rs/Ls \times LVPWs \times \{1 + LVPWs/Rs\} \quad (2)$$

(SBP = systolic blood pressure; Rs = end-systolic left ventricular short axis dimension; Ls = end-systolic left ventricular long axis dimension; LVPWs = systolic left ventricular posterior wall thickness)

Diastolic LV sphere index (LVSI_d):

$$LVSI_d = Rd/Ld \quad (3)$$

(Rd = end-diastolic left ventricular short axis dimension; Ld = end-diastolic left long axis dimension)

Examination of Transmitral Filling

Left ventricular diastolic filling was examined by conventional pulse wave Doppler method [9]. For recordings of the transmitral filling velocity, the sample volume of the pulsed wave Doppler was placed between the tips of the mitral leaflets in apical 4-chamber view. Three consecutive beats were measured and averaged for each parameter. Isovolumic relaxation time (IVRT), early diastolic filling velocity and late diastolic filling velocity were measured and the Doppler index calculated according to the formula:

$$\text{Doppler Index (DI)} = E/A \quad (4)$$

(E = early diastolic filling velocity; A = late diastolic filling velocity)

Chemicals and Reagents

Losartan, aspirin and isosorbide dinitrate were kindly donated by Merck Sharp and Dohme Inc. (USA), Bayer (Germany) and Schwarz Pharma (Germany), respectively. Digoxin and furosemid were supplied free of charge by Darnitsa (Ukraine).

Statistical Analysis

All results are given as mean \pm SEM. Differences between values obtained were evaluated by ANOVA, followed by Tukey's test for multiple comparisons, if ANOVA revealed

significant differences. Differences were considered significant at the level of $p < 0.05$. These statistical comparisons were performed with the statistical program NCSS, Unisoft.

Results

The clinical characteristics of patients are given in Table 1. The majority of patients presented with NYHA class III, CCS class III and a history of myocardial infarction.

The analysis of results obtained showed that 36 patients (45 %) in the first group, 41 patients (51.3 %) in the second group and 49 patients (61.3 %) in the third group improved NYHA functional class of congestive heart failure (NYHA CHF FC).

Some data concerning the change of cardiohaemodynamics in patients with CHF are presented in Table 2. The analysis of the results showed that LVEDV progressively increased during the study in all groups of patients. On the other hand, the changes of LVEDV in the third group were not significant. The increase of LVESV in patients of the first and second group and the decrease of LVESV in the third group are marked. There was no statistically significant LVESV evolution within 48 weeks.

However, in all patients, SV demonstrated a dramatic increase. In fact the losartan 50 mg/d dose contributed to the more significant decrease of LVESV and increase of SV in comparison with losartan 25 mg/d and placebo. At the same time LVEF in the first and second group decreased progressively. On the other hand, after 48 weeks LVEF in the third group was not significantly higher than at baseline ($p > 0.5$).

The present data demonstrated that PVR showed a serious tendency to decrease. A more pronounced reduction of PVR was registered in the losartan 50 mg/d group. The change of PVR in the placebo and losartan 25 mg/d group was the same (-9.07% vs -9.99%). However, there were no significant changes of PVR in the placebo group.

Table 1. Clinical characteristics of patients with congestive heart failure

Characteristics	No. of patients	%
Age 31–49 years	58	24.17
Age 50–59 years	103	42.92
Age 60–68 years	79	32.92
Mean age (years)	56.17 \pm 11.25	
Male sex	163	67.92
Smoker	53	22.08
Hypertension	83	34.58
Diabetes mellitus	27	11.25
Insulin-dependent diabetes mellitus	2	0.83
Angina pectoris class II	45	18.75
Angina pectoris class III	174	72.50
Angina pectoris class IV	21	8.75
History of myocardial infarction	118	49.17
CHF-duration (months)	103 \pm 4.55	
NYHA CHF FC II	41	17.08
NYHA CHF FC III	157	65.42
NYHA CHF FC IV	42	17.50
Cardiothoracic index (chest X-ray)	0.57 \pm 0.09	
Mitral regurgitation	213	88.75
NYHA CHF FC = New York Heart Association Congestive Heart Failure Functional Class		

It was also revealed that LVSI_d did not change to a statistically significant degree in any group of patients. Placebo and low dose losartan contributed to an increase of LVSI_d. High dose losartan influenced the parameters more positively and contributed to a (not significant) reduction of them. After analysis of two dimensional echo-images and change of BP it was noticeable that there were significant changes of MSI in all groups of patients.

Placebo and low dose losartan led to the same dynamics of MSI. However, administration of high dose losartan caused more pronounced MSI decrease in the third group of subjects. During the 48 weeks, the alteration of IVRT and DI was not statistically pronounced. There was a tendency to a reduction of the mean values of IVRT and DI. At the same time, more pronounced decreases of IVRT and DI were seen in the losartan 50 mg/d group.

The results of multifactorial regression analysis are presented in Table 3. The dose of AT₁-antagonist losartan was the parameter that correlated best with PVR ($r = -0.78$; $p = 0.041$), LVEF ($r = 0.70$; $p = 0.0428$). The dose of losartan correlated moderately with other cardiohaemodynamic indices: MSI ($r = -0.66$; $p = 0.0135$), LVEDV ($r = -0.58$; $p = 0.037$) and DI ($r = -0.48$; $p = 0.0475$). Correlation coefficient with NYHA CHF FC was 0.62 ($p = 0.0226$).

Discussion

In previous research, the favourable influence of AT₁-antagonist losartan on cardiohaemodynamics was detected which makes it preferable in the treatment of CHF-patients [10, 11]. Originally it was supposed that it was of great importance for those heart failure patients who for some reason cannot tolerate ACE-inhibitors [12].

Table 2. The evolution of cardiohaemodynamics in patients with congestive heart failure

Parameter	Group	Baseline	48 weeks	Δ %
LVEDV, ml	1	162.0 ± 3.95	173.3 ± 3.99*	+6.00
	2	166.2 ± 2.83	175.9 ± 3.87*	+5.51
	3	165.7 ± 3.76	170.1 ± 2.96	+2.59
LVESV, ml	1	114.3 ± 2.19	115.10 ± 5.00	+0.70
	2	118.9 ± 2.15	126.7 ± 4.83	+6.10
	3	116.5 ± 2.38	115.8 ± 3.96	-0.60
SV, ml	1	48.60 ± 2.23	51.20 ± 2.16	+5.10
	2	47.30 ± 3.00	49.20 ± 2.17	+3.86
	3	49.20 ± 3.15	54.30 ± 2.39	+9.40
LVEF, %	1	29.84 ± 2.01	29.50 ± 1.87	-1.14
	2	28.46 ± 2.23	27.97 ± 2.5	-1.72
	3	29.70 ± 2.19	31.90 ± 2.23	+6.90
PVR, unit	1	43.88 ± 3.04	39.90 ± 2.30	-9.07
	2	50.83 ± 2.04	45.75 ± 1.80*	-9.99
	3	47.50 ± 2.61	41.86 ± 1.50*	-11.87
LVSI _d , unit	1	0.69 ± 0.022	0.703 ± 0.029	+1.85
	2	0.701 ± 0.025	0.702 ± 0.028	+0.14
	3	0.702 ± 0.035	0.701 ± 0.030	-0.14
MSI, unit	1	185.171 ± 17.55	163.298 ± 11.50*	-11.81
	2	204.30 ± 18.33	173.41 ± 13.91*	-15.12
	3	208.68 ± 19.00	163.69 ± 10.40*	-21.56
IVRT, sec	1	0.130 ± 0.027	0.123 ± 0.025	-5.38
	2	0.133 ± 0.024	0.125 ± 0.023	-6.02
	3	0.129 ± 0.023	0.120 ± 0.024	-6.98
DI, unit	1	0.84 ± 0.052	0.80 ± 0.060	-4.76
	2	0.86 ± 0.063	0.81 ± 0.070	-5.81
	3	0.84 ± 0.071	0.78 ± 0.090	-7.14

Δ % = the degree of increase or decrease of values; * significant differences between values at baseline and at 48 weeks

On the other hand, the recently completed ELITE-II study did not demonstrate substantial advantages of AT₁-antagonist losartan versus ACE-inhibitor captopril in elderly heart failure patients concerning survival [5]. In this connection we can suppose that the combination of AT₁-antagonist and ACE-inhibitor could render positive influence on current CHF [13]. However, RESOLVD did not demonstrate actual advantages of the same combination for long-term prognosis in patients with CHF in comparison with AT₁-antagonist or ACE-inhibitor alone. Nevertheless, the AT₁-antagonist candesartan and ACE-inhibitor enalapril combination not only prevented the lowering of LVEF, but contributed to a more pronounced increase of LVEF compared to administration of enalapril or candesartan alone during a period of 48 weeks. Besides, in the enalapril + candesartan group patients, LVEDV was slightly decreased, whereas in other groups this effect was not registered [14]. Therefore, AT₁-antagonist + ACE-inhibitor influenced the haemodynamic status positively, but did not render noticeable additive operation for the long-term prognosis.

The present data show that the influence of AT₁-antagonist on haemodynamics and LV remodelling in heart failure patients can have a dose-dependent nature. Thus, the low doses of losartan do not increase essentially the efficiency of CT. In comparison, high doses rendered more favourable influence on haemodynamics and LV remodelling.

The recent study showed that AT₁-antagonists are capable of enhancing survival in cases of CHF due to limitation of LV-remodelling [15]. At the same time, it is known that the haemodynamic effects of the first dose of losartan is slightly reduced by the first dose of captopril. [16]. The research data demonstrate that the high doses of losartan during the 48 weeks prevented the progression of LV-dysfunction. Taking into consideration that, in spite of the usage of a standard combination ACE inhibitor + diuretic + vasodilator, LVEDV continues progressively to increase and LVEF to decrease. This process is precluded only by the addition of losartan in a high dose (50 mg/d) for not less than 48 weeks.

In conclusion, losartan in a dose of 50 mg daily in comparison to losartan 25 mg daily in patients with congestive heart failure promotes a more significant improvement of LV-function and myocardial remodelling, associated with decrease of NYHA CHF FC. It is possible to interpret that a positive influence of high doses of the drug not only on clinical status and haemodynamics, but also on the long-term outcomes can be connected with this phenomenon. Therefore, it is possible to regard usage of AT₁-antagonist in low doses as well as in high doses added to ACE inhibitor in therapy of CHF as a clinical experiment.

Table 3. The correlation between clinical, echo- and Doppler parameters and dose of losartan

Parameter	Correlation coefficient (r)	P
NYHA CHF FC	-0.62	0.0226
LVEDV	-0.58	0.0370
LVEF	+0.70	0.0428
PVR	-0.78	0.0410
MSI	-0.66	0.0135
IVRT	-0.12	1.072
DI	-0.48	0.0475

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