Original Article

Smoking and Antihypertensive Medication: Interaction between Blood Pressure Reduction and Arterial Stiffness

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To investigate how cigarette smoking and antihypertensive drug therapy may interact to affect cardiovascular disease, in this prospective study we administered amlodipine to hypertensive smokers and non-smokers and compared blood pressure reduction and indices of arterial stiffness. We measured blood pressure (BP), heart rate (HR), brachial-ankle pulse wave velocity (baPWV), and the carotid augmentation index (AIx) by using a non-invasive automated device in 101 hypertensive patients at baseline and at 1, 3, and 6 months of amlodipine administration (5.0 mg). At baseline, the AIx was significantly lower in smokers ($n=27$) than in non-smokers ($n=74$) ($27.3\% \pm 13.3\%$ vs. $33.3\% \pm 11.4\%$). After amlodipine administration, in both the groups, the mean BP, baPWV, and AIx were significantly reduced; however, the HR did not show a statistically significant difference. The reduction in the baPWV (cm/s) at 1 and 3 months was less marked in smokers than in non-smokers (mean $\pm$ SD: -186.6 ± 36.5 vs. -283.6 ± 24.5 at 1 month; -136.6 ± 42.2 vs. -280.1 ± 29.6 at 3 months, respectively, both $p < 0.05$). At 6 months, these intergroup differences in the reductions of baPWV disappeared. The blunted reduction of baPWV, particularly at 3 months, was significantly associated with the extent of smoking (lifetime pack-years smoked). Changes observed in the AIx and mean BP were similar between groups throughout the study period. In the short term, cigarette smoking blunts the effect of amlodipine on the reduction of arterial stiffness, independently of the mean BP level. (*Hypertens Res* 2005; 28: 631–638)

Key Words: smoking, hypertension, arterial stiffness, amlodipine

Introduction

Cigarette smoking and hypertension have been established as independent risk factors for cardiovascular disease and atherosclerosis (1–6). Furthermore, cigarette smoking is known to increase the risk of cardiovascular disease in patients with hypertension (6). Possible mechanisms for this interaction are based on studies showing that long-term cigarette smoking and chronic hypertension are independently and synergistically associated with increased arterial stiffness (7–12). Arte-

rial stiffness affects the transmission velocity of the ventricular pulse wave and the circumferential pressure load of the arterial wall, and might play an important role in the onset of cardiovascular disease. However, exactly how cigarette smoking and antihypertensive drug therapy may interact to affect arterial stiffness remains unknown.

Recent studies have shown that pulse wave velocity (PWV) and the augmentation index (AIx), both measures of arterial stiffness, are important and independent markers of cardiovascular risk (13–15). Moreover, it has been reported that the PWV is a strong predictor of prognosis in patients with hyper-

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Table 1. Baseline Characteristics of Study Patients

Variable	Smokers (<i>n</i> =27)	Non-smokers (<i>n</i> =74)	<i>P</i>
Age (years)	66.9±9.2	69.3±8.0	NS
Male sex (%)	81.5	18.9	<0.0001
Body height (cm)	159.3±8.1	152.1±7.7	<0.1
Body mass index (kg/m ²)	24.3±3.0	24.1±3.5	NS
Hypertension duration (years)	8.4±7.4	7.6±6.8	NS
Antihypertensive medication (%)	40.7	54.1	NS
ACE inhibitor	14.8	17.6	NS
AT1 receptor blocker	25.9	32.4	NS
Calcium channel blocker	11.1	8.1	NS
Diuretics	14.8	16.2	NS
α/β blocker	18.5	13.5	NS
Hyperlipidemia (%)	40.7	45.9	NS
Diabetes mellitus (%)	18.5	17.6	NS
Cerebrovascular disease (%)	14.8	9.5	NS
Coronary heart disease (%)	3.7	5.4	NS
Total cholesterol (mg/dl)	207.2±30.0	212.6±30.2	NS
HDL-cholesterol (mg/dl)	54.9±19.5	58.2±14.9	NS
Triglyceride (mg/dl)	156.4±104.2	122.4±52.4	<0.05
Fasting plasma glucose (mg/dl)	98.6±14.2	96.5±12.2	NS
Serum creatinine (mg/dl)	0.78±0.21	0.73±0.16	NS
CIMT (mm)	0.83±0.21	0.82±0.19	NS

Values are expressed as means±SD or the percentages. NS, not significant; ACE, angiotensin converting enzyme; AT1, angiotensin type 1; HDL, high density lipoprotein; CIMT, carotid intima-media thickness.

tension (16). Clinical trials have shown that amlodipine is of benefit in the prevention and treatment of cardiovascular disease and atherosclerosis (17, 18), suggesting that amlodipine might provide vasculoprotection independent of its blood pressure-lowering effect.

The present study investigated the effects of amlodipine on both PWV and the AIx as indices of arterial stiffness in patients with hypertension who smoke cigarettes and in similar patients who do not smoke. We used the brachial-ankle PWV (baPWV) as a newly developed measurement of PWV in this study. Although the carotid-femoral PWV (cfPWV) is established as a global standard measurement of PWV, it has recently been shown that the baPWV has better reproducibility and can be substituted for the cfPWV (19–21).

Methods

Study Population

One hundred and eight consecutively recruited outpatients with essential hypertension were enrolled in this study. Hypertension was defined as a clinic systolic blood pressure (SBP)≥140 mmHg and/or diastolic blood pressure (DBP)≥90 mmHg on at least two visits at 2-week intervals, or the use of antihypertensive medication. We also selected hypertensive patients in whom the dosage of antihypertensive

medication remained unchanged during the 6 months before the subject's enrolment in the study. In this study, we defined smokers as current smokers who had smoked at least 20 cigarettes per day for at least 1 year, while non-smokers were defined as individuals who had never smoked. Pack-years of cigarette smoking were calculated as average packs per day times the number of years smoked by smokers. Smokers did not quit or reduce cigarette smoking during the study period. In this study, past smokers were excluded, because past smokers differ from current smokers and from non-smokers with respect to the effects of smoking on arterial properties and atherosclerosis (3). The following exclusion criteria were applied: secondary hypertension, hypertension complicated by a recent cardiovascular event (within 6 months), and/or atrial fibrillation. The study was approved by the Research Ethics Committee of Miwa Municipal Hospital, and informed consent was obtained from all patients.

During the run-in period, we excluded 4 patients with an ankle-brachial blood pressure index (ABI) of less than 0.9, because baPWV could be intrinsically distorted in the presence of peripheral arterial disease. Three patients did not complete the protocol as a result of side effects; one patient had general fatigue, one patient experienced dizziness, and one patient presented with leg edema. Of the initially enrolled patients, 101 patients completed the protocol. The results obtained from a total of 101 patients (mean age: 68.6 years;

Table 2. Hemodynamic Baseline Parameters of Study Patients at Pulse Wave Analysis

Variable	Smokers (n=27)	Non-smokers (n=74)	<i>p</i>
Systolic BP (mmHg)	157.5±19.1	156.5±19.0	NS
Diastolic BP (mmHg)	89.3±12.2	85.5±11.7	NS
Mean BP (mmHg)	112.0±13.3	109.2±12.8	NS
Pulse pressure (mmHg)	68.2±13.9	71.0±14.5	NS
Heart rate (bpm)	65.3±10.2	66.1±9.3	NS
baPWV (cm/s)	2,176.7±504.0	2,144.9±418.2	NS
AIx (%)	27.3±13.3	33.3±11.4	<0.05

Values are expressed as means±SD. NS, not significant; BP, blood pressure; baPWV, brachial-ankle pulse wave velocity; AIx, augmentation index.

27 smokers and 74 non-smokers) were analyzed in this study.

Hyperlipidemia was defined as follows: total cholesterol (TC)≥220 mg/dl, triglyceride (TG)≥150 mg/dl, or the use of antihyperlipidemic medication. Diabetes mellitus was defined as a fasting blood glucose of ≥126 mg/dl or the current use of antidiabetic medication. The body mass index (BMI) was calculated as weight (kg)/height² (m²).

Study Protocol

Each patient completed a 1-month run-in period to establish baseline values before the onset of 6 months of amlodipine administration. No antihypertensive medications were allowed during this run-in period. After the run-in period, the administration of amlodipine was initiated with a 2.5-mg dose, which the subject took once daily in the morning. The dose was subsequently increased by 2.5 mg at 2-week intervals to a maximal dose of 5.0 mg, unless adverse events occurred. The measurement of blood pressure (BP), heart rate (HR), baPWV, and AIx were analyzed at the run-in period, and before, 1 month (M1), 3 months (M3), and 6 months (M6) after the onset of active drug administration. Drug doses were not altered during this study period. Before the initiation of amlodipine administration, a detailed history of risk factors and medical conditions was obtained by the attendant doctor. After the subjects had undergone an overnight fast, blood samples were obtained for the analysis of the biochemical parameters.

Pulse Wave Analysis

Patients were examined in a quiet and temperature-controlled laboratory (23°C) after 5 min of lying supine at 9:00–11:00 AM. Smokers were asked to refrain from smoking for the 12-h period prior to the study. The baPWV was measured by using the volume-plethysmographic method with previously validated equipment (19–23) (form PWV/ABI; Colin Medical Technology, Komaki, Japan). A detailed description of this device has been reported previously (19, 20, 22). Cuffs were connected to both the plethysmographic and oscillomet-

ric sensors and were wrapped around both arms and both ankles while the patient was in the supine position. The phonocardiograph was placed on the right second parasternal border in order to detect the heart sounds, and the ECG was taken by using lead I. Transit time (ΔT_{ba}) between the brachial and ankle pulse waves was automatically measured based on the time delay between the feet (sharp initial systolic upstroke of the wave) at the arm and ankle. The distance between the 2 recording sites was calculated automatically based on the height of the patient (H) and anthropomorphic data for the Japanese population. The path length from the suprasternal notch to the brachium (L_b) and ankle (L_a) was calculated by using the following equation: $L_b = 0.2195 \times H$ (cm) – 2.0734, $L_a = 0.8129 \times H$ (cm) + 12.328. The baPWV was then calculated by using the following equation: $baPWV = (L_a - L_b) / \Delta T_{ba}$. We used the right baPWV value in this study because there was a strong and positive correlation ($r=0.91$, $p<0.0001$) between the left and right baPWV. The brachial and ankle BP can be simultaneously obtained according to this oscillometric method. We applied this brachial BP as the follow-up BP in this study. The pulse pressure (PP) was calculated as follows: SBP – DBP. The mean BP (MBP), a major determinant of arterial distending pressure, was calculated as follows: $MBP = DBP + [(SBP - DBP)/3]$.

The measurement of the carotid AIx was performed by using a multi-element applanation tonometry sensor for the left common carotid artery (21, 24). A multi-element tonometry sensor, which consists of 15 pressure-sensitive small elements aligned side-by-side, is coupled to this device. The carotid tonometry sensor is compact and lightweight and can be easily attached around the neck. The sensor element manually located at the center of the carotid artery can be identified by screening the pulse pressure levels of the 15 elements. The reliability of this tonometry sensor has been reported previously (21, 24). All measurements were carried out by the same trained investigator. We have recently demonstrated the good intraobserver-intersession reproducibility of both the baPWV and AIx, and confirmed that these indices, when obtained using this device, are suitable for longitudinal clinical studies (21).

Fig. 1. Changes in mean blood pressure (Δ MBP) (A), brachial-ankle pulse wave velocity (Δ baPWV) (B), and AIx (Δ AIx) (C) during amlodipine administration. Values are mean $\pm$ SEM. * $p < 0.01$ vs. 0 month. † $p < 0.05$ for hypertensive smokers vs. non-smokers.

Carotid Ultrasonography

Carotid intima-media thickness (CIMT) is generally regarded as an early marker of systemic atherosclerosis (3, 5, 17). Here, CIMT was assessed by high-resolution B-mode ultrasonography of the right and left common carotid arteries. An ultrasound instrument with a 7.5-MHz transducer (model EUB 6500, Hitachi, Tokyo, Japan) was used in this study. CIMT was measured at 3 points proximal to the bilateral carotid bulb (far wall) in 10-mm segments at end diastole (peak of the R wave of the ECG), and these three points were always located in plaque-free segments. The mean of the right and left CIMT measurements (total: 6 points) was used in the

analysis. In our laboratory, the mean intraobserver and interobserver coefficients of variation for average CIMT were 3.9% and 4.5%, respectively.

Statistical Analysis

The baseline data are expressed as mean $\pm$ SD values for continuous variables and as percentages for categorical variables. The two-sided Student's unpaired *t*-test was used for continuous variables and χ^2 analysis, and Fisher's exact test was used for categorical variables. Hemodynamic responses to amlodipine were compared between smokers and non-smokers, and the results were analyzed using repeated-measures analysis of variance (ANOVA). When significance was observed, between-group differences at each month were analyzed post hoc using multiple *t*-tests, and the significance levels were adjusted with the Bonferroni correction. The changes in the hemodynamic parameters were expressed as mean $\pm$ SEM. The relationship between pack-years smoked and reduction in the baPWV (Δ baPWV) was assessed using correlation analysis. Multiple regression analysis was performed in order to assess the effects of independent variables on the Δ baPWV at 3 and 6 months. Variables for the multiple regression models consisted of variables chosen based on simple correlation analyses, as well as on those variables known or thought to be associated with PWV. All analyses were carried out with SPSS/Windows, version 11.0J (SPSS Inc., Chicago, USA). *p* values < 0.05 were considered to indicate statistical significance.

Results

Patient Characteristics

The baseline characteristics of the smokers and non-smokers are shown in Table 1. The percentage of men was higher in the group that smoked than in the group that did not smoke. Smokers were taller, and had higher TG values than did non-smokers. Smokers had a history of 35.2 ± 19.0 pack-years. There were no significant differences between groups with respect to other parameters. CIMT, is an indicator of systemic atherosclerosis, has been shown to be increased in smokers (3, 12); however, in this study, no statistical significance between smokers and non-smokers was observed in terms of CIMT. Table 2 shows the baseline hemodynamic parameters upon pulse wave analysis. At baseline, MBP and baPWV did not significantly differ between smokers and non-smokers; however, the AIx was significantly lower in smokers than in non-smokers.

Hemodynamic Responses to Amlodipine Administration

After amlodipine treatment, the MBP, baPWV, and AIx of both smokers and non-smokers decreased significantly (Fig.

Table 3. Multiple Regression Analysis of Determinants of Δ baPWV (M3)

Variable	β	SEM	<i>t</i>	<i>p</i>
Age (years)	-0.09	2.95	-0.91	0.37
Male sex	0.06	68.00	0.48	0.63
Body mass index (kg/m ²)	0.09	6.97	0.95	0.34
Smoking status	0.28	56.64	2.69	0.01
Antihypertensive medication	0.20	47.86	2.03	0.07
Hypertension duration (years)	0.13	3.29	1.32	0.19
Serum creatinine (mg/dl)	0.01	161.91	0.08	0.93
Total cholesterol (mg/dl)	-0.06	0.82	-0.63	0.52
HDL-cholesterol (mg/dl)	0.10	1.58	1.04	0.30
Triglyceride (mg/dl)	0.09	0.36	0.84	0.40
Fasting plasma glucose (mg/dl)	-0.10	1.21	-1.07	0.29
CIMT (mm)	0.11	124.66	1.11	0.27
Δ MBP (mmHg)	0.45	2.27	5.03	<0.0001

Multiple regression analysis ($n=101$); Model $r^2=0.43$; $F=5.17$; Model $p<0.0001$. β , standardized regression coefficient; M3, 3 months; Δ baPWV, reduction of baPWV; sex: female=0/male=1; smoking status: absence=0/presence=1; antihypertensive medication: absence=0/presence=1; Δ MBP, reduction of mean blood pressure. Abbreviations as in Tables 1 and 2.

Table 4. Multiple Regression Analysis of Determinants of Δ baPWV (M6)

Variable	β	SEM	<i>t</i>	<i>p</i>
Age (years)	0.02	3.13	0.19	0.85
Male sex	-0.15	73.51	-1.08	0.28
Body mass index (kg/m ²)	0.06	7.25	0.61	0.54
Smoking status	0.17	62.12	1.58	0.13
Antihypertensive medication	0.05	50.95	0.47	0.64
Hypertension duration (years)	0.02	3.64	0.24	0.81
Serum creatinine (mg/dl)	0.22	171.12	1.81	0.08
Total cholesterol (mg/dl)	-0.02	0.90	-0.16	0.88
HDL-cholesterol (mg/dl)	0.02	1.67	0.21	0.83
Triglyceride (mg/dl)	0.04	0.39	0.37	0.72
Fasting plasma glucose (mg/dl)	-0.08	1.24	-0.92	0.36
CIMT (mm)	-0.02	131.40	-0.24	0.81
Δ MBP (mmHg)	0.54	2.09	5.77	<0.0001

Multiple regression analysis ($n=101$); Model $r^2=0.36$; $F=4.48$; Model $p<0.0001$. M6, 6 months. Abbreviations as in Tables 1–3.

1). The HR did not significantly change during the study period. No significant differences in terms of reductions in the MBP and the AIx from the baseline value was observed between smokers and non-smokers ($[\Delta$ MBP] M1: -10.9 ± 1.5 vs. -10.3 ± 1.2 mmHg, $p=0.96$; M3: -11.6 ± 2.0 vs. -11.5 ± 1.2 mmHg, $p=0.93$; M6: -12.2 ± 1.9 vs. -12.0 ± 1.3 mmHg, $p=0.78$) ($[\Delta$ AIx] M1: -5.1 ± 1.6 vs. $-4.0 \pm 0.9\%$, $p=0.60$; M3: -3.3 ± 1.4 vs. $-3.6 \pm 1.1\%$, $p=0.28$; M6: -4.4 ± 1.3 vs. $-3.8 \pm 1.3\%$, $p=0.55$) (Fig. 1A and C). Δ baPWV in smokers was significantly less pronounced than that in non-smokers (-186.6 ± 36.5 vs. -283.6 ± 24.5 cm/s, $p<0.05$) at M1 and (-136.6 ± 42.2 vs. -280.1 ± 29.6 cm/s, $p<0.05$) at M3; however, such significant differences between groups were not observed at M6 (-216.2 ± 45.6 vs. -268.4 ± 29.2 cm/s, $p=0.27$; Fig. 1B). In a multiple regres-

sion analysis at M3, both smoking status and Δ MBP were significant predictors of Δ baPWV (Table 3), whereas at M6, only Δ MBP was a significant predictor of Δ baPWV (Table 4).

As shown in Fig. 2, there was a positive correlation between Δ baPWV at M3 and pack-years smoked, suggesting a dose-dependent effect of smoking on the blunted reduction of baPWV. Even when men only ($n=22$) were taken into consideration, the same positive association was observed ($r=0.82$, $p<0.0001$).

Discussion

This study demonstrated that in hypertensive patients, long-term cigarette smoking modified the beneficial effects of

Fig. 2. Associations between changes in brachial-ankle pulse wave velocity (Δ baPWV) and pack-years smoked in smokers at 3 months of amlodipine administration.

amlodipine on baPWV. Furthermore, this blunting of the reduction of baPWV was proportional to lifetime pack-years smoked; in other words, the impact of smoking was cumulative. However, these differences between smoking and non-smoking subjects diminished at 6 months from the initiation of amlodipine administration and thereafter.

PWV is known to reflect functional as well as structural arterial wall stiffness. Levenson *et al.* showed that cigarette smoking and hypertension were independently associated with higher PWV and that this effect was cumulative (11). Liang *et al.* (12) found cigarette smoking and hypertension interacted in a manner that increased arterial stiffness. Smoking has been shown to increase sympathetic activation, which leads to the stiffening of muscular arteries (9). Wollersheim *et al.* (7) and McVeigh *et al.* (8) showed that long-term smokers exhibited an increase in stiffness in their peripheral muscular arteries, but not in their central elastic arteries, as compared with non-smokers. The baPWV reflects the stiffness not only of the elastic arteries, but also of the muscular arteries (23); therefore, cigarette smoking might have a relatively strong impact on baPWV.

Major determinants of arterial stiffness are structural components (collagen metabolism) of the arterial wall, MBP, and transmural distending pressure (25). In particular, stiffness of the peripheral muscular arteries is strongly influenced by the MBP (26). In this study, the changes of baPWV were strongly influenced by those of MBP. However, in the presence of structural changes in the muscular arteries, arterial stiffness is less dependent on the MBP (27). Thus, the blunted reductions in the baPWV seen in this study might have indicated a progression of peripheral artery stiffness in hypertensive smokers. This study also revealed that the impact of smoking on the stiffness of the muscular arteries might be amplified in

proportion to increased pack-years smoked, suggesting that the extent of cumulative smoking may render arterial stiffness gradually irreversible in hypertensive patients. In this regard, several studies (1–3, 6, 12) have shown a dose-dependent effect of smoking on cardiovascular risk.

Here, there were significant differences in the changes in the baPWV with respect to the corresponding changes in the MBP at both M1 and M3. This discrepancy between the extent of changes in the baPWV and MBP was also seen in a follow-up study of patients with end-stage renal failure treated with antihypertensive medication (14). In the investigation by Guerin *et al.* (14), the survival period was longest in those patients in whom medication successfully reduced both PWV and MBP, rather than just the MBP alone. Poor prognosis, which was associated in that study with the irreversibility of an unfavorable PWV, might have been caused by structural changes to the arteries. However, it should be noted that the clinical characteristics of the patients enrolled in the study by Guerin and co-workers (14) differed from those of the patients included in our study. In our study, the significant differences in baPWV between hypertensive smokers and hypertensive non-smokers disappeared at M6. It is possible that the effects of smoking on the stiffness of the peripheral muscular arteries could be gradually reversible, particularly during treatment with amlodipine.

This study investigated the effects of amlodipine treatment for 6 months on arterial stiffness. It is unlikely that structural changes in arterial stiffness could be observed in such a relatively short time. Arterial stiffness is also known to be modulated by functional changes in smooth muscle tone, and it has been recognized that the vascular endothelium plays an important role in the dynamic regulation of arterial stiffness (25). Recent studies have shown that endothelium-derived nitric oxide (NO) regulates arterial stiffness (25, 28). NO is an important modulator of endothelial function and also exerts protective effects on the cardiovascular system due to its anti-atherosclerotic activity (28). It has been demonstrated that NO exerts no effect on PWV modulation in human central elastic arteries (29); however, NO has a significant effect on the stiffness of peripheral muscular arteries (28). Increases in the baPWV have been significantly correlated with decreases in flow-mediated dilation of the brachial artery, a non-invasive assessment of endothelial function (30), thus suggesting that baPWV might be partly regulated by endothelial function.

Amlodipine was found to have a late-appearing effect on arterial properties in hypertensive smokers. Endothelial dysfunction is a central feature of vascular disease induced by cigarette smoking and hypertension (31), and these risk factors might synergistically cause functional arterial stiffness, which is characterized by reduced NO bioavailability. Amlodipine has an intrinsically positive influence on the compliance of muscular arteries (32); therefore, this may in turn reduce baPWV, which primarily reflects peripheral arterial components (22). By measuring the increased NO output in

exhaled air, Kato and colleagues have recently shown that amlodipine increases NO production in hypertensive patients (33). Therefore, amlodipine might not only normalize BP, but may also reverse endothelial dysfunction by restoring NO availability in hypertensive smokers. In other words, amlodipine may reduce baPWV indirectly by lowering the MBP, but it may also exert a direct effect on baPWV by acting as an NO donor. However, in hypertensive smokers, it would take considerable time for the latter mechanism to take effect.

As regards the AIx, there were no significant differences between groups at any month of this study period. The AIx is intrinsically influenced by aortic PWV, as well as by the site and the extent of wave reflection, which might be modulated by endothelium-derived NO (25, 29). However, It has been demonstrated that the AIx and PWV cannot be used interchangeably as indices of arterial stiffness (21, 24, 29). The results of the present study are consistent with the findings of recent reports (29, 34) in which vasoactive drugs alter the AIx independently of the PWV. A possible explanation for this phenomenon might be that the AIx, unlike the PWV, is strongly influenced by several physiologic factors other than conduit arterial properties, *e.g.*, body height (distance traveled by pressure waves) and HR (left ventricular ejection time).

Study Limitations

The present study has several potential limitations. First, we did not match smokers and non-smokers in terms of sex; therefore, the smokers had a much higher proportion of men than did the non-smokers. However, even when only male subjects were considered, we observed the same positive correlation between Δ baPWV and pack-years smoked. Second, we did not apply the cfPWV, which has been established as a predictor of cardiovascular risks (13, 16), but rather used the baPWV, for which neither the prognostic significance nor the physiological significance has been determined. However, because the impact of cigarette smoking on blood vessel walls is more pronounced in muscular arteries than in elastic arteries (7–9), we believe the baPWV was preferable as a marker of muscular artery stiffness, particularly when considering the purpose of this study. Third, we did not confirm whether or not the intima-media thickness of the muscular arteries was similar between the smokers and non-smokers. Therefore, even if CIMT reflects systemic atherosclerosis, we could not completely eliminate the possibility of progressive atherosclerosis of the muscular arteries in the hypertensive smokers. Finally, further studies will still be needed to evaluate whether or not the discrepancy in Δ baPWV with similar Δ MBP values between hypertensive smokers and hypertensive non-smokers could be observed by using antihypertensive medications that contain renin-angiotensin system inhibitors. In other reports, it has been shown that amlodipine was less effective than angiotensin-converting enzyme (ACE) inhibitors at reducing central elastic artery stiffness, as evalu-

ated by cfPWV, even when similar BP reductions were achieved by these two drugs (35).

Conclusions

The present study demonstrated that the impact of long-term cigarette smoking concomitant with hypertension delayed the beneficial effects of amlodipine on PWV, even when similar MBP reductions were achieved. Thus, the results suggest that arterial stiffness may have been advanced in the hypertensive smokers examined here. Furthermore, this blunting of the reduction of PWV due to smoking was cumulative. PWV is known to be an independent predictor of cardiovascular disease; therefore, long-term cigarette smoking and hypertension might have synergistic effects that can lead to a poor cardiovascular prognosis. Considering the present results, quitting cigarette smoking should be recommended to patients with hypertension. However, it should be noted that in hypertensive smokers, a time-dependent improvement of baPWV was still observed, suggesting that stiffness in the peripheral muscular arteries, which is regulated by endothelial function, could be gradually improved by treatment with amlodipine. Additional investigations including the actual measurement of endothelial function will be required to precisely elucidate this mechanism.

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