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The Impact of Chronic Cigarette Smoking on Arterial Stiffness in Korea

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Background: Cigarette smoking is an important modifiable cardiovascular risk factor, which is known to acutely increase arterial stiffness. But the chronic effects of smoking on arterial stiffness are still controvertial. We studied the effects of chronic cigarette smoking on arterial stiffness in Korean subjects.
Methods: Our subjects included those >18 years of age (n=2685, 991 females) who had undergone a pulse wave velocity from July 2004 to June 2008. They were classified into two groups, smokers (n=641) and non-smokers (n=2044). In addition to the pulse wave velocity (PWV), we reviewed the highly sensitive C-reactive protein levels in a random manner when it was available.
Results: Males were predominant in the smokers group. Smokers had significantly higher heart-femoral PWVs than non-smokers (1083.6±264.1 cm/sec vs. 1041.3±257.3 cm/sec; p<0.001). There was no linear relationship between smoking duration and PWV (r= -0.225, p=0.506) even after adjusting for age, sex, and body mass index. Furthermore, there was no difference in the ankle-brachial index between the two groups. On the multivariate regression analysis, age, male gender, hypertension, and diabetes were independent predictors of increased arterial stiffness.
Conclusion: In this study, chronic cigarette smoking increased central arterial stiffness in Korean subjects.

Key Words: Cigarette smoking, Arterial stiffness, Pulse wave velocity

INTRODUCTION

Smoking is the most important modifiable risk factor for coronary artery disease[1,2]. Despite extensive research, the pathophysiological mechanisms of smoking-related vascular damage have not been fully explored. Changes in hemostatic factors[3,4], endothelial function[5], and blood lipids[6] have been proposed as mechanisms of vascular damage. Smoking increases arterial wall thickness and stiffness and decreases arterial reactivity, suggesting that active smoking accelerates atherosclerosis in humans. Cross-sectional and longitudinal data show that smoking increases arterial wall thickness and the rate of progression of arterial wall thickness[7]. Arterial stiffness is known to be an important cardiovascular risk factor and an independent predictor of all-cause and cardiovascular deaths. Acute cigarette smoking has been shown to increase the pulse wave velocity (PWV), suggesting there is increased arterial stiffness. However, the effects of chronic cigarette smoking on arterial stiffness are uncertain. Arterial stiffness is easily assessed by measuring the PWV using the recently developed automatic device[8].

The aim of this study was to investigate whether chronic cigarette smoking affects arterial stiffness.

MATERIALS AND METHODS

1. Subjects

A total of 2,685 subjects (1,694 males, 991 females) were randomly enrolled from Gwangju Veterans Hospital between July 2004 and June 2008. Smoking status was determined

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from questions asked durng a face-to-face encounter with the patients. Of the 2,685 subjects, 641 were smokers (636 males, 5 females) and 2,044 were non-smokers (1,058 males, 986 females). Height and weight were obtained from the patient. Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2).

2. Definition

In this study, a 'smoker' was defined as someone with a history of smoking for at least more than one year in their lifetime. The PWV was defined as the distance between two distinct points divided by the pulse wave transit time (cm/sec). The ankle brachial index (ABI) was defined as the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the brachial artery measured simultaneously.

3. Measurement of the PWV and ABI

PWVs and ABIs were measured using an automatic device, VP-2000 (Colin Co., Komaki, Japan). The cuffs were placed around the arms and ankles before the patient was connected to both the plethysmographic and oscillometric sensors. Both the brachial and ankle blood pressure were measured simultaneously, and the ABI was calculated. The femoral arterial wave was measured using a tonometric sensor placed at the left femoral artery. We calculated the PWV from each brachial artery to the ipsilateral ankle (right and left baPWV) and the PWV from the left femoral artery to the heart (hfPWV). We defined that the hfPWV and baPWV represented central arterial PWV and peripheral arterial PWV, respectively. Brachial and ankle blood pressures, heart rate, ABI, and PWV were measured during normal sinus rhy- thm in the supine position.

4. Statistical Analysis

Statistical analysis was performed using the SPSS ver. 12.0. (SPSS Inc., Chicago, IL, USA). The change in PWV according to the smoking duration was analyzed by repeated-measure of ANOVA. Differences between smokers and non-smokers were analyzed using the independent t-test and chi-square. Binary logistic multiple regression was used for independent variables for increased hfPWV. A $p<0.05$ was considered statistically significant.

RESULTS

1. Baseline Characteristics

The demographics of our subjects are summarized in Table 1. There were no differences in age and BMI between the smokers (males, n=636, 23.7%) and non-smokers. Prevalence of diabetes, hypertension, and dyslipidemia was not significantly different between the two groups. The systolic and diastolic arterial blood pressures were not significantly different between the two groups.

2. Arterial Stiffness Index

The hfPWV was significantly higher in the smoker group than the non-smoker group (1083.6±264.1 cm/sec vs. 1041.3± 257.3 cm/sec). The ABI and baPWV were not significantly different between the two groups (Table 2).

There was no difference in hfPWV between the two groups when patients had diabetes or hypertension. However, hfPWV was significantly higher in the smokers when diabetes

Table 1. Baseline characteristics

Variables	Non-smoker (n=2,044)	Smoker (n=641)	p-value
Gender (M:F)*	1,058:986	636:5	<0.001
Age (yr)	61.8±11.9	61.1±10.6	0.139
Body mass index (kg/m^2)	24.7±7.6	24.2±3.1	0.132
Diabetes (%)	30.5	33.0	0.368
Hypertension (%)	56.7	59.7	0.328
Dyslipidemia (%)	16.4	13.3	0.126
Hs-CRP (mg/dL)	1.9±2.5(n=29)	2.6±3.1(n=40)	0.290
Systolic blood pressure (mmHg)	135.3±21.3	134.7±19.3	0.529
Diastolic blood pressure (mmHg)*	80.6±20.0	81.7±11.4	0.157

Hs-CRP, high sensitive-C reactive protein.
*$p<0.05$ significantly different between two groups.

and hypertension were absent (Tables 3, 4, Figs. 1, 2).

3. Independent Predictors for Hfpwv

On the multivariate regression analysis, male gender, age, hypertension, and diabetes were independent predictors for hfPWV (Table 5).

DISCUSSION

In this study, we observed an association between the hfPWV and chronic cigarette smoking. Furthermore, hypertension and diabetes were risk factors for arterial stiffness by increasing the hfPWV.

Smoking is the most important modifiable risk factor for coronary artery disease. Several mechanisms are proposed for the acute increases in blood pressure and arterial stiffness that are seen immediately after smoking. Cigarette smoking acutely exerts a hypertensive effect, mainly through the stim-

Table 2. Comparison of pulse wave velocities and ankle-brachial index in the smoking group vs. the non-smoking group

Variables	Non-smoker (n=2,069)	Smoker (n=753)	p-value
RhfPWV (cm/sec)*	1041.3±257.3	1083.6±264.1	<0.001
RbaPWV (cm/sec)	1565.7±413.0	1568.8±370.2	0.856
LbaPWV (cm/sec)	1614.6±389.9	1608.8±400.7	0.735
Right ABI	1.1±0.2	1.1±0.2	0.114
Left ABI	1.1±0.1	1.1±0.1	0.080

Values are presented as mean±SD.
RhfPWV, right heart femoral pulse wave velocity; RbaPWV, right brachial ankle pulse wave velocity; LbaPWV, left brachial ankle pulse wave velocity; ABI, ankle brachial index.
*p<0.05 significantly different between two groups.

Table 3. Difference of hfPWV according to blood pressure

	Normotensive		Hypertensive	
	Non-smoker	Smoker	Non-smoker	Smoker
No.	885	258	1,159	383
hfPWV (m/sec)	9.84*	10.42*	11.22	11.11

hfPWV, heart femoral pulse wave velocity.
*p<0.05 significantly different between two groups.

Table 4. Difference of hfPWV according to diabetes

	DM (-)		DM (+)	
	Non-smoker	Smoker	Non-smoker	Smoker
No.	1,421	429	623	212
hfPWV (m/sec)	10.10*	10.60*	11.76	11.24

DM, diabetes mellitus; hfPWV, heart femoral pulse wave velocity.
*p<0.05 significantly different between two groups.

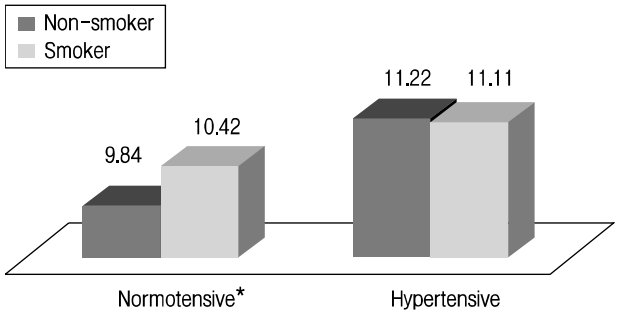

Fig. 1. Differences in heart femoral pulse wave velocity (m/sec) in relation to blood pressure. *p<0.05.

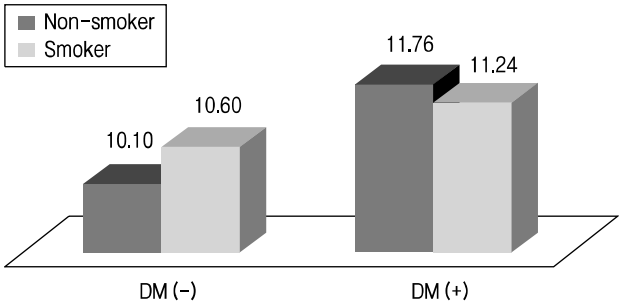

Fig. 2. Differences in heart femoral pulse wave velocity (m/sec) in relation to diabetes. *p<0.05.

Table 5. Risk factors for increased hfPWV in multivariate regression analysis

Variables	Standardized coefficient	p-value
Gender (male)*	0.178	<0.001
Hypertension*	0.156	<0.001
Diabetes*	0.241	<0.001
Age (>65 yr)	0.421	<0.001
Dyslipidemia	-0.067	0.070
BMI (>25 kg/m^2)	0.570	0.120

RhfPWV, right heart femoral pulse wave velocity; BMI, body mass index.
*p<0.05 significantly different between two groups.

ulation of the sympathetic nervous system. The effect of smoking on arterial elastic properties has been studied extensively. Smoking leads to acute stiffening of the elastic and muscular type arteries and enhancement of wave reflections by nicotine's stimulation of the sympathetic nerve[9-12]. Impaired nitric oxide production and endothelial dysfunction are also known to play major roles in altering the mechanical properties of large arteries[13]. But the chronic effects of smoking on the arterial wall dynamics have been controversial[8,14-16]. Our study shows that cigarette smoking affects regional arterial stiffness by increasing the central arterial PWV. There was no difference in the baPWV, defined as peripheral PWV, between smokers and non-smokers, but the hfPWV, i.e., central PWV, was significantly higher in the smokers than in the non-smokers. Different arteries have different proportions of arterial wall structural components. The wall of the aortic artery has good compliance because it is rich in elastin. However, peripheral arteries are less elastic (increased PWV) because their walls contain more collagen and smooth muscle cells. The PWV has a better relationship with the aortic artery than with peripheral arteries because it is inversely correlated with distensibility and relative compliance[17].

The ABI is a simple ratio of the systolic blood pressures of the ankle and the arm. An ABI less than 0.9 is known to be associated with increased cardiovascular diseases. The ABI showed no significant difference between smokers and non-smokers in our study, which coincides with the results of a previous report on the effects of smoking in adolescents[18]. On the other hand, there was a study showing that smoking was independently related to a low ABI in a group of adults with coronary artery disease[19].

No relationship was observed between smoking duration and arterial stiffness in this study after adjusting for age, gender, BMI, diabetes, and hypertension ($r= -0.225$, $p=0.506$). This was in accordance with a previous study[9]. It appears that even small amounts of smoking can produce deleterious effects.

Increased arterial stiffness is associated with several cardiovascular risk factors including age, hypertension, diabetes mellitus, gender, hyperlipidemia, and obesity. We wondered if these risk factors were closely related to arterial stiffness. Thus, we compared smokers to nonsmokers with no underlying diseases such as diabetes and hypertension. The hfPWV was higher in smokers than non-smokers. However, there was no difference in the hfPWV between the two groups when the subjects had diabetes or hypertension. A past study reported that not only smoking but diabetes and hypertension also affect arterial stiffness. Tedesco et al reported a cross-sectional study examining the effects of diabetes and hypertension on arterial stiffness. Using aortic PWV measurements, the authors found significantly higher PWVs in hypertensive-diabetics than in healthy controls[20]. The reasons for this are as follows. The endothelium may affect the elastic properties of the artery by directly affecting vascular tone. The balance between vasoconstrictors such as angiotensin II and endothelin and vasodilators determines the vascular tone of the artery, and nitric oxide (NO) is the key endothelium-derived vasodilator. Certainly, reduced NO bioavailability is closely linked to structural and functional endothelial abnormalities, and endothelial perturbations are well described in diabetes and hypertension. The increased PWV in hypertensive-diabetics are likely to reflect both structural and functional abnormalities of the arterial wall[21]. Age, hypertension, diabetes, and renal disease are already known to increase arterial stiffness.

In this study, we observed a strong association between the hfPWV and risk factors including hypertension, diabetes, age, and male gender. There have been several reports on the relationship between PWV and various biochemical markers. Kullo et al.[22] found a significant correlation between C-reactive protein (CRP) and arterial stiffness but our study showed no significant association between highly sensitive-CRP (hs-CRP) and PWV. However, hs-CRP was measured in only 49 subjects, a number insufficient to adequately evaluate this association.

There are several limitations in this study. Being a retrospective study, we could not control the baseline gender ratio in the two comparison groups. Though our study population was large, the number of female smokers was relatively small. Secondly, we did not specify current smokers from past smokers. Some reports showed that passive smoking affects arterial stiffness but we did not consider passive smoking in our study. Thirdly, because the smoking history was self-reported, accuracy of information such as smoking duration is questionable.

In conclusion, we found a significant difference in the hfPWVs between smokers and non-smokers. We observed

that chronic cigarette smoking increased central arterial stiffness in Korean subjects. A prospective, randomized controlled trial would be helpful in confirming our results on the chronic effects of smoking on arterial stiffness.

요 약

연구배경: 흡연은 중요한 심혈관계 위험요소 중의 하나이고, 흡연 직후에 동맥의 경직도가 증가되는 것은 이미 알려진 사실이다. 우리는 이번 연구를 통하여 만성적인 흡연이 동맥경직도에 어떠한 영향을 끼치는지 연구하였다.

방법: 2004년 7월부터 2008년 6월까지 18세 이상 광주보훈병원 내원 환자를 대상으로 641명의 흡연자와 2,044명의 비흡연자를 대상으로 분석하였다. 동맥경화도 지표인 맥파 전파속도(pulse wave velocity, PWV)와 C-반응 단백 등을 조사하였다.

결과: 남성들이 흡연율이 높았다. 중심동맥 경직도를 반영하는 심장-대퇴동맥(heart-femoral) 맥파전파속도(1083.6±264.1 cm/sec vs. 1041.3±257.3 cm/sec, $p<0.001$)는 비흡연군에 비해 흡연군에서 더 높은 경향을 보였다. 흡연기간과 맥파전파속도 사이에는 선형의 상관관계는 보이지 않았다 ($r= -0.225$, $p=0.506$). 말초 동맥경화 질환을 나타내는 발목-상완 혈압지수(ankle-brachial index)는 두 군간에 차이가 없었다. 다중회귀분석을 통한 심장-대퇴동맥 맥파전파속도(heart-femoral PWV)에 영향을 미치는 인자는 나이, 고혈압, 당뇨, 그리고 남성이었다.

결론: 만성적인 흡연은 중심 대동맥 경직도를 증가시킨다. 이는 심혈관계 질환의 위험요소이다.

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