Comparison of the Effects of Antihypertensive Agents on Central Blood Pressure and Arterial Stiffness in Isolated Systolic Hypertension


Abstract—Isolated systolic hypertension is an important risk factor for cardiovascular disease and results primarily from elastic artery stiffening. Although various drug therapies are used to lower peripheral blood pressure (BP) in patients with isolated systolic hypertension, the effects of the 4 major classes of antihypertensive agents on central BP, pulse pressure (PP) amplification, and arterial stiffness in this condition are not clear. Fifty-nine patients over the age of 60 years with untreated isolated systolic hypertension (systolic BP \(\geq 140\) mm Hg and diastolic BP \(\leq 90\) mm Hg) were randomly assigned to receive 1 of the following 4 antihypertensive agents: perindopril, atenolol, lercanidipine, or bendrofluazide. BP was measured using a mercury sphygmomanometer, and augmentation index and carotid-femoral (aortic) pulse wave velocity were measured at baseline, after 2 weeks of placebo therapy, and at the end of 10 weeks of active therapy. Peripheral systolic BP and peripheral PP were reduced similarly after treatment with all 4 classes of drug. However, central PP was only reduced significantly by perindopril, lercanidipine, and bendrofluazide, whereas atenolol had no effect. Lercanidipine reduced the augmentation index, whereas atenolol increased it. Aortic pulse wave velocity was not changed by any of the drugs. In summary, despite similar reductions in peripheral systolic and PP with the 4 classes of drug, changes in central pressure and augmentation index varied. Because central PP and increased wave reflections are considered important risk factors in patients with isolated systolic hypertension, the choice of therapy may be influenced by these findings in the future. (Hypertension. 2009;54:409-413.)

Key Words: antihypertensive therapy ■ central pressure ■ pulse pressure amplification ■ pulse wave velocity ■ isolated systolic hypertension

Isolated systolic hypertension (ISH) is a common condition in older individuals and is characterized by increased arterial stiffness\(^1\) and an elevated risk of cardiovascular events. Several of the main antihypertensive drug classes are effective in lowering brachial blood pressure (BP) in patients with ISH.\(^2,3\) However, the Losartan Intervention for Endpoint Reduction in Hypertension Study showed that, despite similar reductions in brachial BP, patients randomly assigned to initial therapy with losartan had a better outcome than those randomly assigned to atenolol (with subsequent add-in therapy using hydrochlorothiazide for both study arms) and that this effect was more pronounced in older patients with systolic hypertension.\(^4\) The Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study reported previously that different antihypertensive drugs exert differential effects on brachial versus aortic pressure,\(^5\) and a growing body of evidence now supports these findings\(^6-8\) and provides a potential explanation for the results of the Losartan Intervention for Endpoint Reduction in Hypertension Study. Indeed, more recently, the Conduit Artery Function Evaluation Study\(^9\) showed that atenolol was less effective in reducing central (aortic) BP than an amlodipine-based regime, which translated into a difference in outcome. However, relatively few studies have directly compared the 4 major antihypertensive drug classes on both peripheral and central pressure, as well as arterial stiffness.

Morgan et al\(^8\) compared the effects of 4 different classes of antihypertensive agents with placebo on central pressure in 32 patients with systolic hypertension. Aortic augmentation pressure fell on angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics but rose on \(\beta\)-blockers. However, pulse pressure (PP) amplification, which provides a relative measure of peripheral and central pressures, was not reported, and aortic pulse wave velocity (aPWV), the gold standard measurement of arterial stiffness, was not assessed. Therefore, the aim of this study was to...
compare the effects of representatives of the 4 major classes of antihypertensive drugs on peripheral and central BP, PP amplification, and arterial stiffness in patients with ISH.

Methods

Subjects
Treatment-naive patients with ISH (systolic BP [SBP] ≥140 mm Hg and diastolic BP [DBP] ≤90 mm Hg), confirmed on ≥3 occasions, were recruited from hypertension clinics and local general practices. The study was approved by the relevant local research ethics committees and was performed according to Good Clinical Practice. All of the patients gave written informed consent.

Protocol
After a 2-week placebo run-in, patients were randomly assigned to receive 1 of the following 4 antihypertensive agents for a 10-week period: perindopril 4.0 mg OD, atenolol 50.0 mg OD, lercanidipine 10.0 mg OD, or bendrofluazide 2.5 mg OD in a double-blinded manner. Drug doses were chosen as the midrange dose, according to standard clinical practice. Compliance was assessed by tablet counts at each visit. Hemodynamic measurements were performed at baseline, after 2 weeks of placebo therapy, and at the end of the 10-week period of active therapy.

Hemodynamic Measurements
At each visit, BP was measured in duplicate by trained personnel using a mercury sphygmomanometer in the dominant arm after a 5-minute rest in the seated position with the arm supported. After a further 10 minutes of supine rest, BP measurement was repeated and applanation tonometry performed to record radial artery waveforms using a high-fidelity micromanometer (SPC-301; Millar Instruments). Pulse wave analysis (SphygmoCor; AtCor Medical) was then used to generate corresponding central (ascending aortic) waveforms. PP amplification was measured from integration of the radial artery waveform. The aPWV was calculated from the surface distance between the suprasternal notch and femoral site minus the distance between the suprasternal notch and carotid site using a tape measure. All of the measurements were made in duplicate by trained investigators, and the mean values were used in the subsequent analysis.

Statistical Analyses
Results are reported as absolute values at baseline, after placebo, and after 10 weeks of active therapy. Results were analyzed using 1-way ANOVA and 2-way ANOVA (drug×time) with repeated measures, as appropriate. Multivariate regression analysis was performed using the enter method to determine whether baseline factors, eg, age, sex, baseline SBP, baseline PP, and baseline arterial stiffness measurements, influenced the change in hemodynamic parameters after drug therapy. For all of the statistical analyses, a P<0.05 was considered significant.

Results
In all, 59 patients (31 men and 28 women) completed the study. The mean±SD age of the group was 68.6±6 years, mean body mass index was 28.4±3.9 kg/m², mean brachial SBP was 159±10 mm Hg, and mean brachial DBP was 84±8 mm Hg. Importantly, when patients were stratified according to treatment group, there were no differences between any of the demographic or hemodynamic parameters at baseline (Table 1).

Hemodynamic indices before and after 10 weeks of active therapy are shown for each treatment group in Table 2. All 4 of the drugs significantly reduced brachial SBP and PP with no differences between drugs. In contrast, only perindopril and atenolol reduced DBP. Similarly, all of the drugs significantly reduced aortic SBP, although the response to lercanidipine was significantly greater compared with atenolol. Moreover, atenolol was the only drug that did not significantly lower aortic PP. Unlike the other drugs, atenolol also reduced PP amplification significantly, reflecting the fact that atenolol was the least effective of the 4 drugs at reducing central relative to peripheral pressure. However, after adjusting for differences in heart rate, the influence of atenolol on PP amplification was no longer significant (P=0.3). All 4 of the drugs significantly reduced non-augmented aortic PP (P<0.001), although there were no differences between drugs...
**Table 2. Hemodynamic Indices Before and After the 10-Week Active Therapy Period**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Perindopril</th>
<th>Atenolol</th>
<th>Lercanidipine</th>
<th>Bendroflazide</th>
<th>2-Way ANOVA, Time, Drug</th>
</tr>
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<tbody>
<tr>
<td>Peripheral SBP, mm Hg</td>
<td>Placebo</td>
<td>10 wk</td>
<td>Placebo</td>
<td>10 wk</td>
<td>Placebo 10 wk</td>
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<td>Peripheral DBP, mm Hg</td>
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<td>Peripheral PP, mm Hg</td>
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<td>Central SBP, mm Hg</td>
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<td>Central PP, mm Hg</td>
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<td>P1 height, mm Hg</td>
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<td>PP amplification</td>
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<td>MAP, mm Hg</td>
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<td>HR, bpm</td>
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<td>AP, mm Hg</td>
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<td>AIX, %</td>
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<td>Aortic PWV, m/s</td>
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</table>

| Data are mean±SEM. P1 height indicates nonaugmented central PP; HR, heart rate; AP, augmentation pressure; PWV, pulse wave velocity. Values in the final column represent results of 2-way ANOVA for time (placebo vs 10 weeks) and drug. Posthoc comparisons between before and after drug therapy were made within each drug class, and significant results are represented by *P*<0.05.

In addition, posthoc comparisons between each drug class are represented in the final column by †P<0.05 atenolol vs perindopril, ‡P<0.05 atenolol vs bendroflazide, §P<0.05 atenolol vs lercanidipine, and ¶P<0.05 atenolol vs bendroflazide.

**Discussion**

Although previous studies have investigated the use of different drug classes in patients with ISH,4,8,12,13 this is the first study to measure the effects of the 4 drug classes on both peripheral and central BPs, PP amplification, and aPWV simultaneously in ISH. Our major findings were that, although all 4 of the drugs reduced peripheral systolic pressure to a similar extent, atenolol was significantly less effective in reducing central pressure compared with the other drugs. Consequently, atenolol actually lowered PP amplification, whereas this did not change with the other agents. In addition, our data suggest that aPWV, the current gold standard measure of aortic stiffness, is not improved by traditional antihypertensive therapy in patients with ISH.

Different antihypertensive drug classes reduce BP by a variety of mechanisms. Despite this, in the current study, peripheral PP was reduced to a similar extent by all 4 of the drugs. However, central PP was only reduced significantly by perindopril, lercanidipine, and bendroflazide, whereas atenolol had no effect on central PP. Consequently, atenolol reduced PP amplification, meaning that the influence of the β-blocker on central pressure was greatly attenuated compared with its effects on peripheral pressure. These data confirm the findings of previous studies showing an adverse effect of β-blockers on central pressure.5–8,14 However, after adjusting for heart rate, the reduction in PP amplification with atenolol was no longer significant. Nevertheless, the current data further emphasize the importance of considering the effect of drugs on central pressure, as well as brachial pressure, rather than simply relying on brachial pressure alone. However, large-scale outcome studies are necessary to investigate whether targeting treatment toward central pressure results in better outcomes.

The magnitude of PP amplification is determined largely by differences in vessel stiffness and wave reflections. Therefore, any factor that influences wave reflections is likely to change central pressure independent of brachial pressure. AIX is a measure of wave reflections, which correlates with risk15 and predicts outcome. The only drug that significantly reduced AIX was lercanidipine. In contrast, atenolol increased AIX, although this effect was not significant after correcting for the reduction in the heart rate associated with this drug. Interestingly, there were no differences between drugs when nonaugmented PP or nonaugmented PP amplification was considered. This confirms previous data demonstrating the marked influence of wave reflections on PP amplifica-

(P=0.1). There was also no influence of therapy on nonaugmented PP amplification (P=0.9 both for time and drug comparisons; data not shown).

Lercanidipine had no significant effect on MAP, in contrast to the other 3 drugs. In contrast, heart rate decreased significantly with atenolol compared with the other drugs. Augmentation pressure was significantly reduced by perindopril and lercanidipine. In addition, the augmentation index (AIX) was significantly reduced with lercanidipine but significantly increased with atenolol. To compensate for any effects of changes in heart rate on AIX, the AIX data were also corrected for heart rate (using a correction factor of +3.9% for each 10-bpm negative change in heart rate from a standard 75 bpm).13 There was a reduction in corrected AIX with lercanidipine, which was of borderline significance (P=0.05), but no significant change with any of the other drugs (data not shown). aPWV did not change significantly with any of the 4 treatments over the 10-week period. Finally, multivariate regression analyses showed that the response of brachial PP to therapy was inversely and independently associated with age (P=0.026), baseline PP (P=0.002), and baseline pulse wave velocity (P=0.025) but not sex or class of drug (R² for model=0.3; P=0.007).
Nevertheless, the increase in wave reflections with atenolol may, at least in part, explain why atenolol has repeatedly been found to be inferior to other antihypertensive drugs in studies including older hypertensive patients.2,3

Despite the reduction in SBP observed with all 4 of the drugs, there was no influence of therapy on aPWV. These data conflict with earlier findings from the Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study,4 where perindopril- and atenolol-based therapies caused a significant, although similar, fall in aPWV. One potential explanation for the current finding is that the central arteries of these patients with ISH are stiffer than usual (part of the mechanism of development of this condition). Therefore, these patients may be less responsive to functional changes induced by pharmacological therapy than individuals with more distensible arteries. Another possibility is that the study was underpowered to detect what were relatively small changes in aPWV. To further explore this aspect, we constructed a multiple regression analysis to determine those factors that were associated with the response to therapy. Interestingly, patients with a higher baseline aPWV showed a smaller reduction in brachial PP in response to therapy, even after accounting for age and baseline PP. This is in agreement with recent posthoc observations from the Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study, where baseline aortic stiffness predicted the BP response to antihypertensive treatment.5,18 Taken together, these data support the notion that patients with stiffer arteries might be less responsive to traditional antihypertensive drug therapy. Indeed, we have demonstrated recently that patients with ISH have increased aortic calcification compared with age-matched normotensive individuals,19 suggesting a need for novel “destiffening” therapies in patients with ISH.

The limitations of the current study include the fact that it may have been underpowered to detect small but clinically meaningful changes in pulse wave velocity, or the length of treatment time might have been too short to demonstrate changes in pulse wave velocity that might be seen when patients take antihypertensive therapy for many years. It is also possible that the drug doses were not high enough. However, the standard clinical doses used in this study caused a significant, although similar, fall in aPWV. One possible explanation for the current finding is that the central arteries of these patients with ISH are stiffer than usual (part of the mechanism of development of this condition). Therefore, these patients may be less responsive to functional changes induced by pharmacological therapy than individuals with more distensible arteries. Another possibility is that the study was underpowered to detect what were relatively small changes in aPWV. To further explore this aspect, we constructed a multiple regression analysis to determine those factors that were associated with the response to therapy. Interestingly, patients with a higher baseline aPWV showed a smaller reduction in brachial PP in response to therapy, even after accounting for age and baseline PP. This is in agreement with recent posthoc observations from the Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind Study, where baseline aortic stiffness predicted the BP response to antihypertensive treatment.5,18 Taken together, these data support the notion that patients with stiffer arteries might be less responsive to traditional antihypertensive drug therapy. Indeed, we have demonstrated recently that patients with ISH have increased aortic calcification compared with age-matched normotensive individuals,19 suggesting a need for novel “destiffening” therapies in patients with ISH.

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**Perspectives**

The 4 main classes of antihypertensive therapy were all effective in terms of lowering peripheral systolic pressure and PP in patients with ISH. Despite this, atenolol did not lower central PP and had an adverse effect on PP amplification and wave reflection in comparison with the other drugs. These findings further emphasize the need to consider the effects of antihypertensive therapies on central and brachial pressures, which may increasingly influence the choice of drug therapy in these patients. Moreover, the lack of efficacy of traditional antihypertensive therapies on aPWV, an important and independent determinant of cardiovascular outcome, highlights an urgent need for novel strategies to reduce arterial stiffness in patients with ISH.

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**Disclosures**

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