View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Journal of the American College of Cardiology Vol. 55, No. 18, 2010
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2009.12.042

Continuous Smoking and Progression of Arterial Stiffening

A Prospective Study

Hirofumi Tomiyama, MD,* Hideki Hashimoto, MD, MPH,† Hirofumi Tanaka, PHD,‡ Chisa Matsumoto, MD,* Mari Odaira, MD,* Jiko Yamada, MD,* Masanobu Yoshida, MD,* Kazuki Shiina, MD,* Mikio Nagata, MD,§ Akira Yamashina, MD*

Tokyo, Japan; and Austin, Texas

Objectives We prospectively and longitudinally determined the effects of smoking on the progression of arterial stiffening as well as the involvement of inflammation in this process.

Background Smoking is an important avoidable risk factor for cardiovascular disease, and arterial stiffness might be involved in the pathophysiology. No prospective study has examined the effect of continuous smoking on the age-associated progression of arterial stiffening.

Methods In 2,054 Japanese subjects (40 ± 8 years of age), brachial-ankle pulse wave velocity (baPWV) and serum C-reactive protein (CRP) levels were measured at the baseline and the end of a 5- to 6-year follow-up period.

Results The annual rate of change of the baPWV during the study period was significantly greater in the continuous heavy smokers (11.0 ± 1.9 cm/s/year, n = 181) than in the never-smokers (5.5 ± 0.6 cm/s/year, n = 1,018). This difference remained significant even after adjustments for covariates, including age ($p < 0.05$). In continuous smokers (n = 493), the mean number of cigarettes smoked/day during the study period showed a significant relationship with the changes in baPWV. No significant relationship was found between the change in baPWV and serum CRP levels.

Conclusions Continuous smoking might accelerate the age-associated progression of structural stiffening of the large- to middle-size arteries. We also found a dose–response relationship between cigarette consumption and accelerated arterial stiffening. However, we failed to confirm any significant association between the rate of arterial stiffening and the serum CRP levels in the smokers. (J Am Coll Cardiol 2010;55:1979–87) © 2010 by the American College of Cardiology Foundation

Arterial stiffness plays a key role in the pathophysiology of cardiovascular (CV) disease and is recognized as an independent risk factor for CV disease (1,2). Pulse wave velocity (PWV) is a representative measure of arterial stiffness and has been used as a marker of not only vascular damage but also CV risk (1,3). Several epidemiological studies have demonstrated that smoking is a major risk factor for cardiovascular events (4,5). Acute smoking impairs regional arterial distensibility and increases PWV (6,7), and chronic smokers exhibit impairments of arterial distensibility and elevated PWV (8,9). However, no prospective study has determined whether continuous smoking might accelerate the progression of arterial stiffening with advancing age and, if so, whether there might be a dose–response relationship. Moreover, it is not clear whether inflammation, one of the mechanisms underlying the atherogenic action of smoking (4,10), contributes to the progression of arterial stiffening attributed to smoking.

Accordingly, the present prospective study was conducted on a large cohort of middle-age Japanese workers to determine: 1) the effect of smoking status on the progression of arterial stiffening with age; 2) the relationship between the amount of smoking and the age-associated progression of arterial stiffening; and 3) involvement of inflammation in the progression of arterial stiffening attributed to smoking.

Methods

Design and subjects. This cohort study was initiated on the employees of a single large construction company in the

From the *Second Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan; †Health Management and Policy, University of Tokyo Graduate School of Medicine, Tokyo, Japan; ‡Department of Kinesiology and Health Education, University of Texas, Austin, Texas; and the §Health Care Center, Kajima Corporation, Tokyo, Japan. This study was supported in part by a fund from OMRON Health Care (Kyoto, Japan) (donated to Prof. Yamashima).

Manuscript received October 6, 2009; revised manuscript received December 14, 2009, accepted December 17, 2009.

JACC Vol. 55, No. 18, 2010
May 4, 2010:1979–87

Abbreviations and Acronyms

ABI = ankle-brachial pressure index

ANOVA = analysis of variance

baPWV = brachial-ankle pulse wave velocity

CRP = C-reactive protein

CV = cardiovascular

PWV = pulse wave velocity

year 2000 when annual health checkups were mandated by the Occupational Health and Safety Law. In addition to the evaluation of routine clinical parameters such as blood pressure and serum cholesterol, the checkup included atherosclerotic risk factors and brachial-ankle pulse wave velocity (baPWV). Measurement of the serum C-reactive protein (CRP) levels was begun from the year 2002. Among all the study subjects, those who were working at the company headquarters were invited to undergo follow-up measurements of baPWV and blood and urine examinations from 2007 to 2008. Verbal informed consent was obtained from all of the study participants before their participation in this study. The study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University. Some related data have been presented elsewhere (11).

All the participants were provided feedback on the results of the annual health checkups. Along with other lifestyle modification recommendations, smoking cessation was recommended to the subjects who were identified as smokers. Subjects with positive atherosclerotic risk factors (body mass index [BMI] ≥25 kg/m^2, triglyceride ≥150 mg/dl, high-density lipoprotein [HDL] cholesterol <40 mg/dl, fasting plasma glucose ≥126 mg/dl, blood pressure ≥140/90 mm Hg, and/or total cholesterol ≥240 mg/dl) were advised to visit the health care center within the construction company and were provided with advice with regard to therapeutic lifestyle modifications by health professionals, in accordance with the guidelines of the Japanese Societies of Atherosclerosis, Diabetes Mellitus, and Hypertension (12–17). Subjects requiring medications were prescribed appropriate drugs at either the health care center or at other clinics. Each patient was given the freedom to choose his/her own doctor for such treatment.

Subjects with the following conditions were excluded from the present study: 1) unusually low or unreliable baPWV values (due to ankle/brachial systolic blood pressure index [ABI] <0.95, atrial fibrillation, and/or regular hemodialysis) (11); and 2) serum CRP levels >10.0 mg/l (as the conventional clinical cutoff point for inflammation) (18).

A total of 2,357 subjects who were working at the company headquarters in the year 2002 were enrolled in the study protocol. Of these, 2,175 subjects were successfully followed up until 2007 to 2008, and 182 were excluded because of the lack of complete datasets (n = 18) and missing follow-up data (n = 164), due to moving of the subjects from the company headquarters to branch offices, layoffs, retirement, and so forth. Of the 2,175 subjects, 79 were excluded for the following reasons: ABI <0.95 (n = 17); atrial fibrillation (n = 12); serum CRP ≥10 mg/l (n = 48; 2 of them also had an ABI <0.95); and hemodialysis (n = 2). Finally, 2,096 subjects were successfully enrolled for the 5- to 6-year follow-up study.

Measurement of the baPWV. Brachial-ankle pulse wave velocity was measured with a volume-plethysmographic apparatus (Form/ABI, Colin Company, Ltd., Komaki, Japan), as previously described (11,19). Briefly, electrocardiographic electrodes were placed on both wrists, and a microphone for the phonocardiogram was attached on the left chest. Electrocardiograms and phonocardiograms were used to provide timing markers for the device. Occlusion cuffs, which were connected to both the plethysmographic and oscillometric sensors, were tied around both the upper arms and ankles while the subjects were in the supine position. The brachial and post-tibial arterial pressures were measured by the oscillometric sensor. Ten-second recordings of the brachial and post-tibial arterial pressure waveforms recorded by the plethysmographic sensor were stored. The measurements were conducted after the subjects had rested for at least 5 min in the supine position in an air-conditioned room (maintained at 24°C) allocated exclusively for this study. Blood pressure was determined by the oscillometric sensor, and heart rate was also simultaneously recorded during the measurement of the baPWV. The interobserver and intraobserver coefficients of variation for baPWV measurements were 8% and 10% in our previous study (19).

For the analyses, the mean values of the baPWV and blood pressure measured on both sides (i.e., [value measured on the right side + value measured on the left side] / 2) were used. The annual rate of change in the baPWV during the study period was calculated as: value at the final examination minus value at the baseline examination divided by the duration of follow-up (years).

Laboratory measurements. Serum concentrations of triglyceride, total cholesterol, HDL-cholesterol, creatinine, and CRP as well as plasma glucose concentration were measured with standard enzymatic methods (Falco Biosystems Company, Ltd., Tokyo, Japan) (20). All the blood samples were obtained in the morning, after the patients had fasted overnight.

Blood pressure measurement. Blood pressure was measured in an office setting with the subjects in the seated position by the conventional cuff method with a mercury sphygmomanometer. Measurements were obtained twice after the subjects had rested for at least 5 min, and the mean of the 2 measurements was reported.

Smoking status. Smoking status of the subjects (i.e., never-smoker, former smoker, current smoker) were assessed with a questionnaire. Current and former smokers were requested to provide an average number of cigarettes smoked/day and the duration (number of years) of smoking. The subjects were classified into 5 different categories on the basis of their responses at the baseline and final examinations; never smokers (who had no history of smoking), former smokers (who had a past history of smoking), quitters (who were current smokers in the baseline survey

and former smokers in the final survey), continuous light-to-moderate smokers (who continued to smoke ≤20 cigarettes/day at the time of both the baseline and the final surveys), and continuous heavy smokers (who continued to smoke >20 cigarettes/day at both the baseline and the final survey) (21). The questionnaire was not designed to assess the reason why former smokers quit smoking or the exact date of quitting smoking. Starters or relapsers (who were never-smokers/former smokers at the baseline survey and changed their smoking status to current smokers at the final survey) were excluded, because of a smaller number of subjects in this group (n = 42) and the difficulty in precisely assessing their smoking history.

We estimated the average number of cigarettes smoked/day (amount of smoking) in the subjects who continued to smoke throughout the study period, to examine the dose–response relationship between the amount of smoking and the rate of changes in baPWV. The average number of cigarettes smoked/day during the study period was calculated by the sum of the mean daily number of cigarettes smoked reported at each annual checkup divided by the duration of follow-up (in years).

Statistical analysis. Data were expressed as mean ± SD unless otherwise indicated. The differences in the continuous variables across the 5 smoker categories were assessed by 1-way analysis of variance (ANOVA), and the differences in the measured values between the baseline and final examinations were assessed by the paired *t* test. In the ANOVA, Scheffe's test was applied for post-hoc multiple comparisons.

The categorical variables were categorized as follows: sex (female = 0 and male = 1); alcohol intake (nondrinker = 0, light-to-moderate drinker [ethanol consumption, 1 to 29 g/day] = 1, and heavy drinker [ethanol consumption, over 30 g/day] = 2); medication for coronary heart disease, stroke, hypertension, diabetes mellitus, and/or dyslipidemia (for each medication: no medication = 0, and taking medication = 1); and persistent elevation of the serum CRP level during the study period (i.e., serum CRP levels in the highest tertile range at both the baseline and final examinations) (no persistent elevation = 0, and persistent elevation = 1). Pearson's chi-square test was applied for assessment of the differences in the categorical variables across the 5 smoking status categories (post-hoc comparisons among subgroups were not conducted). McNemar's nonparametric test was applied for assessment of the differences in the medications prescribed between the baseline and final examinations, and Friedman's nonparametric test was applied for assessment of the differences in the amount of alcohol intake between the baseline and final examinations.

In the general linear model analyses, the annual rate of change in baPWV during the study period was entered as a dependent variable, the 5 smoker categories were entered as a fixed factor, and others were entered as covariates for adjustment. Two different adjustment models were applied. In Model 1, the covariates for adjustments were the baseline values of factors already known to be linked to arterial stiffness and/or atherosclerosis (1,3,11,19,20) (i.e., age; sex; body mass index; alcohol intake; mean blood pressure; heart rate; serum total cholesterol; serum HDL-cholesterol; serum triglyceride; serum creatinine; fasting blood glucose; and medication for coronary heart disease, stroke, hypertension, diabetes mellitus, and/or dyslipidemia). In Model 2, the covariates for adjustments were all the variables included in Model 1 plus the changes in these variables (except for sex) during the study period. In the analysis without adjustments for covariates, Scheffe's test was applied for post hoc multiple comparisons. In the analysis with adjustments for covariates (Model 1 and 2), Bonferroni's test was applied for post hoc pair-wise comparisons.

We specifically tested the association between serum CRP and the annual rate of changes in baPWV, because CRP might mediate the effect of smoking on the progression of arterial stiffening. Because serum CRP levels were skewed, the analyses were conducted with and without log-transformation of serum CRP levels. Multivariate linear regression analysis with the aforementioned adjustments (Model 1 and 2) were used to test the influence of serum CRP as well as persistently elevated serum CRP on the annual rate of changes in baPWV. Finally, we conducted multivariate regression analysis with the Model 1 and 2 adjustments mentioned in the preceding text among continuous smokers, to test the dose–response relationship between the amount of smoking and the change in baPWV.

All the analyses were conducted with the IBM/SPSS software (version 17.0J for Windows, IBM/SPSS, Inc., Chicago, Illinois). The p values <0.05 were considered to denote statistical significance.

Results

Among the 2,096 subjects, 42 were identified as relapsers and therefore were excluded from the analyses. The data of the remaining 2,054 subjects (age 40 ± 8 years, 1,648 men and 406 women) were included for the analyses. The follow-up period (study duration) was 6 years for 1,734 of the 2,054 subjects and 5 years for the remaining 320 subjects.

Table 1 shows the clinical characteristics and changes in the body measurements during the study period in the 5 smoking categories. The paired *t* test demonstrated that baPWV increased significantly during the study period in all 5 smoking categories. The ANOVA with Scheffe's test demonstrated that the baPWV at the baseline examination was higher in the quitters and continuous heavy smokers than in the never-smokers. The mean age at the baseline examination was higher in the former smokers and continuous heavy smokers than in the other 3 categories of smokers. However, the group differences in baPWV remained significant even after the adjustments for covariates, including age ($p < 0.05$).

We examined, in the entire subject population (n = 2,054), whether continuous smoking could influence the

Table 1 Changes in Selected Subjects' Characteristics During the Study Period (n = 2,054)

	Never (n = 1,018)		Former (n = 327)		Quitter (n = 181)		Moderate (n = 347)		Heavy (n = 181)	
Parameter	Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final	Baseline	Final
Male/female	697/321	—	303/24	—	160/21	—	308/39	—	180/1	—
Age (yrs)	39 ± 8	—	43 ± 8*	—	41 ± 8†	—	40 ± 8†	—	44 ± 8*‡§	—
BMI (kg/m^2)	22.7 ± 3.3	22.9 ± 3.5‖	23.9 ± 3.1*	24.0 ± 3.0‖*	23.6 ± 3.2*	24.0 ± 3.5‖*	23.3 ± 2.9	23.5 ± 2.9	24.6 ± 3.4*§	24.3 ± 3.2*
Alcohol (non/mod/hvy)	263/723/32	244/717/57‖	47/251/29	37/247/43‖	23/139/19	24/137/20	52/270/25	30/117/34‖	51/239/57	29/112/40
Systolic BP (mm Hg)	120 ± 15	120 ± 15	125 ± 15*	125 ± 15*	124 ± 15*	125 ± 14‖*	123 ± 14	128 ± 15‖	122 ± 14*§	126 ± 15‖*
Diastolic BP (mm Hg)	73 ± 11	75 ± 11‖	77 ± 12*	77 ± 10*	75 ± 11	78 ± 11‖*	75 ± 11	77 ± 11‖	75 ± 11*	77 ± 11‖
Heart rate (beats/min)	63 ± 9	66 ± 9‖	63 ± 10	65 ± 10‖	64 ± 10	65 ± 10	65 ± 9	68 ± 10‖	65 ± 9*†‡§	67 ± 10‖*†‡§
Total-C (mmol/l)	5.1 ± 0.8	5.4 ± 0.8‖	5.3 ± 0.9*	5.5 ± 0.8‖	5.1 ± 0.8	5.5 ± 0.8‖	5.2 ± 0.9	5.3 ± 0.9‖	5.3 ± 0.9	5.4 ± 0.9‖
Triglyceride (mmol/l)	1.0 ± 0.8	1.1 ± 0.8‖	1.4 ± 1.1*	1.5 ± 1.0‖*	1.5 ± 1.0*	1.5 ± 0.9*	1.4 ± 1.1*	1.5 ± 1.1‖*	1.9 ± 2.0*†‡§	1.8 ± 1.6‖*†§
HDL-C (mmol/l)	1.6 ± 0.4	1.8 ± 0.5‖	1.6 ± 0.4*	1.7 ± 0.5‖*	1.5 ± 0.4*	1.7 ± 0.5‖	1.5 ± 0.4*†	1.6 ± 0.4‖*†	1.4 ± 0.3*†‡§	1.5 ± 0.4‖*†‡§
Glucose (mmol/l)	4.9 ± 0.6	5.0 ± 0.7‖	5.2 ± 1.0*	5.1 ± 0.7‖	5.1 ± 1.0	5.2 ± 1.6‖*	5.0 ± 0.4	5.0 ± 0.6‡	5.4 ± 1.5*†‡§	5.2 ± 1.0‖*§
Creatinine (μmol/l)	58.7 ± 6.9	60.0 ± 11.3‖	60.6 ± 6.9*	63.2 ± 9.4‖*	59.7 ± 7.2	62.4 ± 11.1‖*	59.5 ± 6.5	60.5 ± 8.6‖†	58.8 ± 6.1	62.0 ± 9.8‖
CRP (mg/l)	0.8 ± 1.1	0.6 ± 1.0‖	0.9 ± 1.2	0.8 ± 1.2	1.0 ± 1.5	0.9 ± 1.2	0.8 ± 1.3	0.9 ± 1.3	1.2 ± 1.5*	1.1 ± 1.4*§
ElevCRP	143 (14)	—	54 (17)	—	37 (20)	—	58 (17)	—	62 (34)	—
baPWV (cm/s)	1,225 ± 179	1,258 ± 193‖	1,306 ± 207*	1,343 ± 211‖*	1,311 ± 213*	1,340 ± 203‖*	1,274 ± 187*	1,315 ± 210‖*	1,334 ± 209*§	1,399 ± 233‖*§
CHD	2	8‖	4	9*	0	2	1	2	0	2
CBVD	0	3	0	5	0	1	0	0	1	1
Medication (%)										
For hypertension	33 (3.2)	90 (8.8)‖	22 (6.7)*	44 (13.5)‖	7 (3.9)	20 (11.1)‖	15 (4.3)	33 (9.5)‖	11 (6.1)	25 (13.8)‖
For diabetes	5 (0.4)	18 (1.8)‖	5 (1.5)	10 (3.1)	2 (1.1)	6 (3.3)	2 (0.6)	6 (1.7)	5 (2.8)	10 (5.5)
For dyslipidemia	13 (1.3)	41 (4.0)‖	7 (2.1)	12 (3.8)	2 (1.1)	5 (2.8)	3 (0.8)	14 (4.0)‖	5 (2.8)	11 (6.1)‖

Values are n, mean ± SD, or n (%). *$p < 0.05$ versus Never; †$p < 0.05$ versus Former; ‡$p < 0.05$ versus Quitter; §$p < 0.05$ versus Moderate (assessed by 1-way analysis of variance with post hoc multiple comparisons by Scheffe's test). ‖$p < 0.05$ versus Baseline (assessed by paired *t* test for continuous variables, by Friedman's nonparametric test for alcohol intake, and McNemar's nonparametric test for medications).

baPWV = brachial-ankle pulse wave velocity; BMI = body mass index; BP = blood pressure; C = serum cholesterol; CBVD = cerebrovascular disease; CHD = coronary heart disease; CRP = serum C-reactive protein level; ElevCRP = persistently elevated serum CRP levels during the study period; Former = former smokers; Heavy = smokers who continued to smoke >20 cigarettes/day during the study period; hvy = heavy drinker (ethanol intake, ≥30 g/day); mod = light-to-moderate drinker (ethanol intake, 1 to 29 g/day); Moderate = smokers who continued to smoke ≤20 cigarettes/day during the study period; Never = never-smokers; non = nondrinker; Quitter = subjects who quit smoking during the study period.

rate of progression in arterial stiffening with advancing age. Figure 1 shows the crude and adjusted values of the annual rate of increase in baPWV during the study period across the 5 different smoker categories. In Figure 1, the upper panel presents the crude comparison with the Scheffe's method. Continuous heavy smokers were significantly different from never-smokers in the pair-wise comparison. Continuous heavy smokers were also significantly different from other 4 groups in the contrast comparison. In an adjusted model (Model 1), post-hoc pair-wise comparisons by Bonferroni's test demonstrated that the rate of arterial stiffening was significantly greater in the continuous heavy smokers than in the never-smokers and former smokers (Fig. 1, middle panel). In further adjustment including changing scores (Model 2), the rate of arterial stiffening was significantly greater in the continuous heavy smokers than in the never-smokers, former smokers, and quitters (Fig. 1, lower panel). Because there were fewer women than men in the present study, the same analyses were conducted with only male data. The same results shown in Figure 1 were obtained even if we confined the analyses to men only (n = 1,648) (data not shown).

As shown in Table 1, ANOVA with the Scheffe's test demonstrated that the serum CRP concentrations were greater in the continuous heavy smokers than in the never-smokers at both the baseline and final examinations. The results of the Pearson's chi-square test demonstrated that the prevalence of subjects with persistently elevated serum CRP during the study period (as defined in the statistical analysis section) differed among the 5 smoking categories (i.e., the prevalence rate in the continuous smokers was 34%, whereas that in the never-smokers was 14%).

Table 2 Univariate Analyses Showing Relations Between the Annual Rate of Changes in baPWV During Study Period and Parameters Related to Serum CRP Concentration

Variable	Pearson's r Value	p Value
Serum CRP at baseline	0.02	0.45
Log serum CRP at baseline	0.02	0.28
ΔSerum CRP	0.01	0.75
ΔLog serum CRP	0.01	0.69
Persistently elevated serum CRP	0.05	0.03

baPWV = brachial-ankle pulse wave velocity; CRP = C-reactive protein; ΔSerum CRP = absolute changes (mg/l) in serum CRP level (value at the final examination – value at the baseline examination); Persistently elevated serum CRP = subjects with persistently elevated CRP levels during the study period (no = 0 and yes = 1).

Univariate analyses in the entire subject population (n = 2,054) revealed that the annual rate of increase in baPWV was not significantly associated with baseline serum CRP levels, baseline log-transformed serum CRP levels, changes in serum CRP levels during the study period, and changes in log-transformed serum CRP levels. The annual rate of increase in baPWV was significantly correlated only with persistent elevations in serum CRP levels (Table 2). However, in the multivariate linear regression analysis with adjustments using Model 1 and Model 2, the relationships between the annual rate of increases in baPWV and the

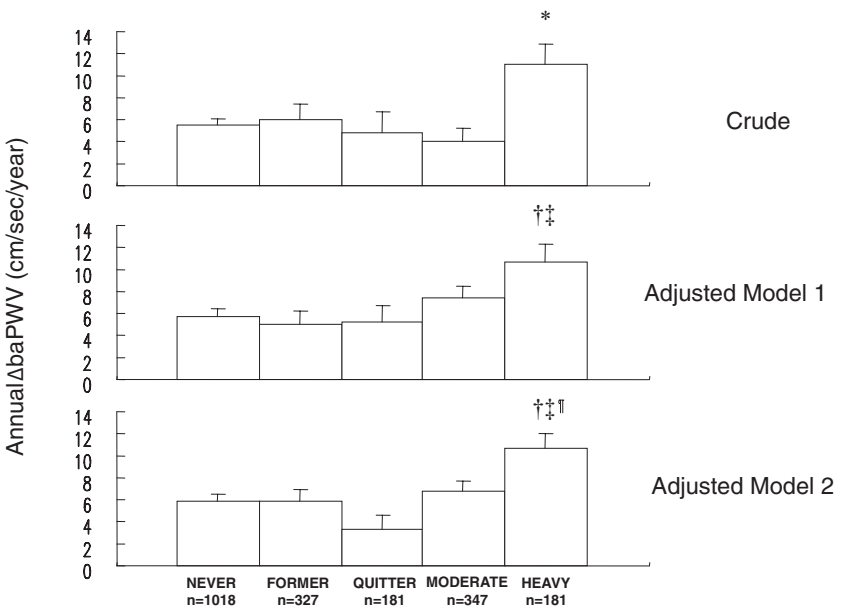

Figure 1 Mean (± SEM) Annual Rate of Increases in baPWV During the Study Period Across the 5 Different Smoker Categories

The details of the covariates in Model 1 and 2 are described in the text. *p < 0.05 versus Never, in Scheffe's test. †p < 0.05 versus Never; ‡p < 0.05 versus Former; ¶p < 0.05 versus Quitter, in Bonferroni's test. baPWV = brachial-ankle pulse wave velocity; Former = former smokers; Heavy = subjects who continued to smoke >20 cigarettes/day during the study period; Moderate = subjects who continued to smoke ≤20 cigarettes/day during the study period; Never = never smokers; Quitter = subjects who quit smoking during the study period.

JACC Vol. 55, No. 18, 2010
May 4, 2010:1979–87

persistent elevation of the serum CRP did not reach statistical significance (Table 3).

The completed questionnaire on the smoking status was available for all the study years (except in year 2005) in 493 of the 528 continuous smokers. On univariate analyses, there was a significant positive relationship between the annual rate of increases in baPWV and the number of cigarettes smoked/day ($r = 0.19$, $p < 0.01$). Furthermore, multivariate linear regression analyses with adjusted Model 1 and Model 2 demonstrated that the number of cigarettes smoked/day was a significant independent correlate with the annual rate of increases in baPWV (Table 4). The results were essentially the same when the sample was limited only to men ($n = 480$) (data not shown).

Discussion

To the best of our knowledge, the present study was the first prospective study to examine the effects of smoking status as well as the amount of smoking on the rate of progression in arterial stiffening with aging. The results revealed that the annual rate of increases in baPWV was significantly greater in the continuous heavy smokers than in the never-smokers. These findings suggest that continuous heavy smoking accelerates the age-associated progression of stiffening of the large conduit arteries and could contribute to the age-related increases in CV disease.

A dose–response relationship between cigarette consumption and risks of CV events has been reported (22–24). Baldassarre et al. (23) described, on the basis of the results of their cross-sectional study, the existence of a significant relationship between the amount of smoking and the severity of carotid atherosclerosis, as assessed by ultrasound examination. The present subanalysis, in which information about the number of cigarettes smoked/day was successfully obtained each year (except year 2005) throughout the study period, demonstrated a significant relationship between the number of cigarettes smoked/day and the annual rate of changes in baPWV. These results suggest the existence of a dose–response relationship between the amount of continuous smoking and age-associated accelerations of arterial stiffening.

Smoking is thought to be involved in the initiation and progression of atherosclerosis via several different mechanisms (4,10,25), and some studies have suggested the involvement of inflammation in the accelerated progression of arterial stiffening in smokers (3,20). In the present study, serum CRP levels were higher in the continuous smokers than in the never-smokers. Although persistently elevated serum CRP levels had a significant association with the progression of arterial stiffening on the basis of the univariate analyses, such associations did not reach statistical significance when the multivariate linear regression model was applied. Serum CRP is a marker of systemic inflammation but not a robust marker of vascular inflammation (26). Recently, Schumacher et al. (27) suggested that CRP does not have a causal role in the progression of arterial stiffening. Thus, further studies are needed to determine the contribution of smoking-related vascular inflammation to the progression of arterial stiffening.

Increased aortic stiffness acts as a CV risk factor via several different mechanisms, including increased cardiac afterload, impaired coronary blood flow, increased arterial wall stress, and microvascular damage (1–3). Carotid-femoral PWV is the most established index for assessment of the aortic stiffness (1,3), but baPWV has been increasingly used in the research and clinical settings because its measurement is extremely simple, allowing repeated measurements in a large number of study subjects. Although baPWV is a marker of stiffness of both large and middle-sized arteries (11,19), baPWV demonstrates a close correlation not only with carotid-femoral PWV (28) but also with aortic PWV, as assessed by a direct catheter-method (19). Furthermore, increased baPWV has been shown as a marker of prognosis in subjects with acute coronary syndrome and end-stage renal disease (29,30).

If continuous smoking itself was a significant determinant of the progression of arterial stiffening, baPWV at the baseline examination should be greater in the continuous heavy smokers than in the former smokers. However, baseline baPWV was not different between the 2 groups. The precise explanation for this apparent discrepancy is unknown. Part of the reason might be related to the questionnaire used to evaluate the smoking status. Several studies have suggested that questionnaire surveys to determine the smoking status might underestimate the prevalence of smoking (31), and no biochemical confirmation of quitting smoking was carried out in the present study. An alternative explanation is that the effects of chronic smoking on arterial stiffness would persist for a long time after the smoking cessation. Indeed, 5 to 6 years of no smoking did not induce any noticeable arterial de-stiffening in the former smokers or in the quitters. Jatoi et al. (8) suggested, on the basis of the results of their cross-sectional study, that it might take more than 1 decade to reverse the smoking-induced arterial stiffening. Another possibility is that smoking is simply one of the various factors that affect arterial stiffening. Indeed, after the adjustments for a number of confounders (Model 1), the association between arterial stiffening and cigarette smoking remained statistically significant but weakened. This would suggest that other pertinent factors (e.g., blood pressure) might be exerting important influences on arterial stiffening.

There are several study limitations in the present study that should be emphasized. First, the subjects were relatively young (mean age of approximately 40 years), and there were fewer women than men. Therefore, the confirmation of the present findings in older subjects and/or in women is warranted. Second, the effects of passive smoking were not examined in the present study.

Table 3 Multivariate Linear Regression Analyses Showing Association Between the Annual Rate of Changes in baPWV During Study Period and Persistently Elevated Serum CRP

Independent Variables	Nonstandardized Coefficient (95% CI)	Standardized Coefficient	p Value
Model 1*			
Persistently elevated CRP (no = 0; yes = 1)	2.226 (−0.268 to 4.720)	0.039	0.08
Age (yrs)	0.788 (0.657 to 0.918)	0.292	<0.01
Sex (female = 0; male = 1)	1.651 (−1.215 to 4.516)	0.030	0.259
BMI (kg/m^2)	0.860 (0.505 to 1.216)	0.128	<0.01
Alcohol intake (none = 0; moderate = 1; heavy = 2)	−3.84 (−2.314 to 1.545)	−0.009	0.696
Mean BP (mm Hg)	−0.598 (−0.699 to −0.497)	−0.335	<0.01
Heart rate (beats/min)	-5.017×10^{-2} (−0.157 to 0.056)	−0.021	0.355
Total cholesterol (mmol/l)	−1.352 (−2.550 to −0.153)	−0.054	0.027
HDL-cholesterol (mmol/l)	−0.328 (−3.398 to 2.741)	−0.006	0.834
Triglycerides (mmol/l)	-9.751×10^{-2} (−1.118 to 0.923)	−0.005	0.851
Creatinine (μmol/l)	−0.162 (−0.308 to 0.015)	−0.051	0.031
Glucose (mmol/l)	2.440×10^{-2} (−1.350 to 1.399)	0.001	0.972
Medication CHD (no = 0; yes = 1)	−0.133 (−15.546 to 15.279)	0.001	0.986
Medication CBVD (no = 0; yes = 1)	−30.821 (−72.569 to 10.927)	−0.031	0.148
Medication HT (no = 0; yes = 1)	−2.072 (−6.863 to 2.719)	−0.019	0.396
Medication DM (no = 0; yes = 1)	2.311 (−9.077 to 13.739)	0.010	0.689
Medication dyslipidemia (no = 0; yes = 1)	6.495 (−1.171 to 14.162)	0.036	0.097
Constant	28.715 (13.998 to 43.432)		<0.01
Model 2†			
Persistently elevated CRP (no = 0; yes = 1)	1.474 (−0.631 to 3.578)	0.026	0.170
Age (yrs)	0.561 (0.448 to 0.674)	0.208	<0.01
Sex (female = 0; male = 1)	−1.334 (−4.042 to 1.375)	−0.024	0.334
BMI (kg/m^2)	0.163 (−0.142 to 0.467)	0.024	0.295
Alcohol intake (none = 0; moderate = 1; heavy = 2)	−0.488 (−2.267 to 1.292)	−0.011	0.591
Mean BP (mm Hg)	−0.162 (−0.258 to −0.067)	−0.091	<0.01
Heart rate (beats/min)	0.101 (0.004 to 0.198)	0.043	0.042
Total cholesterol (mmol/l)	−0.982 (−2.068 to 0.103)	−0.039	0.076
HDL-cholesterol (mmol/l)	−0.625 (−3.260 to 2.009)	−0.011	0.642
Triglycerides (mmol/l)	1.049 (0.008 to 2.089)	0.053	0.048
Creatinine (μmol/l)	-5.792×10^{-2} (−0.184 to 0.069)	−0.018	0.369
Glucose (mmol/l)	−0.256 (−1.723 to 1.211)	−0.010	0.732
Medication CHD (no = 0; yes = 1)	5.547 (−7.384 to 18.749)	0.015	0.400
Medication CBVD (no = 0; yes = 1)	−25.240 (−60.311 to 9.832)	−0.026	0.158
Medication HT (no = 0; yes = 1)	−2.262 (−6.425 to 1.901)	−0.021	0.287
Medication DM (no = 0; yes = 1)	3.695 (−6.464 to 13.855)	0.016	0.476
Medication dyslipidemia (no = 0; yes = 1)	5.847 (−0.626 to 12.319)	0.032	0.077
ΔBMI (Δabsolute value)	−0.395 (−0.621 to −0.169)	−0.072	<0.01
ΔAlcohol intake (Δcategories)	1.692 (−0.157 to 3.541)	0.035	0.073
ΔMean BP (Δabsolute value)	1.231 (1.125 to 1.337)	0.481	<0.01
ΔHeart rate (changes in absolute value)	0.495 (0.384 to 0.606)	0.176	<0.01
ΔTotal cholesterol (Δabsolute value)	3.432×10^{-2} (−0.003 to 0.071)	0.041	0.069
ΔHDL-cholesterol (Δabsolute value)	3.503×10^{-3} (−0.053 to 0.123)	0.017	0.436
ΔTriglycerides (Δabsolute value)	1.761×10^{-2} (0.006 to 0.030)	0.068	<0.01
ΔCreatinine (Δabsolute value)	6.821 (−1.420 to 15.061)	0.033	0.105
ΔGlucose (Δabsolute value)	-4.007×10^{-2} (−0.105 to 0.025)	−0.026	0.227
ΔMedication CBVD (Δcategories)	2.756 (−5.972 to 11.484)	0.011	0.536
ΔMedication HT (Δcategories)	−3.961 (−7.663 to −0.259)	−0.043	0.036
ΔMedication DM (Δcategories)	3.623 (−2.987 to 10.232)	0.022	0.283
ΔMedication dyslipidemia (Δcategories)	4.094 (−0.947 to 9.135)	0.030	0.111
Constant	−14.374 (−42.813 to 14.064)		0.321

Multivariate linear regression analyses showing the association between the annual rate of changes in baPWV during the study period (in centimeters/second/year; dependent variable) and persistently elevated serum CRP with adjustments using the 2 different models (n = 2,054). *R^2 = 0.116: adjustments for the baseline values of factors known to be linked to arterial stiffness and/or atherosclerosis; †R^2 = 0.388: adjustments for the baseline values as well as changing scores of factors known to be linked to arterial stiffness and/or atherosclerosis.

CI = confidence interval; Persistently elevated serum CRP = subjects with persistent elevation of the serum CRP levels during the study period categorized into the highest tertile of the serum CRP level; BP = blood pressure; HT = hypertension; DM = diabetes mellitus; Δ = absolute changes during the study period (value at the final examination − value at the baseline examination); other abbreviations as in Table 1.

JACC Vol. 55, No. 18, 2010
May 4, 2010:1979–87

Table 4 Multivariate Linear Regression Showing the Relationship Between the Annual Rate of Changes in baPWV During Study Period and the Number of Cigarettes Smoked/Day

Independent Variables	Nonstandardized Coefficient (95% CI)	Standardized Coefficient	p Value
Model 1*			
Cigarettes/day, n	0.366 (0.144 to 0.588)	0.154	<0.01
Age (yrs)	0.708 (0.436 to 0.981)	0.254	<0.01
Sex (female = 0; male = 1)	2.349 (−5.821 to 10.520)	0.028	0.572
BMI (kg/m^2)	0.856 (0.109 to 1.602)	0.115	0.025
Alcohol Intake (none = 0; moderate = 1; heavy = 2)	−3.716 (−7.784 to 0.352)	−0.083	0.073
Mean BP (mm Hg)	−0.501 (−0.713 to −0.290)	−0.266	<0.01
Heart rate (beats/min)	-4.584×10^{-2} (−0.268 to 0.177)	−0.019	0.686
Total cholesterol (mmol/l)	−0.615 (−3.023 to 1.792)	−0.024	0.616
HDL-cholesterol (mmol/l)	5.875×10^{-3} (−6.681 to 6.693)	0.001	0.999
Triglycerides (mmol/l)	−0.397 (−2.050 to 1.255)	−0.024	0.637
Creatinine (μmol/l)	−0.158 (−0.479 to 0.163)	−0.044	0.335
Glucose (mmol/l)	−1.508 (−4.162 to 1.145)	−0.063	0.265
Medication CHD (no = 0; yes = 1)	−51.976 (−98.396 to −5.557)	−0.102	0.028
Medication CBVD (no = 0; yes = 1)	−39.509 (−85.608 to 6.591)	−0.078	0.093
Medication HBP (no = 0; yes = 1)	−2.545 (−12.382 to 7.293)	−0.023	0.611
Medication DM (no = 0; yes = 1)	8.707 (−12.539 to 29.953)	0.045	0.421
Medication dyslipidemia (no = 0; yes = 1)	24.949 (6.889 to 43.010)	0.129	<0.01
Constant	23.247 (−8.746 to 55.239)		0.154
Model 2†			
Cigarettes/day, n	0.292 (0.111 to 0.473)	0.123	<0.01
Age (yrs)	0.550 (0.324 to 0.776)	0.197	<0.01
Sex (female = 0; male = 1)	−0.418 (−7.493 to 6.657)	−0.005	0.908
BMI (kg/m^2)	0.277 (−0.342 to 0.896)	0.037	0.380
Alcohol intake (none = 0; moderate = 1; heavy = 2)	−3.016 (−6.579 to 0.546)	−0.068	0.097
Mean BP (mm Hg)	-5.980×10^{-2} (−0.248 to 0.129)	−0.032	0.533
Heart rate (beats/min)	9.769×10^{-2} (−0.097 to 0.292)	0.041	0.324
Total cholesterol (mmol/l)	−1.113 (−3.208 to 0.982)	−0.044	0.297
HDL-cholesterol (mmol/l)	−2.353 (−7.957 to 3.251)	−0.037	0.410
Triglycerides (mmol/l)	0.257 (−1.405 to 1.918)	0.016	0.762
Creatinine (μmol/l)	−0.122 (−0.400 to 0.156)	−0.034	0.389
Glucose (mmol/l)	0.729 (−2.270 to 3.278)	0.030	0.633
Medication CHD (no = 0; yes = 1)	−36.058 (−73.785 to 1.668)	−0.071	0.061
Medication CBVD (no = 0; yes = 1)	−32.946 (−71.422 to 5.531)	−0.065	0.093
Medication HT (no = 0; yes = 1)	−4.619 (−12.800 to 3.563)	−0.043	0.268
Medication DM (no = 0; yes = 1)	−3.669 (−23.420 to 16.082)	−0.019	0.715
Medication dyslipidemia (no = 0; yes = 1)	20.760 (6.060 to 35.459)	0.107	<0.01
ΔBMI (Δabsolute value)	−0.292 (−0.766 to 0.181)	−0.049	0.225
ΔAlcohol intake (Δcategories)	3.166 (−0.485 to 6.817)	0.064	0.089
ΔMean BP (Δabsolute value)	1.284 (1.067 to 1.501)	0.490	<0.01
ΔHeart rate (Δabsolute value)	0.637 (0.394 to 0.879)	0.205	<0.01
ΔTotal cholesterol (Δabsolute value)	-1.764×10^{-3} (−0.078 to 0.075)	−0.002	0.964
ΔHDL-cholesterol (Δabsolute value)	7.778×10^{-2} (−0.110 to 0.266)	0.033	0.417
ΔTriglycerides (Δabsolute value)	1.180×10^{-2} (−0.008 to 0.031)	0.057	0.237
ΔCreatinine (Δabsolute value)	5.973 (−12.455 to 24.400)	0.025	0.524
ΔGlucose (Δabsolute value)	5.978×10^{-2} (−0.077 to 0.196)	0.041	0.389
ΔMedication CBVD (Δcategories)	8.613 (−16.5622 to 33.7886)	0.024	0.502
ΔMedication HT (Δcategories)	−2.864 (−11.010 to 5.282)	−0.029	0.490
ΔMedication DM (Δcategories)	−5.966 (−17.997 to 6.064)	−0.042	0.330
ΔMedication Dyslipidemia (Δcategories)	−1.965 (−11.332 to 7.401)	−0.015	0.680
Constant	−14.374 (−42.813 to 14.064)		0.321

Multivariate linear regression showing the relationship between the annual rate of changes in brachial-ankle pulse wave velocity during the study period (in centimeters/second/year) and the number of cigarettes smoked/day with adjustments using the 2 different models (n = 493 involving continuous smokers whose questionnaire was available for all the study years). *R^2 = 0.161: adjustments for the baseline values of factors known to be linked to arterial stiffness and/or atherosclerosis. †R^2 = 0.475: adjustments for the baseline values as well as changing scores of factors known to be linked to arterial stiffness and/or atherosclerosis.

Abbreviations as in Tables 1 and 3.

Conclusions

The present study was the first prospective study to suggest that continuous smoking could accelerate the age-associated progression of structural stiffening of the large- to middle-sized arteries. Our findings also support a dose–response relationship between cigarette consumption and accelerated arterial stiffening. The elevated serum CRP levels associated with continuous smoking do not seem to be directly associated with the acceleration of arterial stiffening in continuous smokers.

Reprint requests and correspondence: Dr. Akira Yamashina, Second Department of Internal Medicine, Tokyo Medical University, 6-7-1 Nishi-Shinjuku, 160-0023 Tokyo, Japan. E-mail: tomiyama@tokyo-med.ac.jp.

REFERENCES

1. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. Circulation 2003;107:2864–9.
2. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 2007;50:1–13.
3. Laurent S, Boutouyrie P. Recent advances in arterial stiffness and wave reflection in human hypertension. Hypertension 2007;49:1202–6.
4. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol 2004;43:1731–7.
5. Edwards R. The problem of tobacco smoking. BMJ 2004;328:217–9.
6. Rhee MY, Na SH, Kim YK, Lee MM, Kim HY. Acute effects of cigarette smoking on arterial stiffness and blood pressure in male smokers with hypertension. Am J Hypertens 2007;20:637–41.
7. Stefanadis C, Tsiamis E, Vlachopoulos C, et al. Unfavorable effect of smoking on the elastic properties of the human aorta. Circulation 1997;95:31–8.
8. Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. Hypertension 2007;49:981–5.
9. Sassalos K, Vlachopoulos C, Alexopoulos N, Gialernios T, Aznaouridis K, Stefanadis C. The acute and chronic effect of cigarette smoking on the elastic properties of the ascending aorta in healthy male subjects. Hellenic J Cardiol 2006;47:263–8.
10. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. Chest 2007;131:1557–66.
11. Tomiyama H, Hashimoto H, Hirayama Y, et al. Synergistic acceleration of arterial stiffening in the presence of raised blood pressure and raised plasma glucose. Hypertension 2006;47:180–8.
12. Japan Atherosclerosis Society. [Guidelines for diagnosis and treatment of atherosclerotic cardiovascular diseases]. Tokyo, Japan: Life Science Publishing, 2000:4–21.
13. Hata Y, Mabuchi H, Saito Y, et al., Working Committee on JAS Guideline for Diagnosis and Treatment of Hyperlipidemias. Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults. J Atheroscler Thromb 2002;9:1–27.
14. Teramoto T, Sasaki J, Ueshima H, et al. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb 2007;14:45–50.
15. Japan Diabetes Society. [Guidelines for diagnosis of diabetes mellitus]. J Jpn Diabetes Soc 1999;42:385–404.
16. Japanese Society of Hypertension. [Guidelines for the management of hypertension]. Tokyo, Japan: Japanese Society of Hypertension, 2000: 14–21.
17. Japanese Society of Hypertension. [Guidelines for the management of hypertension]. Tokyo, Japan: Japanese Society of Hypertension, 2004: 7–34.
18. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003;107:1514–9.
19. Yamashina A, Tomiyama H, Takeda K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res 2002;25:359–64.
20. Tomiyama H, Okazaki R, Koji Y, et al. Elevated C-reactive protein: a common marker for atherosclerotic cardiovascular risk and subclinical stages of pulmonary dysfunction and osteopenia in a healthy population. Atherosclerosis 2005;178:187–92.
21. Wannamethee SG, Shaper AG, Walker M, Ebrahim S. Lifestyle and 15-year survival free of heart attack, stroke, and diabetes in middle-aged British men. Arch Intern Med 1998;158:2433–40.
22. Jee SH, Suh I, Kim IS, Appel LJ. Smoking and atherosclerotic cardiovascular disease in men with low levels of serum cholesterol: the Korea Medical Insurance Corporation Study. JAMA 1999;282:2149–55.
23. Baldassarre D, Castelnuovo S, Frigerio B, et al. Effects of timing and extent of smoking, type of cigarettes, and concomitant risk factors on the association between smoking and subclinical atherosclerosis. Stroke 2009;40:1991–8.
24. Song YM, Cho HJ. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: a cohort study in Korean men. Stroke 2008;39:2432–8.
25. Guo X, Oldham MJ, Kleinman MT, Phalen RF, Kassab GS. Effect of cigarette smoking on nitric oxide, structural, and mechanical properties of mouse arteries. Am J Physiol Heart Circ Physiol. 2006;291:H2354–61.
26. Jialal I, Devaraj S, Venugopal SK. C-reactive protein: risk marker or mediator in atherothrombosis? Hypertension 2004;44:6–11.
27. Schumacher W, Cockcroft J, Timpson NJ, et al. Association between C-reactive protein genotype, circulating levels, and aortic pulse wave velocity. Hypertension 2009;53:150–7.
28. Sugawara J, Hayashi K, Yokoi T, et al. Brachial-ankle pulse wave velocity: an index of central arterial stiffness? J Hum Hypertens 2005;19:401–6.
29. Tomiyama H, Koji Y, Yambe M, et al. Brachial -ankle pulse wave velocity is a simple and independent predictor of prognosis in patients with acute coronary syndrome. Circ J 2005;69:815–22.
30. Kitahara T, Ono K, Tsuchida A, et al. Impact of brachial-ankle pulse wave velocity and ankle-brachial blood pressure index on mortality in hemodialysis patients. Am J Kidney Dis 2005;46:688–96.
31. Gorber SC, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res 2009;11:12–24.

Key Words: arteriosclerosis ■ inflammation ■ pulse wave velocity ■ risk factors ■ tobacco.