European Review for Medical and Pharmacological Sciences 2017; 21: 1323-1328

Effects of losartan on left ventricular mass: a three-year follow-up in elderly hypertensives with myocardial hypertrophy despite successful conventional antihypertensive treatment

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Abstract. – OBJECTIVE: Reversal of left ventricular hypertrophy (LVH) in hypertensive patients appears to be a desirable goal to the reduction cardiac risk. The Renin-Angiotensin System (RAS) seems to play a major role in the establishment and maintenance of LVH through the activated systemic RAS and the Intracardiac Angiotensin System (IAS).

We focused on the effects of a three-year treatment with losartan supplement in hypertensive patients with LVH not responding to eight years of an effective previous antihypertensive pharmacological treatment.

PATIENTS AND METHODS: Two groups of 28 sex-, age- and therapy-matched subjects with essential hypertension and LVH were taken into consideration. The two groups were in effective pharmacological treatment (BP < 140/90) for eight years previous to their enrollment.

Patients of Group A were treated for three years with a losartan (100 mg/die) on-top treatment, whereas patients of Group B continued the follow-up of the previous conventional therapy. Both groups were submitted to an echocardiographic follow-up.

RESULTS: Group A, showed a significant reduction of the mean LVH since the first step at six months with a further significant trend during the whole period (variance analysis: $p < 0.001$). Group B showed a non-significant trend toward LVH reduction during the three-year follow-up. No significant further reduction of systolic or diastolic blood pressure values was observed in both groups.

CONCLUSIONS: The effects of losartan in hypertensive and hypertrophic patients are in agreement with the results of LIFE Trial. However, the reduction of left ventricular hypertrophy in our patients seems to be related to changes inducted by losartan on the IAS, since no further hemodynamic effects were observed. Losartan induced both a significant reduction of LVH and an improvement of LV diastolic function with a subsequent expected beneficial shift on the prognosis.

Key Words:
Ventricular hypertrophy, Hypertension, Losartan.

Introduction

Left ventricular hypertrophy (LVH) is considered an independent major risk factor for cardiovascular diseases[1,2] and reversal of LVH appears to be a desirable therapeutic goal in hypertensive patients in order to reduce their increased cardiac risk[3-5]. The Renin-Angiotensin System (RAS) seems to play a major role in the establishment and maintenance of LVH[6]. Not only the activated systemic RAS, but also the Intra-cardiac Angiotensin System (IAS) appears to be involved in this mechanism[7-10]. The IAS plays a role in long-term regulation of the structure of the heart and, when activated, promotes myocardial hypertrophy and interstitial fibrosis, which may contribute to the functional and prognostic impact of LVH.

Reversal of LVH with an antihypertensive treatment may be related not only to the degree of blood pressure reduction, but also to changes inducted on the IAS[6,11]. This one is of real importance since a dual enzymatic pathway of Angiotensin II (AngII) formation (ACE-dependent or ACE-independent: Chymase) has been demonstrated in human heart[7-9]. In fact, AngII receptors (AT) blockade can be addressed[11,12]. Since AT1 receptors seem to be responsible for the AngII

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growth-effect on myocardial cells[12], then AT1 selective blockade by losartan can antagonize AngII effects (especially the growth effect), independently of the AngII synthesis' source[13].

The aim of this work is to focus on the effects of a three-year losartan treatment on the left ventricular mass (LVM) in hypertensive patients with LVH regardless of a previous long-term conventional and effective antihypertensive treatment.

Patients and Methods

We took into consideration two groups of 28 sex-, age- and therapy-matched subjects, with grade I or II essential hypertension and left ventricle hypertrophy. The study subjects, already treated with a conventional treatment, which was continued during the study, for at least 8 yy (range 8-15 yy), who presented good BP levels' control didn't show previous left ventricular mass index (LVMI) normalization.

The two groups followed a therapeutic protocol comprising of calcium-antagonists (CA), b-blockers (b-B), diuretics (D) and ACE-inhibitors (ACE-I) until they reached BP values < 140/90 mmHg.

This target was initially achieved with a mono-therapy (appropriate to the clinical features of the subjects) and subsequent implementation with other drug classes in order to minimize side effects and to maximize both BP control and LVM reduction.

At the enrollment, the following therapeutic associations were observed in both groups: 7 subjects treated with b-B+CA+D, 7 subjects treated with b-B+ACE-I+CA+D, 7 subjects treated with ACE-I+CA+D and 7 subjects treated with b-B+ACE-I+CA.

Patients were enrolled in two groups of 28 subjects each:

- Patients of Group A (6 F, mean age 71±4.7 yrs; mean LVMI =170.5 ±18.7 g/m^2) were treated on-top with losartan (100 mg/die) for three years;
- Patients of Group B (6 F, mean age 71.8 ±5 yrs; mean LVMI =160.5 ±20 g/m^2) continued their follow-up and the previous conventional therapy.

Inclusion in Group A or B was based on acceptance of the therapeutic protocol (written informed consent).

The study was approved by the local Ethical Institutional Board.

They were submitted (at the enrollment and at 6, 12, 24 and 36 months) to a single-blinded echocardiography using a Toshiba Aplio CV unit and to a blinded measurement of blood pressure and heart rate. LVM was estimated using the anatomically validated formula from Devereux and Reischeck[14] according to the Penn Convention. Then the LVMI was obtained by normalization of body surface area.

E/A ratio and Isovolumetric Relaxation Time (IRT) were considered for the analysis of the left ventricle diastolic function. All echocardiographic examinations and interpretations were made by the same examiner, who was unaware of the subject's blood pressure or the results of previous recordings.

The blood pressure measurements were conducted in agreement with the ESC Guidelines[15].

Renal function was estimated by eGFR according to the MDRD formula, because the mean GFR was of 63±4 mL/min/1.73 m^2; the mean age range was of 66-76; and there was no relevant decline in muscle mass or abnormal obesity.

Statistical Analysis

Statistical analysis was conducted by means of Variance Analysis and Student's t-test for paired data. A p-value < 0.001 was considered significant.

Results

Clinical and echocardiographic data have been reported in Table I.

The trends for LVMI during the follow-up (regression analysis) have been shown in Figure 1.

Variance Analysis

In group A, a significant trend toward improvement was detected by variance analysis ($p < 0.001$) for LVMI, E/A Ratio and IRT, whereas no significant changes were detected in group B. The observed reduction for LVMI in the group A was not accompanied by any significant reduction of systolic and diastolic blood pressure.

Group A (on-top treatment with losartan 100 mg/die) showed a significant reduction of the mean LVMI at the sixth-month first visit (159.8 g/m^2 vs. 170.52 g/m^2 (baseline); $p = 0.03$) and a further significant trend during the whole period (one year: 155.6 g/m^2; $p = 0.01$ vs. baseline; two years: 143.4 g/m^2; $p < 0.001$ vs. baseline; three years: 125.3 g/m^2; $p < 0.001$ vs. baseline). Three

Table I. Clinical and echocardiographic data.

Group A	Basal	6 months	1 year	2 years	3 years
SBP, mmHg	130.7±8.1	130.2±8.8	129.2±7.3	129.8±7.8	129.7±8.7
DBP, mmHg	83.7±6.3	82.3±7.1	82.1±7.4	82.1±6.8	82.6±7.2
HR, bpm	69.7±9.5	67.9±9.4	68.5±12.2	67.9±10.3	68.7±12.6
LVMI (g/m^2)	170.5±22.3	159.8±22*	155.6±26.7**	143.4±20.6***	125.3±18***
IVSTd (mm)	11.5±1.15	11.1±1.24	10.9±1.3*	10.9±1.16*	10.95±0.98*
PWTd (mm)	11.3±1.2	10.85±1.3	10.85±1.3	10.2±1.26**	9.2±1.3***
LVDd (cm)	5.8±0.5	5.8±0.5	5.8±0.4	5.7±0.5	5.5±0.4**
E/A	0.45±0.12	0.47±0.1	0.56±0.12***	0.9±0.16***	1.1±0.14***
IRT (ms)	122±15	120±16	119±15	106±11***	102±12***
Group A	**Basal**	**6 months**	**1 year**	**2 years**	**3 years**
SBP, mmHg	130.3±8.1	130.1±8.8	131.2±7.3	129.8±7.8	129.2±8.7
DBP, mmHg	82.4±6.3	82.3±7.1	82.1±7.4	82.1±6.8	82.5±7.2
HR, bpm	72.3±9.5	67.9±9.4	68.5±12.2	67.9±10.3	73.5±12.6
LVMI (g/m2)	160.8±16.3	161.8±21	158.6±23	157.3±20.6	156.5±19.2*
IVSTd (mm)	11.3±1.3	11.3±1.4	11.1±1.3	11.1±1.6	11.1±1.1
PWTd (mm)	10.7±1.7	10.6±1.4	10.8±1.2	10.4±0.6	9.8±1.2*
LWDd (cm)	5.7±0.4	5.77±0.5	5.7±0.5	5.7±0.3	5.65±0.4
E/A	0.46±0.14	0.45±0.11	0.46±0.14	0.58±0.18*	0.6±0.14*
IRT (ms)	120±13	120±17	119±12	117±9	118±10

(SBP) systolic blood pressure; (DBP) diastolic blood pressure; (HR) heart rate; (LVMI) left ventricular mass index; (IVSTd) Interventricular septal thickness at end-diastole; (PWTd) Posterior wall thickness at end-diastole; (LWDd) left ventricular wall end-diastolic diameter; (E/A) E/A ratio; (IRT) isovolumic relaxation time. $^{*}= p <0.05$; $^{**}= p \leq 0.01$; $^{***}= p <0.001$.

patients (2 females) treated with calcium-antagonists showed a mild increase of LVMI after the first losartan treatment year. The global LVMI reduction was not accompanied by a further significant reduction of systolic or diastolic blood pressure values (six months/one year/two years/three years vs baseline: p = n.s) and/or any heart rate reduction (six months/one year/two years/three years vs baseline: p = n.s) (Table I). The left ventricle diastolic function (E/A ratio and IRT) didn't show a significant improvement at the first year follow-up. A significant trend improvement appeared during the second year examination (IRT: 106 vs. 122 ms; $p < 0.001$; E/A ratio: 0.9 vs. 0.45; $p < 0.001$) and was confirmed at the third year examination (IRT: 102 vs. 122 ms; $p < 0.001$; E/A ratio: 1.1 vs. 0.45; $p < 0.001$) (Table I).

No relevant side effects (i.e. decline in eGFR) were observed during the follow-up.

Group B showed a non-significant trend toward LVMI reduction during the three-year follow-up (Table I) without any further reduction of blood pressure levels (six months/one year/two years/three years vs baseline: p = n.s) or heart rate (six months/one year/two years/three years vs baseline: p = n.s) (Table I). Furthermore, left ventricle diastolic function (E/A ratio and IRT) didn't show significant variations (Table I).

Discussion

Dual enzymatic pathway of Angiotensin II (AngII) formation (ACE-dependent or Chymase-dependent) has been demonstrated in human heart. Since AT1 receptors seem to be responsible for AngII growth-effect on myocardial cells[7,8,13], AT1 selective blockade by losartan should antagonize AngII effects (especially its growth effect) independently of how AngII is synthesized[16,17]. The positive effects of losartan on LVM reduction in hypertensives and hypertrophic patients was confirmed by the results of LIFE Trial[18]. In particular, in the LIFE echocardiography substudy[19] (designed to observe the long-term effects on morbidity and mortality of LVM reduction in active hypertensive patients[19]), the change of LVM was related to blood pressure reduction in agreement with the results of the Schmieder meta-analysis highlighting the greater decrease in LVM index in patients who showed the greater decline in blood pressure and the longer duration of treatment[20].

However, *in vitro* and *in vivo* experimental studies support the specific role of Angiotensin II in facilitating cardiac fibrosis[21] and also show that drugs that block the RAS may induce regression of fibrosis[22]. The present data are consistent with these experimental observations: the reduction of

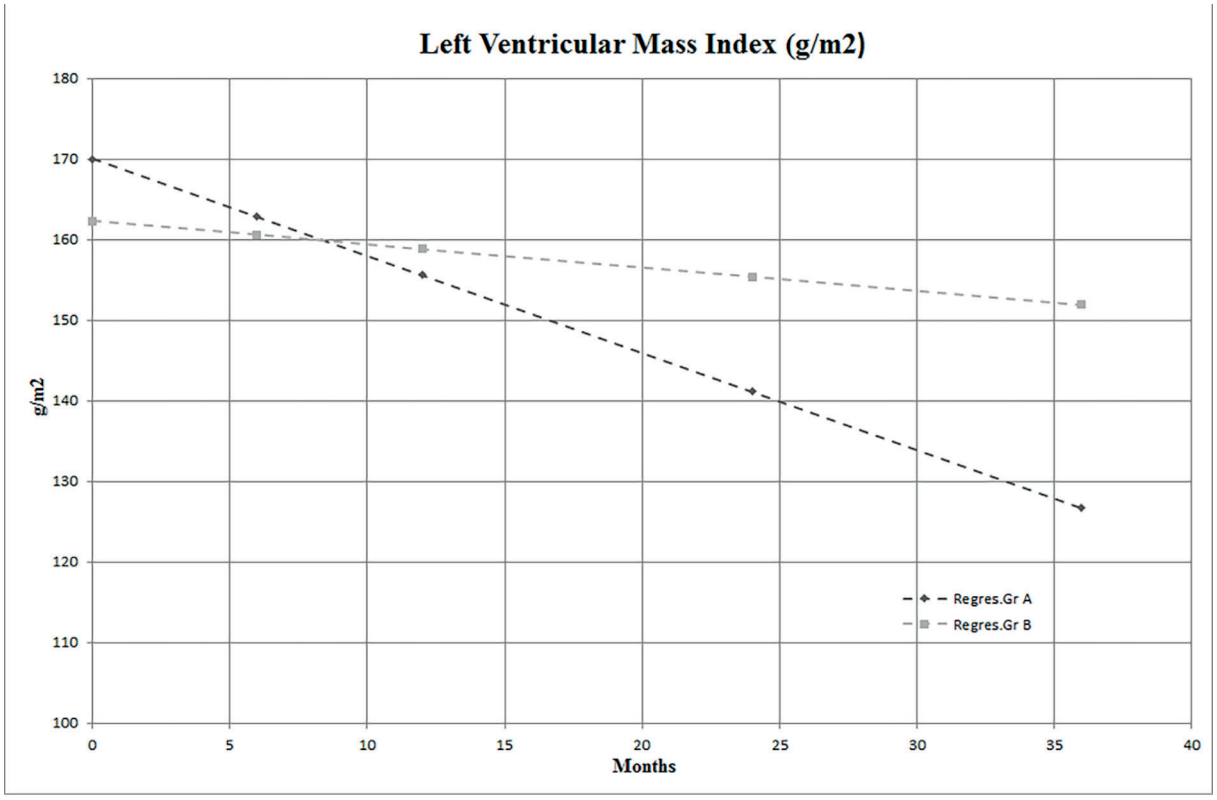

Figure 1. Regression curves of LVM Index of groups A and B.

left ventricular hypertrophy in our patients seems to be related to changes inducted on the IAS by losartan (reduction of interstitial fibrosis due to losartan-induced AT1 selective blockade, thus antagonizing AngII growth effect). This effect on myocardial fibrosis appears to be confirmed by a later improvement of diastolic function.

Moreover, the reduction of left ventricular hypertrophy in our patients who have shown a good blood pressure control for many years seems not to be related to hemodynamic effects (blood pressure values weren't further reduced with the losartan on-top treatment).

Nevertheless, the reduction of LVM in patients still hypertrophic after many years of conventional treatment could have interesting prognostic implications. The persistence of left ventricular hypertrophy after treatment has been demonstrated to be a stronger indicator of cardiovascular events than the baseline LVM[2,23]. In our research, based on a different patient-setting with respect to the LIFE-trial (effectively treated hypertensive patients with non-responding LVH), losartan induced both a LVMI significant reduction and a later improvement of LV diastolic function. The expected losartan-induced decrease in myocardial collagen content[24] could justify this combined morpho-functional improvement, whereas apparent divergent results with respect to other reports[19,20] could be explained by the different patient-setting.

Conclusions

The present study provides evidence that losartan, an AT1 selective blocker, appears to be effective in reducing left ventricular mass in still-hypertrophic hypertensives, regardless of many years of effective conventional antihypertensive therapy. This effect could be related to changes in the Intra-cardiac Angiotensin System (i.e. Chymase system): no significant further reduction of systolic or diastolic blood pressure values was observed.

Since the persistence of left ventricular hypertrophy after treatment seems to be a stronger indicator of cardiovascular events with respect to

baseline left ventricular mass[2], our results could have relevant prognostic implications.

Conflicts of interest

The authors declare no conflicts of interest.

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