

# Effect of Amlodipine, Quinapril, and Losartan on Pulse Wave Velocity and Plasma Collagen Markers in Patients With Mild-to-Moderate Arterial Hypertension

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**Background:** Carotid–femoral pulse wave velocity (PWV) is a prognostic factor in arterial hypertension. Modification of PWV, apart from blood pressure (BP) lowering seems to be important in the evaluation of anti-hypertensive drugs. One of the underlying causes arterial stiffening is arterial wall fibrosis. Plasma collagen I metabolites: carboxy (PICP) and amino (PINP) propeptides are considered as a valuable approach in the assessment of arterial fibrosis. The purpose of the present study was to compare changes in BP, PWV, plasma aldosterone, and collagen metabolites after treatment with amlodipine, quinapril, and losartan.

**Methods:** One hundred eighteen patients with mild-to-moderate essential arterial hypertension were randomized to treatment with 10 mg/d of amlodipine (group 1), 20 mg/d of quinapril (group 2), or 2 × 50 mg/d of losartan (group 3). At baseline, and after 3 and 6 months analysis of variance was performed to compare changes in BP, PWV, aldosterone, PICP, and PINP among subjects with

adequate BP control on monotherapy (group 1,  $n = 38$ , group 2,  $n = 37$ , group 3,  $n = 24$ ).

**Results:** Blood pressure decreased equally in all groups. Among patients with comparable BP values on monotherapy, only quinapril-treated patients showed a significant decrease in PWV, aldosterone, and PICP as compared with baseline values. Multiple regression analysis showed that PWV was significantly affected by: age ( $\beta = 0.36$ ;  $P = .021$ ), systolic BP ( $\beta = 0.45$ ;  $P = .014$ ), and PICP ( $\beta = 0.27$ ;  $P = .038$ ).

**Conclusions:** In hypertensive subjects PWV depends on age, systolic BP, and collagen synthesis. Of the three drugs with comparable BP-lowering efficacy only quinapril significantly decreases PWV, plasma aldosterone, and PICP. *Am J Hypertens* 2003;16:439–444 © 2003 American Journal of Hypertension, Ltd.

**Key Words:** Pulse wave velocity, arterial compliance, collagen metabolites, amlodipine, quinapril, losartan.

The World Health Organization–International Society of Hypertension (WHO/ISH) guidelines on management and treatment of hypertension<sup>1</sup> and recent trends antihypertensive therapy aim not only at lowering blood pressure (BP) but also at the improvement of a number of factors determining long-term prognosis. Compliance of muscular and elastic arteries is one of these factors. It has been recently shown that compliance of aorta and elastic arteries is a strong independent prognostic factor<sup>2–4</sup> determining pulse pressure, left ventricular preload and mass, and subendocardial perfusion.<sup>5,6</sup> Modification of arterial compliance by pharmacotherapy is associated with the class of antihypertensive drugs.<sup>7</sup> Some of the drugs affect compliance through systemic BP lowering, others act by different

mechanisms. Compliance of central (elastic) arteries seems to depend especially on the metabolism of connective tissue proteins, elastin, and collagen.<sup>8,9</sup> Some antihypertensive drugs probably act on arterial stiffness, influencing collagen metabolism especially angiotensin converting enzyme (ACE) inhibitors and angiotensin II (AT<sub>1</sub>) receptor antagonists.

Pulse wave velocity (PWV) is an accepted noninvasive technique to evaluate arterial compliance.<sup>3,4,7,10</sup> Noninvasive identification of changes in the connective tissue is not clearly defined in contrast to histopathologic techniques. The measurement of serum collagen metabolites seems to be a promising approach.<sup>11</sup> It is a nonspecific technique, but is significantly correlated with histologic markers of myocardial fibrosis.<sup>12</sup>

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## Methods

The study population consisted of 118 patients with mild-to-moderate arterial hypertension according to the WHO/ISH guidelines of 1999.<sup>1</sup> All patients gave their informed consent to participate in a study approved by the Local Ethics Committee. Of them 95 patients had never been given an antihypertensive drug, whereas 23 had been receiving one BP-lowering drug other than a calcium antagonist, ACE inhibitor, or AT<sub>1</sub> receptor antagonist. This drug was withdrawn for 2 weeks before study entry.

The patients were randomized to treatment in the following way: a) subjects received an ACE inhibitor, quinapril, in a dose of 20 mg daily once a day; b) subjects received a third generation calcium antagonist, amlodipine, in a dose of 10 mg daily once a day; c) subjects received an AT<sub>1</sub> receptor antagonist, losartan, in a dose of 50 mg twice a day (100 mg/daily); and d) in the case of ineffective BP control (BP >140/90 mm Hg) at 3-month follow-up a second drug was added (in patients “a”—10 mg/day of amlodipine, in patients “b”—20 mg/day of quinapril, and in patients “c”—20 mg/day of quinapril).

The present report only includes those patients in whom adequate BP control was achieved on monotherapy. These patients were accordingly designated as: group 1, 38 patients (quinapril); group 2, 37 patients (amlodipine); and group 3, 24 patients (losartan).

The treatment was open label for all patients. The staff measuring BP, performing all other examinations, and entering the data was not informed about the type of therapy used in the patients.

In all subjects the following measurements were obtained: anthropometric indices, BP (averaged from three sphygmomanometric measurements in standard conditions), ambulatory BP monitoring (ABPM) data using SpaceLabs 90207 (SpaceLabs, Medical Inc., Redmond, WA), plasma lipids and basic biochemical tests including glycemia, creatinine, urea and uric acid, plasma aldosterone, plasma collagen markers (ie, carboxy- (PICP) and amino-terminal (PINP) peptides using RIA kits; Orion Diagnostica, Espoo, Finland).

Carotid-femoral PWV was evaluated as described by Asmar et al<sup>13</sup> using an automatic device Complior (Colson AS, Paris, France). Echocardiograms were obtained using Sonos 5500 (Hewlett-Packard Co., Andover, MA) and 2.5-mHz transducer. The left ventricular mass was calculated according to Devereux and Reichek with Penn convention ( $LVM = 1.04[(IVS + EDD + PW)^3 - EDD^3] - 13.6$ ).<sup>14</sup> The left ventricular mass index (LVMI) was obtained from formula LVM/body surface area (in meters squared).

The measurements of BP, PWV, LVMI, aldosterone, PICP, and PINP were analyzed at baseline and then at 3 and 6 months after antihypertensive therapy.

## Statistical Analysis

All statistical tests were performed using Statistica 5.1 (StatSoft Inc., Tulsa, OK). All variables were presented as descriptive statistics. Analysis of differences in time was performed by means of multiple analysis of variance (ANOVA) with repeated measurements. In the presence of significant effects post-hoc analysis (Scheffe test) was carried out. The variables in the present study met the criteria of this analysis (normal distribution, homogenous variance, sphericity). *P* value < .05 was regarded as statistically significant.

## Results

At baseline the study groups did not differ significantly in age (mean age was  $53.7 \pm 9.06$  years), male-to-female proportion (64 women and 54 men), body mass index (mean BMI  $28.3 \pm 4.5$  kg/m<sup>2</sup>), and waist-to-hip ratio ( $0.94 \pm 0.04$ ).

Baseline plasma creatinine ( $83 \pm 17.8$  μmol/L, uric acid ( $315 \pm 78.7$  μmol/L, glucose ( $5.3 \pm 1.34$  mmol/L), total cholesterol ( $5.76 \pm 1.2$  mmol/l), and LDL ( $3.66 \pm 1.10$  mmol/L) were comparable between the study groups.

### Effects of Antihypertensive Therapy: Conventional BP Values

Detailed results for systolic BP and diastolic BP in all groups (treated with quinapril, amlodipine, or losartan in monotherapy) are shown in Table 1. For all groups a significant decrease in systolic BP and diastolic BP was observed in repeated measurements. There was no significant interaction between various antihypertensive therapies in systolic BP or diastolic decrease (Table 2). Post-hoc analysis did not show significant differences in the magnitude of BP decrease between the study groups.

### Effects of Antihypertensive Therapy: 24-Hour ABPM

The main effect for systolic BP and diastolic BP in the entire 24 h was their decrease (Tables 1 and 2). There was no significant relationship between 24-h systolic BP and 24-h diastolic BP and various antihypertensive therapies (Table 2). Planned comparisons and post-hoc analyses did not show any significant differences in 24-h systolic BP and 24-h diastolic BP decrease between various antihypertensive therapies, with these variables being significantly lower for all study groups.

Systolic BP at night decreased after treatment (Table 2) and was significantly related to antihypertensive therapy (Fig. 1A shows intergroup differences). Systolic BP at night was lower at 3 months as compared with baseline only in group 1 patients ( $120.95 \pm 11.3$  mm Hg v  $108.52 \pm$  mm Hg, *P* < .0001). The patients treated with amlodipine (group 2) and losartan (group 3) had a significant decrease in systolic BP at night only at 6 months as compared with baseline (for amlodipine  $115.70 \pm$

**Table 1.** Blood pressure values in standard measurements and from 24-h ABPM for groups 1 to 3

Measurements	Group 1	Group 2	Group 3
At baseline			
Standard			
SBP	154 ± 22.5	149 ± 15.2	155 ± 18.6
DBP	97 ± 14.1	94 ± 8.7	91 ± 13.5
Mean of 24-h ABPM			
SBP	129 ± 14.9	126 ± 13.7	125 ± 9.4
DBP	81 ± 12.2	78 ± 9.9	84 ± 10.1
After 3 months			
Standard			
SBP	141 ± 23.7	134 ± 14.8	132 ± 15.8
DBP	92 ± 8.7	87 ± 7.9	83 ± 9.2
Mean of 24-h ABPM			
SBP	121 ± 10.6	118 ± 9.7	114 ± 7.9
DBP	75 ± 8.8	73 ± 8.9	76 ± 9.1
After 6 months			
Standard			
SBP	113 ± 14.6	122 ± 18.6	125 ± 16.8
DBP	86 ± 7.1	85 ± 8.7	84 ± 8.1
Mean of 24-h ABPM			
SBP	121 ± 13.0	117 ± 11.1	115 ± 7.2
DBP	72 ± 7.7	71 ± 8.0	72 ± 4.9

ABPM = ambulatory blood pressure monitoring; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Group 1: quinapril (20 mg/d); group 2: amlodipine (10 mg/d); group 3: losartan (2 × 50 mg/d).

14.4 mm Hg v 106.83 ± 13.3 mm Hg,  $P < .05$ ; and for losartan 119.23 ± 12.8 mm Hg v 107.53 ± 11.1 mm Hg,  $P < .001$ ).

### Changes in Arterial Compliance Evaluated By PWV

No significant differences in PWV between groups were observed at baseline.

During the study duration decrease of PWV was observed in the whole study population. There was also a significant interaction between changes in PWV and antihypertensive therapy (Table 2 and Fig. 1B). Planned comparison showed a significant linear decrease in PWV in group 1 patients (receiving quinapril) ( $F = 30.666$ ,  $P < .0001$ ).

Post-hoc analysis using Scheffe test revealed a significant PWV decrease only in patients receiving quinapril. After 6 months of therapy the mean value of PWV in this group (9.55 ± 1.32 m/sec) was significantly lower than at baseline (11.23 ± 1.67 m/sec,  $P < .0001$ ) and after the first 3 months (10.79 ± 1.43 m/sec,  $P < .001$ ). The PWV in the quinapril-treated group at the end of the study (6 months) was significantly lower than in the amlodipine group (9.55 ± 1.32 m/sec v 10.53 ± 1.05 m/sec,  $P < .001$ ) and losartan group (9.55 ± 1.32 m/sec v 10.54 ± 1.67 m/sec,  $P < .05$ ).

### Echocardiography

Left ventricular systolic function was normal in all patients entering the study. Mean left ventricular ejection

fraction (EF) according to Teichholz formula was 69.4% ± 6.3%.

There were no significant differences in EF among all groups at all study follow-up points. Mean LVMI at baseline was comparable in all groups (116.9 ± 23.9 g/m<sup>2</sup>). The LVMI did not change after antihypertensive therapy at 3 and 6 months.

### Aldosterone

Analysis of changes in aldosterone concentration revealed its decrease (Table 2). There was a significant relationship between changes in aldosterone concentration and antihypertensive therapy (Fig. 1C). Post-hoc analysis revealed a significant decrease in aldosterone concentration only in patients receiving quinapril after 6 months of treatment (230.5 ± 45.6 pg/mL v 124.8 ± 47.8 pg/mL,  $P < .05$ ).

### Collagen Metabolism Markers

The PINP at baseline did not differ significantly among the study groups and it was not significantly affected by antihypertensive therapy. However, PICP decreased significantly at the consecutive study time points (Table 2) and showed interaction with the type of antihypertensive therapy (Fig. 1D). This interaction resulted from the significant decrease in PICP concentration only in patients on quinapril (from 203.13 ± 43.4 μg/L at baseline to 140.02 ± 38.2 μg/L at 3 months,  $P < .05$  and to 130.2 ± 32.1 μg/L,  $P < .001$  at 6 months of therapy). This effect was not observed in the remaining study groups.

**Table 2.** Main results for study groups 1 to 3 (variable, GR) and selected dependent variables

Variable By ANOVA Analysis	F	P
SBP in conventional measurements		
GR	3.3870	<.0378
SBP	67.260	<.000000
SBP/GR interaction	1.21029	NS
DBP in conventional measurements		
GR	6.24241	<.00281
DBP	22.5974	<.000000
DBP/GR interaction	1.15519	NS
SBP mean from 24-h ABPM		
GR	2.66502	NS
24-SBP	48.2299	<.000000
24-SBP/GR interaction	0.54057	NS
DBP mean from 24-h ABPM		
GR	1.36219	NS
24-DBP	48.2299	<.000000
24-DBP/GR interaction	2.08719	NS
SBP in nighttime		
GR	0.48512	NS
SBPN	76.3199	<.000000
SBPN/GR-interaction	4.0109	<.003780
Carotid femoral pulse wave velocity		
GR	0.82986	NS
PWV	21.21935	<.000000
PWV/GR interaction	6.78938	<.000000
Serum aldosterone		
GR	0.836421	NS
ALD	9.356464	<.000132
ALD/GR-interaction	2.808882	<.026811
Carboxy-terminal propeptide		
GR	1.39184	NS
PICP	10.80576	<.000036
PICP/GR interaction	2.56415	<.03662

GR = variable group (representing treatment groups 1 to 3); NS = not significant; 24-SBP = SBP mean from 24-h ABPM; 24-DBP = DBP mean from 24-h ABPM; SBPN = SBP in nighttime; PWV = pulse wave velocity; ALD = aldosterone; PICP = carboxy-terminal propeptide; other abbreviations as in Table 1.

## Determinants of Arterial Compliance

A multiple regression model was constructed to analyze the effect of study variables on PWV at 6 months after the onset of antihypertensive treatment. In the presence of multiple regression ratio  $R = 0.621$ , determination ratio  $R^2 = 0.383$ , and standard estimation error = 1.70 PWV was significantly related to age ( $B = 0.449$ ,  $P = .014$ ), mean 24-h systolic BP ( $B = 0.364$ ,  $P = .021$ ) and PICP concentration ( $B = 0.270$ ,  $P = .038$ ). The model of multiple regression in the present study accounts for a PWV variation in 38%.

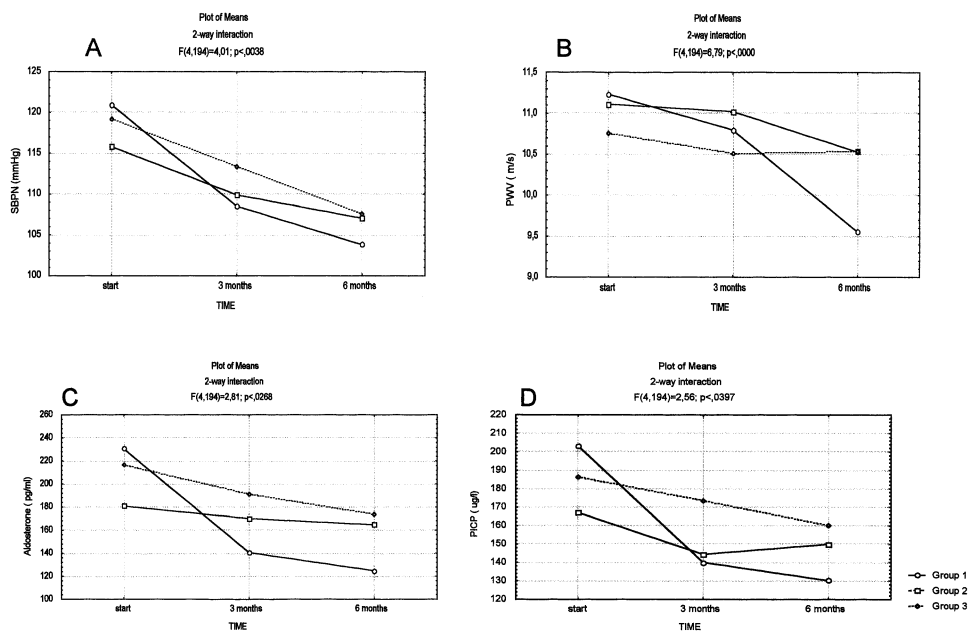
## Conclusions

Elastic arterial compliance measured from the carotid-femoral PWV is a function of age and systolic BP. Decreased collagen synthesis is related to decreased carotid-femoral PWV. Of the three drugs with comparable BP-lowering efficacy only quinapril significantly decreases PWV, as well as aldosterone and PICP plasma concentration.

## Discussion

Improved arterial compliance has been found as a result of various antihypertensive therapies. Asmar<sup>7</sup> provided ample evidence to support this finding. The ACE inhibitors seem to be more effective than other classes of antihypertensive drugs in reducing arterial stiffness. However, recent studies demonstrate a significantly improved compliance not only of muscular but also of elastic arteries after treatment with dihydropyridine calcium antagonists.<sup>15–17</sup> In the present study amlodipine was chosen for its positive influence on muscular arterial compliance,<sup>18</sup> effect on myocardial collagen metabolism demonstrated in an experimental study on animals,<sup>19</sup> and the collagen content in the vascular wall.<sup>20</sup>

The findings in the present study do not confirm the significant effect of losartan on arterial compliance previously reported by Klemsdal et al.<sup>21</sup> The choice of losartan was dictated by the fact that AT<sub>1</sub> blockade by losartan affects the aldosterone level,<sup>22</sup> collagen metabolism,<sup>23</sup> including myocardial collagen<sup>24</sup> and left ventricular dia-



**FIG. 1.** Interaction of various therapies: group 1, quinapril (20 mg/d); group 2, amlodipine (10 mg/d); group 3, losartan (2 × 50 mg/d) and selected variables. **A)** Interaction between therapy and systolic blood pressure in the nighttime (SBPN). **B)** Interaction between therapy and carotid femoral pulse wave velocity (PWV). **C)** Interaction between therapy and serum aldosterone. **D)** Interaction between therapy and carboxy-terminal propeptide of procollagen type I (PICP).

stolic function, as shown in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study.<sup>25</sup> In our study there was no significant effect of losartan on aldosterone concentration as well as on PINP and PICP. At 6-month follow-up losartan did not affect left ventricular mass, similar to other drugs. In the light of available studies this period seems to be too short to determine any effect on LVMI.<sup>26,27</sup>

The most important findings in the present study are the effects observed for quinapril. Patients receiving quinapril achieved the antihypertensive effect comparable to that of amlodipine and losartan (only the results of systolic BP in 24-h ABPM were slightly better). However, arterial compliance measured from carotid–femoral PWV improved only after quinapril therapy. Quinapril also significantly modified the level of collagen markers (PICP) and multiple regression analysis in our study revealed a clear negative relationship between PICP (collagen synthesis) and PWV (arterial compliance).

The PICP is now considered an important and valuable marker of fibrosis in hypertensive heart disease, correlating with histomorphometric indices.<sup>28</sup> Increased collagen content in skin resistance vessels has been reported as an indicator of hypertensive heart disease.<sup>29</sup> It is difficult to make such a comparison, but the clinical effect for quinapril in our study confirms the observations of Benetos et al<sup>30</sup> in an animal model. They demonstrated a significantly more reduced collagen deposition in the aortic wall of rats receiving quinapril as compared with AT<sub>1</sub> receptor antagonist.

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