Ventricular Mass and Atrial Size in Diabetic Hypertensive Patients Using Losartan or Benazepril

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Abstract

Background: Hypertensive diabetic patients are more likely to develop left ventricular hypertrophy and atrial fibrillation. Evidence suggests that renin-angiotensin-aldosterone system blockers should be used in this group of patients.

Objective: To evaluate if there are differences between the effects of angiotensin-converting enzyme benazepril and the angiotensin-receptor blocker losartan on left atrial size and ventricular mass when associated to the treatment of diabetic hypertensive patients using amlodipine.

Methods: 34 hypertensive type-2 diabetic outpatients from the Internal Medicine service of Universidade do Estado do Rio de Janeiro were randomized into two groups, after a period of 6 weeks receiving only amlodipine, to receive losartan or benazepril. At the beginning and end of the combined treatment, patients were submitted to echocardiography for cavity assessment, wall thickness and flow measurements.

Results: There was reduction in left ventricular mass index in the losartan group (from 81.1 ± 23.5 to 76.9 ± 23.8 g/m²; p = 0.044), with no difference in the benazepril group (from 81.8 ± 10.8 to 79.7 ± 12.1 g/m²; p = 0.520). The left atrial diameter index was lower at 12 weeks (p = 0.034) in the losartan group, which ranged from 2.12 ± 0.23 to 2.03 ± 0.22 cm/m² (p = 0.103) when compared to the benazepril group, which ranged from 2.12 ± 0.30 to 2.23 ± 0.29 cm/m² (p = 0.064).

Conclusion: The losartan and amlodipine combination was better than the benazepril and amlodipine combination for left ventricular mass and left atrial size reduction in this sample of type 2 diabetic hypertensive patients. (Int J Cardiovasc Sci. 2016;29(3):181-188)

Keywords: Diabetes Mellitus; Hypertrophy, Left Ventricular; Hypertension; Atrial Fibrillation; Renin-Angiotensin System.

Introduction

In addition to the cardiovascular complications of atherosclerosis, diabetic patients are also more likely to develop left ventricular hypertrophy and atrial fibrillation (AF). The pathophysiology of these alterations is poorly defined and seems to be multifactorial, involving the coexistence of hypertension, coronary heart disease, increased sympathetic autonomic tone and possibly the direct action of diabetes on the heart.1-3

Studies have shown changes in the left atrium (LA) mechanical function in diabetic patients, before the increase in diameter,4 even without systemic arterial hypertension (SAH)5,6 and alterations in LA dimensions and in the absence of diastolic dysfunction or ventricular hypertrophy,7 suggesting that Diabetes Mellitus (DM) alone leads to structural changes in the LA. Additionally, diabetic hypertensive patients have worse diastolic function than nondiabetic hypertensive ones.3
Studies suggest that type 2 diabetic hypertensive patients should receive drugs that act on the renin-angiotensin-aldosterone system (RAAS).\textsuperscript{8-11} Very often, these patients will require more than one drug to control blood pressure (BP),\textsuperscript{8,9} and the combination of RAAS blocking with CCB seems to be the most appropriate.\textsuperscript{11} There are several advantages of this combination, among which are: better BP control, favorable metabolic effects, reduced vasodilatory edema and a synergistic effect on proteinuria reduction and glomerular filtration rate decline.\textsuperscript{9}

Few studies have been carried out comparing the cardiovascular effects of Angiotensin-Converting Enzyme (ACE) inhibitors and angiotensin II AT1-receptor blockers (ARB) specifically in diabetic hypertensive patients.\textsuperscript{1,9,12,13} No studies have compared the effects on LA dimensions in hypertensive diabetic patients.

The aim of this study was to compare the effects of the combined therapy with losartan and amlodipine vs. benazepril and amlodipine on the echocardiographic parameters of ventricular mass and LA dimensions in type 2 diabetic patients with SAH.

**Methods**

Fifty-two patients with a previous diagnosis of SAH and type 2 diabetes, followed at the Internal Medicine Outpatient Clinic of Universidade do Estado do Rio de Janeiro were selected. Inclusion criteria were age between 40 and 70 years, systolic blood pressure (SBP) > 130 mmHg and/or diastolic blood pressure (DBP) > 80 mmHg, assessed by BP measurement in the office setting and treatment with up to two antihypertensive drugs with no changes in antidiabetic treatment in the past 4 weeks. Patients with evidence of secondary SAH, uncontrolled DM, need for insulin use, stage 4 or 5 chronic kidney disease, cardiac arrhythmias with irregular heart rate, significant mitral or aortic valve disease, suspected or confirmed pregnancy, previous history or evidence obtained from complementary tests of myocardial infarction, cerebrovascular accident, peripheral vascular disease, retinopathy with loss of visual acuity and/or symptomatic neuropathy, were excluded.

All patients signed the study Free and Informed Consent form, approved together with the project by the Research Ethics Committee of Hospital Universitário Pedro Ernesto (number 01539612.6.0000.5259), which is in accordance with the Declaration of Helsinki. The study was registered at *Clinical Trials* and its identifier is NCT01603940.

This is an open-label randomized trial, consisting of four phases, with two arms in phases 2, 3 and 4, as shown in figure 1. At the first consultation, all antihypertensive medications were replaced by amlodipine 5 mg daily aiming at a period without drugs that had a direct action on the RAAS. At the second consultation, after a period of six weeks, six patients were excluded for having achieved systolic BP < 130 and diastolic BP < 80 mmHg (assessed by BP measured in the office) with only one drug, nine patients for needing insulin use, one for developing AF, one patient for deep vein thrombosis and another who did not want to continue participating in the study. The remaining 34 patients were submitted to clinical consultation to perform Ambulatory BP Monitoring (ABPM) and to undergo anthropometric index measurement and echocardiographic assessment, after which they were randomized by an independent investigator into two groups: 18 patients to losartan 50 mg daily and 16 patients to benazepril 10 mg day, which were added to the antihypertensive treatment, both in a single daily dose. The echocardiographic assessment was performed by an examiner who had no knowledge of the group the patients belonged to. At the third consultation, after a 4-week interval, when necessary (patients with BP ≥ 130/80 mm Hg, assessed by BP measured at the office), the dose of benazepril was titrated to 20 mg/day and losartan to 100 mg/day. After another 4 weeks, at the fourth consultation, hydrochlorothiazide 25 mg/day was added when necessary, to achieve the target systolic BP < 130 and diastolic BP < 80 mmHg measured at the office. Twelve weeks after randomization (fifth consultation), laboratory tests, echocardiography and ABPM were repeated, and the study was completed. Hypoglycemic drug doses were maintained throughout the study. Control of adherence and drug use was carried out by assessing the number of remaining tablets at the consultations.

An Omron Healthcare Automatic Blood Pressure Monitor, model HEM-705CP, (Illinois, USA) was used for BP measurement at the office; three measurements were obtained in each of the upper limbs and the mean of these measurements was calculated, with the highest value being used. ABPM was performed with a SpaceLabs 90207 device (SpaceLabs Inc, WA, USA), scheduled to
start the assessment between 8 and 9 AM, lasting for at least 24 hours. BP was measured every 20 minutes from 6 AM to 11 PM and every 30 minutes from 11 PM to 6 AM. The test was considered satisfactory when there was at least 70% of valid readings and a minimum of 16 readings during wakefulness and eight during sleep, and no period longer than two hours without measurements.

The echocardiographic assessments were performed at the end of the 6th and 18th weeks of the study, using a GE Vivid 3 device, equipped with a 3.5 MHz transducer (USA), according to the recommendations of the American Society of Echocardiography and the European Association of Echocardiography.\textsuperscript{14} The following were assessed: left ventricular end diastolic (LVEDD) and systolic diameter (LVESD), interventricular diastolic septal thickness (IVSDT) and left ventricular posterior wall (LVPW), aortic (Ao) root diameter and LA. Left ventricular ejection fraction of the (LVEF) was calculated using the Teicholz method.\textsuperscript{14} Left ventricular mass (LVM) was calculated from the linear measurements and the length-area method (two-dimensional). Left atrial volume was calculated using the area-length equation. The results were indexed by body surface area.\textsuperscript{14} The following flow measurements were performed at the pulsed Doppler: velocity of E and A waves at the mitral flow, with the E/A velocity ratio being calculated.\textsuperscript{15} The measurements of the e' wave velocities in the septal and lateral mitral annulus were obtained by tissue Doppler and the ratio of the mean E/e' velocities was calculated.\textsuperscript{15}

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 18.0. Results were expressed as median and interquartile range (IQR) or in absolute numbers with percentages. The continuous variables of each group were compared before and after treatment by paired t test, and between groups using Student’s t test, with a 95% confidence interval and p values < 0.05 being considered statistically significant. Pearson’s coefficient was obtained for variable correlation test. Considering an alpha error of 5% and a standard deviation of 3.5%, a sample of 17 patients in each group had an 80% power to detect a difference of 4%.

**Results**

Basal clinical and laboratory characteristics of the groups are shown in Table 1. Basal echocardiographic parameters are shown in Table 2.
There was a similar decrease in BP assessed by ABPM in both groups at the end of the 12 weeks of combined treatment protocol (systolic BP of 135.4 ± 18.7 mmHg pre-treatment to 123.7 ± 8.0 mmHg after treatment in the losartan group and 134.9 ± 13.5 mmHg to 133.2 ± 18.9 mm Hg in the benazepril group, with p = 0.786; diastolic BP of 78.9 ± 11.6 mmHg to 73.1 ± 8.9 mmHg in the losartan group and 81.9 ± 12.1 mmHg to 80.3 ± 13.1 mm Hg in the benazepril group, with p = 0.813). Adjustment of the losartan dose was necessary in seven patients (38.9%) and also of the benazepril dose in seven patients (43.8%). It was necessary to add a diuretic to the treatment regimen of two patients in the losartan group (11.1%) and two patients in the benazepril group (12.5%). One patient in the benazepril group had cough during treatment, without need for interruption. Two patients had edema with amlodipine, before randomization, without need for medication interruption.

There was a significant reduction in the indexed Left Ventricular Mass (iLVM) calculated by the two-dimensional method (Figure 2) in the losartan group, from 81.1 ± 23.5 g/m² to 76.9 ± 23.8 g/m² (p = 0.044), with no difference in the benazepril group (81.8 ± 10.8 g/m² to 79.7 ± 12.1 g/m²; p = 0.520). There was no correlation between LV mass reduction and reduction in systolic BP (R = 0.099; p = 0.582). iLVM calculated by the one-dimensional method did not differ between the treatment groups (p = 0.108), being 83.6 ± 22.8 g/m² (pre-treatment) and 78.1 ± 21.3 g/m² (post-treatment) in the losartan group (p = 0.148) and 89.1 ± 12.6 g/m² (pre-treatment) and 88.0 ± 12.5 g/m² (post-treatment) in the benazepril group (p = 0.721).

There was no change in the indexed left atrial diameter (Figure 3) in the losartan group (2.12 ± 0.23 cm/m² to 2.03 ± 0.22 cm/m²; p = 0.103), and there was a trend to increase in the benazepril group, from 2.12 ± 0.30 cm/m² to 2.23 ± 0.29 cm/m² (p = 0.064) with a significant difference between the groups at 12 weeks (p = 0.034) and when comparing diameter variation at 12 weeks (decrease from 0.08 ± 0.20 cm/m² in the losartan group

### Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Losartan (n = 18)</th>
<th>Benazepril (n = 16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57 ± 8</td>
<td>58 ± 5</td>
<td>0.695</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>7 (38.9)</td>
<td>5 (31.3)</td>
<td>0.653</td>
</tr>
<tr>
<td>Black ethnicity, n (%)</td>
<td>6 (33.3)</td>
<td>3 (19.8)</td>
<td>0.346</td>
</tr>
<tr>
<td>24h-SBP, mmHg</td>
<td>135 ± 19</td>
<td>135 ± 13</td>
<td>0.943</td>
</tr>
<tr>
<td>24h-DBP, mmHg</td>
<td>79 ± 12</td>
<td>82 ± 12</td>
<td>0.526</td>
</tr>
<tr>
<td>BMI</td>
<td>30.4 ± 5.1</td>
<td>29.9 ± 4.9</td>
<td>0.799</td>
</tr>
<tr>
<td>Abdominal circumference, cm</td>
<td>99.9 ± 10.3</td>
<td>101.6 ± 13.2</td>
<td>0.703</td>
</tr>
<tr>
<td>Time of SAH, years</td>
<td>11 ± 9</td>
<td>12 ± 9</td>
<td>0.740</td>
</tr>
<tr>
<td>Time of DM, years</td>
<td>4 ± 5</td>
<td>5 ± 5</td>
<td>0.678</td>
</tr>
<tr>
<td>Glycemia, mg/dL</td>
<td>139 ± 67</td>
<td>121 ± 42</td>
<td>0.341</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.68 ± 0.26</td>
<td>0.81 ± 0.19</td>
<td>0.112</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>193 ± 30</td>
<td>196 ± 30</td>
<td>0.844</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>52.2 ± 10.1</td>
<td>50.8 ± 15.6</td>
<td>0.773</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>134 ± 43</td>
<td>136 ± 58</td>
<td>0.895</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.5 ± 1.5</td>
<td>13.1 ± 1.4</td>
<td>0.444</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.91 ± 0.77</td>
<td>6.75 ± 1.19</td>
<td>0.728</td>
</tr>
</tbody>
</table>

24h-SBP: systolic blood pressure by 24-hour ambulatory monitoring; 24h-DBP: diastolic blood pressure by 24-hour ambulatory monitoring; BMI: body mass index; time of SAH: time since systemic arterial hypertension diagnosis; time of DM: time since diabetes mellitus diagnosis; HDL: high-density lipoprotein; HbA1c: glycated hemoglobin.
### Table 2
Basal echocardiographic parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>Losartan (n = 18)</th>
<th>Benazepril (n = 16)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>iLAD (cm/m²)</td>
<td>2.12 ± 0.23</td>
<td>2.12 ± 0.30</td>
<td>0.930</td>
</tr>
<tr>
<td>iLAV (ml/m²)</td>
<td>32.9 ± 8.5</td>
<td>34.4 ± 8.3</td>
<td>0.704</td>
</tr>
<tr>
<td>LVDD (cm)</td>
<td>4.87 ± 0.60</td>
<td>5.01 ± 0.45</td>
<td>0.434</td>
</tr>
<tr>
<td>LVSD (cm)</td>
<td>3.10 ± 0.67</td>
<td>3.17 ± 0.35</td>
<td>0.705</td>
</tr>
<tr>
<td>EF by Teicholz</td>
<td>0.66 ± 0.09</td>
<td>0.66 ± 0.05</td>
<td>0.925</td>
</tr>
<tr>
<td>IVST (cm)</td>
<td>0.91 ± 0.07</td>
<td>0.94 ± 0.07</td>
<td>0.287</td>
</tr>
<tr>
<td>LVPWT (cm)</td>
<td>0.92 ± 0.06</td>
<td>0.92 ± 0.09</td>
<td>0.994</td>
</tr>
<tr>
<td>Relative thickness</td>
<td>0.38 ± 0.04</td>
<td>0.37 ± 0.04</td>
<td>0.598</td>
</tr>
<tr>
<td>iLVM-D (g/m²)</td>
<td>83.6 ± 22.8</td>
<td>89.1 ± 12.6</td>
<td>0.381</td>
</tr>
<tr>
<td>iLVM-2D (g/m²)</td>
<td>81.1 ± 23.5</td>
<td>81.8 ± 10.8</td>
<td>0.915</td>
</tr>
<tr>
<td>E/e’ ratio</td>
<td>9.62 ± 2.33</td>
<td>8.73 ± 1.26</td>
<td>0.175</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.93 ± 0.29</td>
<td>0.83 ± 0.12</td>
<td>0.174</td>
</tr>
<tr>
<td>Sept e’ wave (cm/s)</td>
<td>7.47 ± 1.74</td>
<td>7.27 ± 2.18</td>
<td>0.770</td>
</tr>
<tr>
<td>Lat e’ wave (cm/s)</td>
<td>9.77 ± 2.53</td>
<td>10.02 ± 1.54</td>
<td>0.725</td>
</tr>
</tbody>
</table>

iLAD: indexed left atrial diameter; iLAV: indexed left atrial volume; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; EF: ejection fraction; IVST: interventricular septal thickness; LVPWT: left ventricular posterior wall thickness; iLVM-D: indexed left ventricular mass by the Devereaux method; iLVM-2D: indexed left ventricular mass by the two-dimensional method; E/e’ ratio: ratio of the mitral flow ‘E’ wave and mean mitral annulus ‘e’ wave velocities; E/A ratio: ratio of the mitral flow ‘E’ and ‘A’ wave velocities; sept e’ wave: e’ wave velocity in the septal mitral annulus by tissue Doppler; Lat e’ wave: e’ wave velocity in the lateral mitral annulus by tissue Doppler.

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**Figure 2**
Left ventricular mass in each group.
and increase from $0.11 \pm 0.21 \text{ cm/m}^2$ in the benazepril group, $p = 0.013$). There was a trend to greater indexed left atrial volume at the end of 12 weeks of treatment in the benazepril group (35.9 ± 8.0 mL/m²) when compared to losartan group (31.2 ± 6.9 mL/m²), with $p = 0.079$, with no difference between the basal values (34.4 ± 8.3 mL/m² vs. 32.9 ± 8.5 mL/m²; $p = 0.603$) or between the variations of values in the groups with treatment ($p = 0.186$). There was no correlation between the left atrial diameter with the E/e’ ratio ($R = 0.136$, $p = 0.442$).

**Discussion**

Most studies comparing ACE inhibitors and ARB in hypertensive individuals showed no difference in ventricular mass reduction. The largest comparative study was the one by Tedesco et al. with 259 patients, which demonstrated a similar reduction in LVM with losartan (12.3%) and enalapril (7.5%). Spolestra-of-Mann et al. carried out a comparative study in diabetic hypertensive patients and obtained an 8% reduction in LVM, with no difference between the groups during a 12-month follow-up period. Meta-analyses carried out with the group of diabetic patients in comparative studies of ACE inhibitors and ARB, such as the ONTARGET study in 2009, which compared telmisartan and ramipril, showed no significant differences in cardiovascular outcomes or LVM when comparing ACE inhibitors vs. ARB.

Our results showed a better effect of losartan on ventricular mass reduction when compared to benazepril. The RAAS has a very important role in the pathophysiology of several systemic arterial hypertension-related outcomes. Hypertrophy development is related not only to the BP, but also the RAAS activity, whereas angiotensin II levels correlate with the hypertrophy degree, irrespective of blood pressure levels. It can be postulated that AT1 angiotensin-receptor blocking in the heart has a larger benefit than blocking the locally formed angiotensin action. Angiotensin II can be formed from other pathways rather than the Angiotensin-Converting Enzyme (ACE), present in tissues, such as chymase, cathepsin and kallikrein, which would reduce its effect.

There are reports in the literature of comparative studies of ACE inhibitors and ARB on left atrial size. One of the few studies that evaluated LA diameter in this group of patients was the CALM II study, which compared the effect of candesartan and lisinopril combination with lisinopril alone. In this study, LA diameter did not change with antihypertensive treatment during the follow-up period and the results were not compared between the groups.

Our study showed a better result of the therapy combining amlodipine with losartan on LA diameter, compared to the group receiving amlodipine with benazepril. There was a trend of better results...
regarding left atrial volume in the group receiving losartan. Greater expression of chymases in the left atrial muscle has been described, with local formation of angiotensin by independent ACE pathways becoming more important in the atrium.23,24 There seems to be angiotensin participation in atrial remodeling and increased expression of AT2 receptors in the LA has been described in individuals with AF.26,27

Data from comparative studies on the protective effect of these drug classes on AF recurrence prevention show more favorable results for ARBs,26,27 which may suggest that the action of chymases in fact has a clinical relevance. Diastolic function showed few significant differences between the groups and the E/e’ ratio, which is an indicator of left BP, did not differ between the groups and, therefore, should not justify the results on left atrial dimensions. No correlation was demonstrated between the E/e’ ratio and BP or between E/e’ ratio and LA dimensions, either.

Future studies focusing on the reduction of left atrial volume and left ventricular mass with a larger sample size are needed to support a better effect of the ARBs. A long-term prospective study could be carried out comparing the incidence of AF and other cardiovascular outcomes in diabetic patients using ARBs or ACE inhibitors. One limitation of our study was the small sample size. The profile of patients in our service, connected to a tertiary hospital, has a large number of complications, which constitute exclusion criteria for our study.

Conclusions

In this sample of diabetic hypertensive patients, the combined treatment of losartan with amlodipine showed to be better than the combined treatment of benazepril with amlodipine in the reduction of left ventricular mass and left atrial size.

Author contributions

Conception and design of the research: Bedirian R, Gismondi RAOC, Castier MB. Acquisition of data: Bedirian R, Gismondi RAOC, Pozzobon CR, Ladeira MCB. Analysis and interpretation of the data: Bedirian R, Neves MF, Oigman W, Gismondi RAOC, Castier MB. Statistical analysis: Neves MF, Gismondi RAOC. Writing of the manuscript: Bedirian R. Critical revision of the manuscript for intellectual content: Bedirian R, Neves MF, Oigman W, Castier MB.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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References


