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Article: Treatment

Losartan and amlodipine on myocardial structure and function: a prospective, randomized, clinical trial

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Abstract

Aims To compare the effects of losartan and amlodipine on myocardial structure and function in hypertensive patients with Type 2 diabetes and left ventricular hypertrophy.

Methods After a 4-week placebo period, patients were randomized to losartan 50 mg (n = 90) or amlodipine 5 mg (n = 91) for 12 months, with a doubling of the dose in patients who did not respond after 4 weeks. Blood pressure was measured in the clinic every month, while conventional echocardiography and acoustic densitometry (integrated backscatter analysis) were performed at the end of the placebo period and after 12 months of treatment.

Results Both drugs reduced systolic/diastolic blood pressure to a comparable extent. Losartan significantly reduced left ventricular mass index (−19%, $P < 0.001$), interventricular septal thickness (−16.6%, $P < 0.01$) and left ventricular posterior wall thickness in diastole (−13.7%, $P < 0.01$). Amlodipine also decreased such measurements (−10%, $P < 0.01$ for left ventricular mass index, −9.3%, $P < 0.05$ for interventricular septal thickness in diastole and −10.1%, $P < 0.05$ for posterior wall thickness in diastole), but to a lesser extent than losartan. Both drugs significantly increased the ratio of peak filling velocity at early diastole to that at atrial contraction (E/A ratio) and decreased isovolumetric relaxation time: +13.7% and −8.5% with losartan,(both $P < 0.01$), and +7.9% and −4.9%, with amlopidine (both $P < 0.05$). Losartan, but not amlodipine, significantly reduced the relative integrated backscatter compared to baseline of the intraventricular septum (−10%, $P < 0.01$), and of the left ventricular posterior wall (−12%, $P < 0.01$), while increasing the cyclic variation of integrated backscatter of both the intraventricular septum (+35%, $P < 0.001$) and the left ventricular posterior wall (+32%, $P < 0.001$).

Conclusions Losartan provided a greater attenuation of left ventricular hypertrophy than amlodipine, seemingly as a result of a greater reduction of myocardial fibrosis.

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Keywords amlodipine, hypertension, losartan, myocardial structure, Type 2 diabetes mellitus

Abbreviation E/A ratio, ratio of peak early diastolic filling velocity to peak filling velocity at atrial contraction

Introduction

Left ventricular hypertrophy, which is well known to be a powerful, independent risk factor for cardiac morbidity and mortality [1,2], is often present in patients with Type 2 diabetes [3]. When hypertension coexists with diabetes, as it frequently does, the development of this cardiac abnormality is further accelerated and the risk of cardiovascular diseases is doubled [4]. Reduction of left ventricular mass brought about by anti-hypertensive therapy may be beneficial in improving prognosis, especially in patients with diabetes and with left ventricular hypertrophy [5,6]. However, the various anti-hypertensive agents may differ in their ability to regress left ventricular hypertrophy. There is evidence that anti-hypertensive drugs that affect the renin–angiotensin aldosterone system, i.e. angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor (AR) blockers, are more effective than traditional anti-hypertensive classes of drugs (e.g. beta-blockers) in causing regression of left ventricular hypertrophy [7,8]. Beyond the reduction of left ventricular mass, studies to date also suggest an anti-fibrotic effect of AR blockers on the hypertensive heart, an effect which has been demonstrated in animal models [9,10], as

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well as in humans, by using invasive methods (e.g. endomyocardial biopsy) [11].

Myocardial integrated backscatter, which analyses the variations of myocardial reflectivity in decibels, working on a radio frequency signal, is a non-invasive measure of the acoustic characterization of myocardial tissue, which has been demonstrated to reflect physiological and/or pathological changes in myocardial tissue [12–14]. The extracellular matrix has been shown to represent an important source of myocardial integrated backscatter [15], and several experimental and clinical studies have suggested that integrated backscatter measures may be related to myocardial collagen content [16–18]. In particular, cardiac cycle-dependent variation of the integrated backscatter is negatively correlated with myocardial collagen deposition in hypertensive hearts [19,20].

In the present study, acoustic densitometry was used in addition to conventional ecocardiography to assess non-invasively the qualitative and quantitative effects of treatments with the AR blocker losartan as compared with the calcium channel blocker amlodipine on ventricular structure and function in patients with diabetes and with hypertension and echocardiographic evidence of left ventricular hypertrophy.

Patients and methods

This 12-month, prospective, randomized, open-label, blinded end point, parallel-arm study was conducted at the Department of Internal Medicine and Therapeutics, University of Pavia (Pavia, Italy). The study protocol was approved by the Ethical Committee of the University of Pavia. All the enrolled patients gave written informed consent.

Study population

Outpatients with mild to moderate hypertension with well-controlled Type 2 diabetes (American Diabetes Association criteria) [21] and left ventricular hypertrophy were enrolled from 2 January 2007 to 30 July 2008. For enrolment in the study, the inclusion criteria were: (1) blood pressure > 130/80 mmHg and < 160/100 mmHg after a 4-week placebo period; (2) HbA_{1c} < 53 mmol/mol (< 7%); (3) left ventricular mass index > 131/110 g/m^2 in men and women, respectively; (4) sinus rhythm. The exclusion criteria were: administration of ACE inhibitors or AR blockers, atrial fibrillation, abnormal heart rest function (ejection fraction < 55%), valvular heart disease, previous myocardial infarction, nephropathy (creatinine ≥ 1.5 mg/dl), connective tissue disease, pregnancy or lactation, or known intolerance to the study drugs. No statistical significant was observed in the previous anti-hypertensive therapy.

Study design

At screening visit, medical history and medications were evaluated, a venous blood sample was drawn and blood pressure was measured. Sphygmomanometer blood pressure measurement was performed after a 5-min rest in the sitting position, and at least two measurements were averaged. The patients fulfilling the inclusion and exclusion criteria after a 4-week single blind placebo washout period were blindly randomized to losartan 50 mg or amlodipine 5 mg for 12 months. At the end of the first month of treatment, the dosage was increased (losartan 100 mg and amlodipine 10 mg) in patients whose blood pressure was > 130/80 mmHg. After 2 months, clonidine transdermal therapeutic system 1 (2.5 mg) was associated with non-responder patients. Patients who did not achieve the target blood pressure after 3 months of treatment were excluded from the study. Blood pressure and HbA_{1c} were measured every month, while conventional echocardiographic evaluation and integrated backscatter evaluation were performed at the end of the washout placebo period and after 12 months of treatment.

Measurements

Blood pressure was measured using a standard-cuff mercury sphygmomanometer (Korotkoff I and V) after at least 5 min of rest in a sitting position. The average of three consecutive measurements (with at least a 1-min interval between them) was recorded. Heart rate was measured by pulse palpation over a 60-s period. HbA_{1c} was measured by high-performance liquid chromatography.

Conventional echocardiographic data acquisition

Transthoracic echocardiographic assessment was performed in the left lateral decubitus position, using an ultrasound machine with a 2- to 4-MHz transducer. Images were obtained in the standard tomographic views of the left ventricle (parasternal long and short axis and apical four-chamber, two-chamber views). The peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio and isovolumetric relaxation time were measured online. The left ventricular end-diastolic volumes at rest were computed from two- and four-chamber views, using a modified Simpson's method, and left ventricular ejection fraction was calculated. Each representative value was obtained from the average of three measurements. The operator was blinded to the clinical details and results of the other investigations of each patient and control subject.

Acoustic densitometry data acquisition

Integrated backscatter images were obtained using a real-time two-dimensional ultrasonic backscatter imaging device equipped with an acoustic densitometry measurement package for the analysis of backscatter signals (Sonos 5500, Hewlett-Packard Co, Andover, MA, USA). With the ultrasound machine operating in the acoustic densitometry acquisition mode, real-time integrated backscatter images (the parasternal long axis view of the left ventricle) were acquired for 60 consecutive frames at a rate of 30 frames/s (2–3 cardiac cycles), displayed, stored to magneto-optical disc and subsequently analysed. The system setting was optimized in fundamental mode by adjusting the

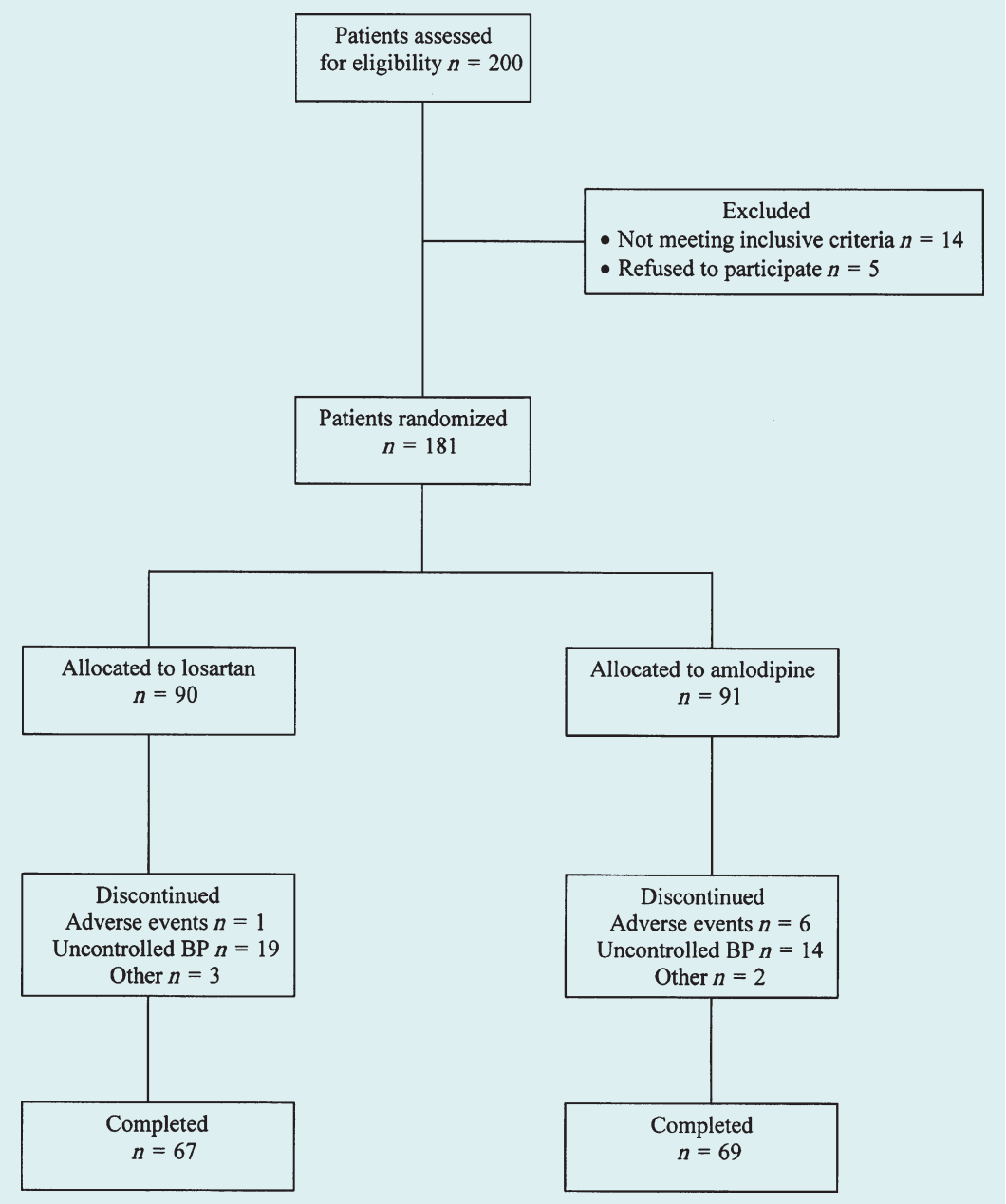

FIGURE 1 Study design. BP, blood pressure.

depth, total gain and time–gain compensators so that all segments of the myocardium were clearly visualized. All controls were held constant during the studies in each subject after the adjustment. During analysis, an elliptical region of interest of 21 × 21 pixels was placed in either the mid-anterior septum or in those portions of the posterior wall of the left ventricle and the same portion of the epicardium. Thus, regions of interest were placed in a maximum of three segments for each patient. Relative integrated backscatter of both the interventricular septum and the left ventricular posterior wall were calculated as the ratio between the mean integrated backscatter values and pericardial integrated backscatter × 100. The magnitude of cardiac cycle-dependent variation of integrated backscatter of both the interventricular septum and the left ventricular posterior wall was calculated as the difference between the minimum and maximum values in a cardiac cycle averaged for at least two consecutive beats.

Intra- and interobserver variations of echocardiographic and integrated backscatter measurements were < 5%.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). The differences between the two groups in baseline characteristics

Table 1 Main demographic, clinic and echocardiographic baseline characteristics of patients in the two treatment groups

	Losartan (n = 90)	Amlodipine (n = 91)	P
Age (years)	63.8 ± 9.2	64.1 ± 8.9	NS
Sex (male/female)	47/43	46/45	NS
BMI (kg/m^2)	26.9 ± 3.9	27.4 ± 4.3	NS
Systolic blood pressure (mmHg)	147.9 ± 12.6	148.1 ± 11.5	NS
Diastolic blood pressure (mmHg)	92.1 ± 7.3	92.5 ± 6.9	NS
Heart rate (beats/min)	74.5 ± 8.1	75.1 ± 8.9	NS
Fasting glucose (mmol/l)	6.63 ± 0.39	6.56 ± 0.38	NS
HbA_{1c} (mmol/mol) (%)	49 ± 15; 6.6 ± 0.8	49 ± 17; 6.6 ± 0.6	NS
Duration of diabetes (years)	8.6 ± 5.8	9.1 ± 6.3	NS
Duration of hypertension (years)	8.9 ± 7.1	9.7 ± 7.2	NS
Serum creatinine (μmol/l)	83.10 ± 21.2	84.86 ± 18.6	NS
Creatinine clearance (ml/s)	1.49 ± 0.32	1.48 ± 0.30	NS
Sodium (mmol/l)	142.4 ± 4.7	140.1 ± 4.2	NS
Potassium (mmol/l)	4.3 ± 0.5	4.1 ± 0.4	NS
Total cholesterol (mmol/l)	5.42 ± 0.58	5.50 ± 0.62	NS
Triglycerides (mmol/l)	1.87 ± 0.78	1.91 ± 0.81	NS
LVMI (g/m^2)	134.5 ± 24.9	133.2 ± 26.8	NS
IVSTd (mm)	11.01 ± 1.1	10.97 ± 1.1	NS
PWTd (mm)	10.45 ± 1.1	10.41 ± 1.1	NS
Ejection fraction (%)	64.1 ± 4.3	64.1 ± 4.5	NS
E/A ratio	0.87 ± 0.18	0.87 ± 0.21	NS
IVRT (ms)	86.4 ± 13.2	86.3 ± 13.3	NS

Data are means ± SD.
E/A ratio, ratio of peak early diastolic filling velocity to peak filling velocity at atrial contraction; IVRT, isovolumetric relaxation time; IVSTd, interventricular septal thickness in diastole; LVMI, left ventricular mass index; NS, not significant; PWTd, posterior wall thickness in diastole.

Table 2 Effect of the two treatments on blood pressure values in the two treatment groups

	Losartan (n = 67)	Amlodipine (n = 69)
Systolic blood pressure (mmHg)		
Placebo	147.1 ± 12.1	147.4 ± 11.4
Treatment	127.4 ± 8.3	126.9 ± 8.1
P-value	< 0.001	< 0.001
Diastolic blood pressure (mmHg)		
Placebo	91.7 ± 6.9	92.1 ± 6.8
Treatment	76.6 ± 4.8	76.2 ± 4.9
P-value	< 0.001	< 0.001

Data are means ± SD.

Table 3 Effects of the two treatments on conventional echocardiographic parameters

	Losartan (n = 67)		Amlodipine (n = 69)	
LVMI (g/m^2)				
Placebo	133.3 ± 24.2	P < 0.001	132.1 ± 23.7	P < 0.01
Treatment	107.2 ± 16.7		118.7 ± 19.1	
IVSTd (mm)				
Placebo	10.95 ± 1.1	P < 0.01	10.89 ± 1.1	P < 0.05
Treatment	9.13 ± 0.8		9.88 ± 0.9	
PWTd (mm)				
Placebo	10.36 ± 1.1	P < 0.01	10.32 ± 1.1	P < 0.05
Treatment	8.94 ± 0.8		9.27 ± 0.9	
Ejection fraction (%)				
Placebo	64.2 ± 4.4	NS	64.1 ± 4.3	NS
Treatment	66.1 ± 4.5		65.2 ± 4.6	
E/A ratio				
Placebo	0.87 ± 0.19	P < 0.01	0.88 ± 0.20	P < 0.05
Treatment	0.99 ± 0.24		0.95 ± 0.23	
IVRT (ms)				
Placebo	86.3 ± 13.6	P < 0.01	86.1 ± 13.5	P < 0.05
Treatment	78.9 ± 12.1		81.2 ± 12.8	

Data are means ± SD.
E/A ratio, ratio of peak early diastolic filling velocity to peak filling velocity at atrial contraction; IVRT, isovolumetric relaxation time; IVSTd, interventricular septal thickness in diastole; LVMI, left ventricular mass index; NS, not significant; PWTd, posterior wall thickness in diastole.

Table 4 Effects of the two treatments on acoustic densitometry characteristics

	Losartan (n = 67)		Amlodipine (n = 69)	
IVS-IBS %				
Placebo	70.4 ± 9.5	P < 0.01	69.9 ± 9.4	NS
Treatment	63.1 ± 8.1		67.8 ± 9.1	
IVS-CVIBS %				
Placebo	5.26 ± 0.86	P < 0.01	5.32 ± 0.78	NS
Treatment	7.09 ± 0.79		5.91 ± 0.88	
LVPW-IBS %				
Placebo	65.6 ± 8.9	P < 0.01	65.7 ± 8.8	NS
Treatment	57.5 ± 7.2		63.9 ± 8.4	
LVPW-CVIBS %				
Placebo	6.71 ± 1.1	P < 0.01	6.84 ± 1.1	NS
Treatment	8.82 ± 1.3		7.15 ± 1.2	

Data are means ± SD.
IVS-CVIB, cyclic variation of integrated backscatter of intraventricular septum; IVS-IBS, relative integrated backscatter of intraventricular septum; LVPW-CVIB, cyclic variation of integrated backscatter of left ventricular posterior wall; LVPW-IBS, relative integrated backscatter of left ventricular posterior wall; NS, not significant.

were analysed by two-tailed Student's t-test. Comparisons within and between groups were assessed by a two-way ANOVA for repeated measurements. Differences between baseline and after 12 months' treatment in each group in blood pressure and echocardiographic determinations were analysed with the Wilcoxon signed rank test. Comparisons of changes in blood pressure and echocardiographic determinations between the two groups were performed with the Mann–Whitney U-test. Findings of $P < 0.05$ were considered significant. Considering as clinically

significant a difference of at least 10% compared with the baseline and an alpha error of 0.05, the actual sample size was adequate to obtain a power higher than 0.80 for all measured variables.

Results

A total of 200 consecutive outpatients with hypertension with diabetes and with left ventricular hypertrophy were referred to our hypertensive centre and 181 were finally randomized to participate in this study (Fig. 1). Fourteen patients were excluded because they did not meet the inclusion/exclusion criteria and five patients refused to participate. A total of 90 patients were allocated to treatment with losartan and 91 to treatment with amlodipine. In the losartan group, 23 patients discontinued the treatment, one because of adverse events (hypotension), 19 because of uncontrolled blood pressure and three were lost at follow-up. In the amlodipine group, 22 patients discontinued the treatment, six because of adverse events (ankle oedema), 14 because of uncontrolled blood pressure and two were lost at follow-up. The baseline demographic, clinic and echocardiographic characteristics of each group are shown in Table 1. The two treatment groups were well matched and similar with regard to all pretreatment clinic and echocardiographic characteristics.

There were substantial reductions in systolic and diastolic blood pressure values in the two treatment groups (Table 2). At the end of the 12 months of follow-up, systolic blood pressure was reduced by 19.7 mmHg ($P < 0.001$ vs. baseline) in the losartan group and by 20.5 mmHg ($P < 0.001$ vs. baseline) in the amlodipine group, with no significant difference between treatments. Corresponding changes for diastolic blood pressure were 15.1 and 15.9 mmHg ($P < 0.001$ vs. baseline), respectively, again without any significant difference between treatments. Heart rate showed no significant change with either treatment.

Conventional echocardiography results are shown in Table 3. In the losartan group, the left ventricular mass index was significantly decreased after 12 months vs. the corresponding baseline value (−19%, $P < 0.001$) and losartan also reduced both interventricular septal thickness in diastole (−16.6%, $P < 0.01$ vs. baseline) and posterior wall thickness in diastole (−13.7%,

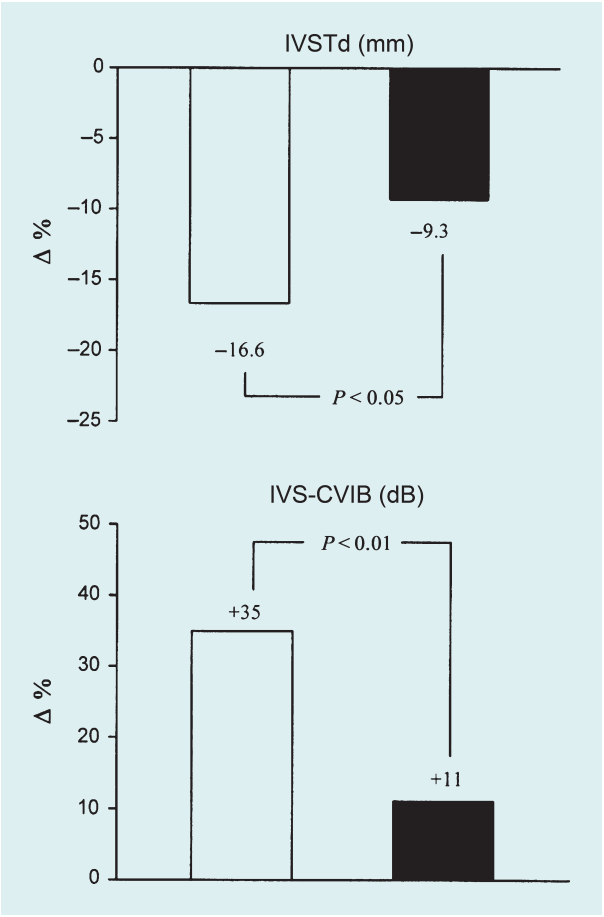

FIGURE 2 Effect of the two treatments on the interventricular septal thickness in diastole (IVSTd) and on the cyclic variation of integrated backscatter of the intraventricular septum (IVS-CVIB) changes; (?) losartan, (?) amlodipine.

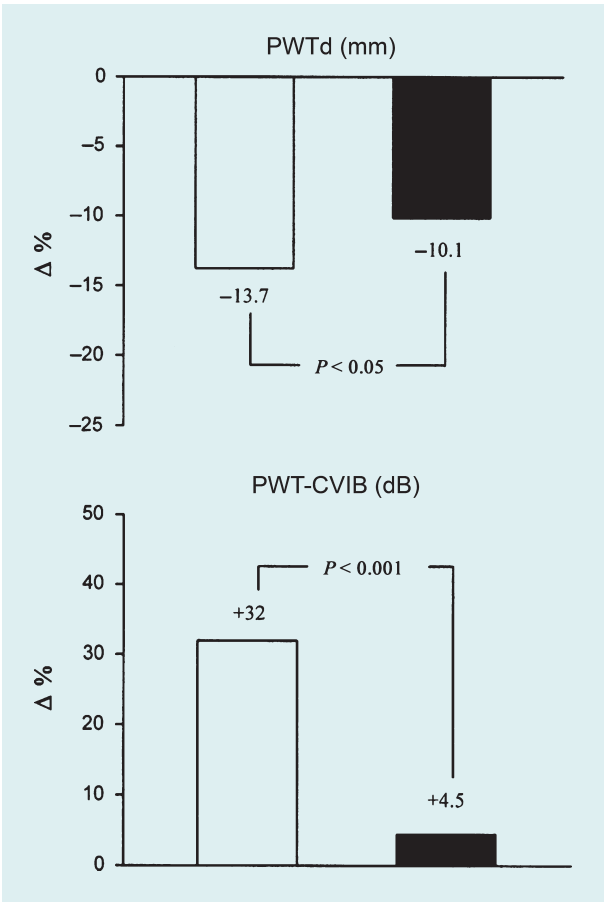

FIGURE 3 Effect of the two treatments on posterior wall thickness (PWT) and on cyclic variation of integrated backscatter of the posterior wall thickness (PWT-CVIB) changes; (?) losartan, (?) amlodipine.

$P < 0.01$ vs. baseline). Amlodipine treatment also significantly decreased the left ventricular mass index (−10%, $P < 0.01$ vs. baseline), and both the interventricular septal thickness in diastole (−9.3%, $P < 0.05$ vs. baseline) and posterior wall thickness in diastole (−10.1%, $P < 0.05$ vs. baseline), but such reductions were all significantly less pronounced as compared with those produced by losartan ($P < 0.05$ for each measurement). Both treatments significantly increased the E/A ratio compared with baseline, but again such an increase was more marked in the losartan (+13.7%, $P < 0.01$ vs. baseline) than in the patients treated with amlodipine (+7.9%, $P < 0.05$ vs. baseline). Similarly, the left ventricular mass index decreased more in the losartan (−8.5%, $P < 0.01$ vs. baseline) than in the amlodipine group (−4.9%, $P < 0.05$ vs. baseline). Ejection fraction was not significantly modified by either treatment. The proportion of patients who attained a normalized left ventricular mass was 55% in the losartan group and 45% in the amlodipine group.

Acoustic densitometry results are shown in Table 4. Losartan treatment significantly reduced both relative integrated backscatter of the interventricular septum (−10.3%, $P < 0.01$ vs. baseline) and of the left ventricular posterior wall (−12%, $P < 0.01$ vs. baseline), while it significantly increased cyclic variation of integrated backscatter of both the intraventricular septum (+35%, $P < 0.01$ vs. baseline) and of the left ventricular posterior wall (+32%, $P < 0.01$ vs. baseline). None of these measurements was significantly modified by amlodipine treatment. Consequently, significant differences in change in both cyclic variation of integrated backscatter of the intraventricular septum and of the left ventricular posterior wall were observed between the two treatment groups ($P < 0.01$ and $P < 0.0001$, respectively; Figs 2 and 3). Such a different effect on integrated backscatter measures was independent of the reduction of blood pressure, which was similar with losartan and amlodipine. As results from Figs 2 and 3 show, the different degree of both interventricular septal thickness in diastole and posterior wall thickness in diastole reduction with the two drugs did not seem sufficient to account for their more markedly different effect on cyclic variation of integrated backscatter of both the intraventricular septum and of the left ventricular posterior wall.

There were no significant changes in blood glucose and HbA_{1c} during the treatment period with either drug. No variations of sodium or potassium were recorded during the study in either group and no differences between the groups were observed (at the end of the study, sodium levels were 141.2 ± 4.5 mmol/l with losartan and 142.7 ± 4.8 mmol/l with amlodipine; potassium levels were 4.4 ± 0.6 mmol/l with losartan and 4.0 ± 0.3 mmol/l with amlodipine).

Discussion

The results of this study indicated that, in patients with Type 2 diabetes and with hypertension and left ventricular hypertrophy, 1-year treatment with losartan and amlodipine, despite having similar blood pressure-lowering efficacy, produced different effects on myocardial structure and function, as assessed non-invasively by conventional echocardiography and acoustic densitometry. While the echocardiography provided the well-known quantitative and functional information, the acoustic densitometry was used to assess myocardial tissue characteristics, in particular collagen content and fibrosis, otherwise obtainable only invasively by myocardial biopsy. In fact, serological markers of tissue collagen synthesis (such as the C-terminal peptide of procollagen type 1) are not exclusively heart-specific.

In the present study, conventional echocardiographic data indicated that losartan was significantly more effective than amlodipine in reducing left ventricular hypertrophy, as demonstrated by the greater decrease in left ventricular mass index, interventricular septal thickness in diastole and posterior wall thickness in diastole produced by losartan. These findings are in keeping with previous observations showing a more marked reduction in left ventricular mass with this and other AR blockers as compared with amlodipine [22,23]. From a functional point of view, the E/A ratio increased more and isovolumetric relaxation time decreased more with losartan than with amlodipine, which suggests a greater improvement of diastolic left ventricular function with losartan. Neither drug induced any changes in systolic ventricular function.

The most original findings of this study were those obtained by acoustic densitometry: losartan, but not amlodipine, significantly reduced relative integrated backscatter of the interventricular septum and the left ventricular posterior wall and increased relative cyclic variation of integrated backscatter of the intraventricular septum and the left ventricular posterior wall. As these integrated backscatter measures have been shown to reflect structural changes of the fibrous components of the myocardium, these findings suggest attenuation of myocardial fibrosis by losartan, but not by amlodipine. The losartan-induced reduction in myocardial fibrosis is an agreement with previous studies using biopsied tissues [11] and resembles the findings obtained using the same non-invasive technique in another recent study with valsartan [24].

The differences in the effects on left ventricular mass and integrated backscatter measures between losartan and amlodipine were independent of the reduction of blood pressure, which was similar with the two drugs. The presumed mechanisms of losartan effects is thought to be related to inhibition of angiotensin II, the role of which is critical in the development of left ventricular hypertrophy and myocardial fibrosis.

Angiotensin II, via its interaction with the AT1 receptor, is a potent promoter of cardiomyocyte growth through a variety of mechanisms, including increased production of growth factors, vasoconstrictor agents, adhesion molecules, tumour necrosis factor alpha and integrins [25]. Angiotensin II also induces the accumulation of extracellular matrix and fibrosis and it may also exert its effects on remodelling and fibrosis by stimulating aldosterone [26]. Enhanced activity of

the renin–angiotensin aldosterone system, including hyperglycaemia-induced increase in angiotensin II [27] and up-regulation of myocardial AT1 receptors [28], has been described in diabetes. Increased stimulation of AT1 receptors by angiotensin II in a hyperglycaemic environment may lead to myocardial fibrosis and, to a larger extent, to myocyte hypertrophy [29].

As alteration of myocardial acoustic densitometry associated with increased myocardial collagen content has been shown to correlate with diastolic function in patients with diabetes [30], the improvement of integrated backscatter measures by losartan might partly explain its improved effect on E/A ratio and isovolumetric relaxation time.

However, even if losartan was definitely better than amlodipine in improving left ventricular mass index, amlodipine also made an improvement to that measure compared with baseline. On that basis, the next step could be to study the effects of the combined use of these two different drugs, taking advantage of the positive effect of losartan on myocardial fibrosis and the positive effect of amlodipine on myocite volume to obtain a more pronounced effect on left ventricular hypertrophy regression.

In conclusion, the present study using non-invasive ecocardiographic techniques demonstrated that, in hypertensive patients with Type 2 diabetes and with left ventricular hypertrophy, losartan was more effective than amlodipine in reducing left ventricular mass and improving diastolic left ventricular function, despite comparable hypotensive effects between the two agents. In addition, unlike amlodipine, losartan attenuated myocardial fibrosis as assessed by integrated backscatter measures. Thus, losartan appeared to provide more beneficial effects than amlodipine on left ventricular structure and function.

Competing interests

Nothing to declare.

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