Influence of Systolic Blood Pressure and Cigarette Smoking on Endothelial Function in Young Healthy People

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Background  Flow-mediated dilatation (FMD) of the brachial artery represents systemic endothelial function, so the relationship between FMD and blood pressure (BP) profile, in relation to the effects of cigarette smoking, was investigated in young healthy subjects.

Methods and Results  The 62 healthy subjects (14 females, 48 males; mean 29.7±5.5 years old), were divided into a smoking group (n=30) and non-smoking group (n=32). FMD was induced by reactive hyperemia. It was lower in the smoking group than in the non-smoking group (P<0.05). In the non-smoking group, there was an inverse correlation (r=–0.59, P<0.0005) between FMD and systolic BP (SBP), which was not recognized in the smoking group. Multiple stepwise regression analysis revealed that FMD was predicted by either the SBP or the brachial artery diameter in the non-smoking group, whereas it was predicted by the brachial artery diameter in the smoking group. Subdivision by cut-off value of SBP=120mmHg demonstrated that although FMD with SBP<120mmHg was preserved in subjects in the non-smoking group, it was depressed to a level comparable with SBP≥120mmHg in the smoking group.

Conclusions  Highly-preserved FMD in subjects with SBP<120mmHg appears to be impaired by cigarette smoking, resulting in a loss of association between FMD and SBP.  (Circ J 2009; 73: 174–178)

Key Words:  Blood pressure; Endothelial function; Flow-mediated dilatation; Smoking

Endothelial dysfunction is a disease process that occurs throughout the vascular system and results in abnormal regulation of blood vessel tone and the loss of the atheroprotective properties of normal endothelium.1-2 Endothelial dysfunction is, therefore, emerging as an important pathogenic mechanism for atherosclerosis and may be an early manifestation of certain cardiovascular diseases.3 Flow-mediated dilatation (FMD) of the brachial artery, as induced by reactive hyperemia, has been convincingly demonstrated to reflect systemic endothelium-dependent vasodilatory capacity, which is mediated by nitric oxide (NO).3-8 FMD correlates with systolic blood pressure (SBP) and diastolic blood pressure (DBP) in relatively young healthy individuals,9 and FMD of the brachial artery is known to be impaired by hypertension in middle-aged individuals.10 However, less is known regarding the relationship between FMD and blood pressure (BP) profile in young healthy individuals. Cigarette smoking is an established risk factor for cardiovascular disease and the leading preventable cause of coronary artery disease and death.11 It reduces FMD in asymptomatic, young adults, consistent with an early stage of endothelial dysfunction,12,13,14 which we recently confirmed in the present study, therefore, we investigated whether an inverse relationship between FMD and SBP would be observed even in young healthy subjects, with special attention to the effects of cigarette smoking.

Methods

Study Population

We enrolled 62 healthy subjects, 20–40 years of age (mean 29.7±5.5 years; 14 females, 48 males). None of the participants had a history of hypertension (SBP≥140mmHg or DBP≥90mmHg), a pulse pressure (PP) >60mmHg, hypercholesterolemia, dyslipidemia, thyroid disease, or diabetes mellitus. Further, none of the participants took antioxidants or cardiovascular medications before or during this study. Of the 62 subjects, 30 (30.1±5.5 years) were active cigarette smokers with a mean cumulative nicotine consumption of 10.3±8.1 pack/years, and were thus assigned to the smoking group. The remaining 32 subjects (29.3±5.5 years) did not have a history of cigarette smoking and were assigned to the non-smoking group. Based on the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004), the subjects in each group were subdivided into those with SBP<120mmHg (optimal) or SBP>120mmHg (normal/high-normal). One pack/year was defined as smoking 20 cigarettes per day for 1 year.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the institutional ethics review board. Written informed consent was given by all subjects.

Assessment of FMD and NMD

Endothelium-dependent FMD in response to reactive hyperemia and endothelium-independent nitroglycerin-induced dilatation (NMD) were examined in the brachial
artery according to the method described by Celermajer et al. Using a 7.5-MHz linear array transducer (model SSH-160A; Toshiba, Tokyo, Japan) longitudinal B-mode ultrasound images of the right brachial artery above the antecubital fossa were taken after a 10-min rest. The ultrasound images were recorded on a Super-VHS videocassette recorder (model BR-S601M; Victor, Tokyo, Japan). The arterial diameter was measured at a fixed distance from an anatomical marker. The measurements were taken from the anterior to the posterior interface between the media and adventitia (ie, the “m” line) at end-diastole, coincident with the R wave on the continuously recorded electrocardiogram. After initial automatic measurements (model BP-203RPE; Nihon Colin) of SBP, DBP, mean BP (MBP), PP, and heart rate (HR), the subjects lay down and rested for 10 min. After the initial brachial arterial diameter was measured, a BP cuff was placed proximal to the imaging transducer and inflated to at least 50 mmHg above SBP for exactly 5 min. The diameters during 3 cardiac cycles were analyzed for each scan, and the measurements were averaged. The diameter measurements for reactive hyperemia were obtained 45–90 s after deflation of the cuff in order to measure the peak diameter. The baseline resting brachial artery dimension was again obtained 10 min later. Thereafter, subjects were given 0.3 mg sublingual nitroglycerin spray, and the brachial artery was imaged 3–5 min later to determine the peak diameter. The FMD and NMD were calculated as the percent change in diameter compared with the baseline. The ultrasound scans were analyzed by 1 observer who was unaware of the identity of the volunteer and the study phase. The coefficients of variation of FMD and NMD for repeated within-subject measurements were 2.7% and 3.0%, respectively.

**Statistical Analysis**

Data are presented as the mean ± SD. Statistical analysis was performed using StatView statistical software, version 5.0. Differences between 2 groups were analyzed by Student’s t-test, chi-square test or Fisher’s exact probability test. A value of P<0.05 was considered statistically significant. Pearson correlation analysis was performed to assess potential relationships between the brachial-ankle pulse wave velocity and other clinical variables. A value of P<0.05 was considered statistically significant. Stepwise multiple regression analysis was performed to determine the independent variables for FMD. In our multivariate analysis, F values ≥ 4 were considered significant. One-way ANOVA was used to test differences in FMD between optimal BP groups and normal/high-normal BP groups.

**Results**

**Study Population**

The clinical characteristics of the non-smoking and
smoking groups are summarized in Table 1. No significant differences existed between the 2 groups with respect to age, gender, body mass index, SBP or DBP, MBP, PP or HR. FMD was lower in the smoking group than in the non-smoking group (P<0.05); however, there was no significant differences between the 2 groups regarding NMD or brachial artery diameter.

**Correlation Between FMD and Clinical Variables**

Table 2 shows the Pearson’s correlation of FMD with various clinical variables in each group. In the non-smoking group, the FMD correlated with SBP (P<0.0005), DBP (P<0.05), MBP (P<0.005), PP (P<0.01), and brachial artery diameter (P<0.0005). In the smoking group, it correlated with the subject’s age (P<0.05), cumulative nicotine con-
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Discussion

The core findings of the present study are that (1) FMD was lower in the smoking group than in the non-smoking group, (2) although SBP showed an inverse correlation with FMD as a predictor for FMD by multiple stepwise regression analysis in the non-smoking group, such a correlation could not be observed in the smoking group, and (3) FMD in subjects with SBP <120 mmHg was higher than that in subjects with SBP ≥120 mmHg. Thus, our results indicate that, even in normotensive young health subjects, endothelial function in subjects with SBP ≥120 mmHg is impaired when compared with those with SBP <120 mmHg. Our results also demonstrated that highly-preserved endothelial function in optimal BP subjects can be particularly impaired by cigarette smoking, resulting in a loss of association between FMD and SBP. All subjects with SBP <120 mmHg had DBP <80 mmHg, indicating that they had optimal BP (JSH 2004). Smoking and hypertension are important factors that impair forearm endothelial function, as evaluated by the FMD method16,17 which is essentially consistent with our observations.

Brachial artery diameter was comparable in the non-smoking and smoking groups by multivariate analysis, and was a predictor for FMD. In our study, there was no difference between the non-smoking and smoking groups for brachial artery diameter. There have been several studies of the relationship between FMD and brachial artery diameter, all of which have demonstrated an inverse correlation.18-20 Although the physiological mechanism remains undetermined, Gnasso et al hypothesize that a greater diameter might reflect partial vasodilation, such that the residual capacity to dilate in response to ischemia is reduced.18 Consistent with that theory, our analysis revealed an inverse correlation between brachial artery diameter and nitroglycerin-induced vasodilation in the non-smoking group, which was not observed in the smoking group (Fig 2). Taken together, these results suggest that the brachial artery in the non-smoking group was already partially dilated at baseline, the underlying mechanisms of which should be studied in the future.

The effects of BP on FMD have been established.11,21 Ward et al demonstrated that the prevailing 24-h ambulatory SBP was inversely related to FMD in 155 patients with hypertension and 40 normotensive control subjects, independent of potential influences of antihypertensive treatment or the presence of cardiovascular disease risk factors, and they suggested that for every 10 mmHg increase in SBP there would be a corresponding 0.5% decrease in FMD response.11 More recently, Plavnik et al showed that in a healthy normotensive (SBP <140 mmHg) population aged 35–50 years, without any risk factor for atherosclerotic disease, subjects with SBP ≥115 mmHg, when compared with subjects with SBP <115 mmHg, had a significant reduction in FMD for every 10 mmHg increase in SBP.22 In agreement with them, our study demonstrated that FMD was lower in subjects with SBP <120 mmHg than in those with >120 mmHg in the non-smoking group.

Besides SBP, there is evidence that cigarette smoking depresses endothelial function.13,14,23 Celermajer et al3 investigated the consequences of long-term cigarette smoking in 200 young adults by using external ultrasound imaging with analysis of vessel diameter changes because of hyperemia and after nitrate application, and demonstrated an inverse relationship between FMD and lifetime cigarette exposure, which is in agreement with our findings. However, they treated all subjects as normotensive and did not estimate the detailed effects of BP on FMD.3 It is noteworthy that it has been recently demonstrated that FMD is impaired by passive smoking in a much younger population. Kallio et al demonstrated that exposure to environmental tobacco smoke, confirmed by serum cotinine concentration, a metabolite of nicotine in a dose-dependent manner impairs endothelial function in 11-year-old children.23 Those observations suggest that smoking can impair the well-preserved FMD in young healthy subjects. Oxidative stress may largely account for the nicotine-induced endothelial dysfunction in humans. In fact, a recent experimental study demonstrated that chronic exposure to nicotine and an acute infusion of nicotine impairs endothelium-dependent arteriolar dilatation by increasing oxidative stress.24 On the other hand, cigarette smoking increases the release of the sympathetic neurotransmitter, norepinephrine, and the adrenomedullary hormone, epinephrine.25,26 Supposing that these hormones are increased in smoking subjects, their potential vasoconstrictive effects may partly explain our finding that FMD was depressed in the smoking group, whereas no difference in NMD was observed between the non-smoking and smoking group.

In the present study, it is noteworthy that FMD had a negative correlation with the BP components in the non-smoking group, but that such a correlation could not be observed in the smoking group. The fact that greatly-preserved FMD in subjects with SBP <120 mmHg were particularly impaired in the smoking group may explain the disappearance of the inverse relationship between FMD and SBP.

Study Limitation

We included several young female subjects and previous studies have shown that during the menstrual cycle, FMD is higher in healthy, young women during the follicular
phase than in either the luteal or menstrual phase\textsuperscript{26,27}. Large and small vessel endothelial function increases during the follicular phase, declines after ovulation, and then rises again during the luteal phase\textsuperscript{27}. Dividing the subjects into female and male subgroups, clinical variables that influence FMD are distinct between female and male subjects (data not shown). We need to clarify the sex-specific effects of the BP components and cigarette smoking on endothelial function in future studies.

Conclusions

Our results suggest that FMD negatively correlates with SBP even in healthy subjects. In such a population, smoking might depress FMD, with a large influence of cumulative nicotine consumption, resulting in the loss of the negative correlation between FMD and BP.

References