Oral Vitamin C Ameliorates Smoking-induced Arterial Wall Stiffness in Healthy Volunteers

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We have investigated whether the oral administration of vitamin C could prevent smoking-induced acceleration of arterial stiffness in healthy volunteers. Subjects were pre-treated with 2 g vitamin C and their heart rate (HR), mean blood pressure (MBP), and brachial-ankle pulse wave velocity (baPWV) were measured before and after smoking. Smoking significantly increased the HR, MBP, baPWV (13, 6.4, 7.0%). Vitamin C treatment significantly reduced the smoking-induced elevation in baPWV at 0 min (– 58.5%, p = 0.0002) without affecting HR or MBP. These findings suggest that oral vitamin C treatment prevents smoking-induced acceleration in arterial stiffness through reducing endothelial dysfunction. J Atheroscler Thromb, 2004; 11: 354–357.

Key words: Arterial stiffness, Smoking, Vitamin C, Endothelial function

Introduction

Cigarette smoking is a major risk factor for cardiovascular disease (1) and has been reported to cause endothelial dysfunction (2). The mechanisms of smoking-induced endothelial dysfunction are not fully understood, although this pathology has been attributed to increased oxidative stress reducing the bioavailability of endothelium-derived nitric oxide in arteries (3, 4). Pulse wave velocity (PWV) is known to be an indicator of arterial stiffness, which has been shown to be an independent predictor of all-cause cardiovascular mortality (5). Recently, smoking has been reported to increase PWV in young chronic smokers (6), which is more prominent than that in non-smokers. Antioxidant vitamin C has been reported to improve endothelial function in chronic smokers (7), indicated by forearm blood flow responses.

Therefore, the present study was designed to investigate whether the oral administration of vitamin C could prevent the smoking-induced PWV acceleration in healthy volunteers.

Research Design and Methods

Seventeen healthy male volunteers were recruited from 4 day health check up program participants in the Japan Self Defense Forces Central Hospital. They were aged between 51–55 (52.9 ± 0.1) with no history of illness or medication. Criteria for exclusion included fasting plasma glucose > 7 mmol/l, systolic blood pressure > 160 mmHg, diastolic blood pressure > 95 mmHg, history of myocardial infarction, cerebral infarction, or peripheral vascular disease, any use of regular medication including supplements or any previous surgical therapy. The hospital ethical review committee approved all procedures and protocols, and written informed consent was obtained from all subjects before enrollment.

The subjects received a placebo on day 2 and vitamin C on day 3 during the 4 day medical check up program. All subjects were not allowed to smoke for at least 3 h before each examination. All hemodynamic measurements were performed after 15 to 20 min of supine rest in a quiet room with a controlled temperature of 23°C. Each subject was studied at 2 h after a single oral administration of either 2 g of vitamin C or placebo. This dose was chosen to replicate the beneficial effects observed by Levine et al. (7) and Raitakari et al. (8). In the former study, plasma ascorbic acid levels in response to a 2 g oral dose reached plateau after 2 hours and re-
mained elevated 5 hours after the administration. Measurements were performed three times before, and 0, 5, 10 and 15 minutes after, smoking one cigarette containing 1.0 mg nicotine (Mild Seven filter, JT, Tokyo, Japan). The way of smoking a cigarette was not standardized unless the whole cigarette had to be smoked within 5 min. The baseline value for each parameter was expressed as an average of three measurements. baPWV was measured using a volume-plethymographic apparatus (Form PWV/ABI; Colin, Co., Ltd., Komaki, Japan), recording PWV, blood pressure, electrocardiogram, and heart sounds simultaneously, and the reproducibility and coefficient of variation of interobserver and intraobserver for each measurement was 0.98, 0.87; 8.4%, 10.0%, respectively, as previously described (9).

Data are expressed as mean ± standard error. Statistical analyses of the time-response curves for smoking, with or without pretreatment of vitamin C, used two way repeated-measures analysis of variance (ANOVA) followed by parametric tests (Student pared t tests). All statistical analyses were performed using the Stat View software version 4.5 (SAS Institute). A level of \( p < 0.05 \) was considered the minimum level for statistical significance.

**Results**

The characteristics of the study subjects were as follows: history of smoking, 34.5 ± 1.8 pack-years; body mass index, 22.5 ± 0.3 kg/m²; total cholesterol, 5.8 ± 0.3 mmol/l; LDL cholesterol, 3.5 ± 0.3 mmol/l; HDL cholesterol, 1.64 ± 0.10 mmol/l; triglycerides, 1.43 ± 0.19 mmol/l; and blood pressure, 117 ± 3/75 ± 9 mmHg with mean blood pressure (MBP) 98.1 ± 2.7 mmHg (Table 1).

Mean values of heart rate (HR), MBP and baPWV were significantly increased immediately after smoking by 12.9 ± 2.1 (\( p < 0.0001 \)), 6.4 ± 1.6 (\( p = 0.0011 \)) and 7.1 ± 0.9%, (\( p < 0.0001 \)), respectively (Fig. 1, Fig. 2, Fig. 3). While SBP and DBP were also significantly increased after smoking by 7.0 ± 1.8 (\( p = 0.0026 \)) and 7.2 ± 1.8% (\( p = 0.0009 \)), pulse pressure was not significantly increased (7.2 ± 3.5%; \( p = 0.057 \), 9.5 ± 3.5%; \( p = 0.052 \)). Elevated HR was sustained at least for 15 minutes after smoking (Fig. 2), whereas baPWV and MBP recovered within 10 minutes (Fig. 1, Fig. 3). Elevated SBP and DBP were also recovered within 10 minutes. With vitamin C treatment, HR and MBP as well as SBP and DBP were still significantly increased after smoking by 13.5 ± 1.6 (\( p = 0.0001 \)) and 6.3 ± 1.5 (\( p = 0.0006 \)), 7.3 ± 1.3 (\( p = 0.0026 \)), 6.4 ± 1.3% (\( p = 0.0002 \)) respectively (Fig. 1, Fig. 2, Fig. 3, data of SBP and DBP not shown), while baPWV was increased by 2.9 ± 0.6%, which was not significant (\( p = 0.0747 \)) (Fig. 1). In other words, vitamin C treatment significantly reduced the smoking-induced elevation in baPWV at 0 min (59.2% reduction, \( p = 0.0002 \)) without affecting HR.

**Table 1.** Baseline characteristics of the study subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>22.5 ± 0.3 kg/m²</td>
</tr>
<tr>
<td>History of smoking</td>
<td>34.5 ± 1.8 pack-years</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.8 ± 0.3 mmol/l</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>3.5 ± 0.3 mmol/l</td>
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<tr>
<td>HDL cholesterol</td>
<td>1.64 ± 0.10 mmol/l</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.43 ± 0.19 mmol/l</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>117 ± 3 / 75 ± 9 mmHg</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>98.1 ± 2.7 mmHg</td>
</tr>
</tbody>
</table>
MBP, SBP or DBP. During the study, no one had significant changes in their electrocardiographs.

**Discussion**

PWV has been reported to correlate with coronary events and is regarded as an early marker of atherosclerosis. Form ABI/PWV is a recently developed device to measure baPWV, which uses a method different from conventional carotid-femoral PWV measurement and yields values of baPWV higher than those of past methods. However, the values of baPWV are reported to correlate significantly with those of PWV obtained using the past methods and with carotid IMT (10).

The acute hemodynamic effects of cigarette smoking have been reported to be mainly attributed to nicotine (11). The increase in HR and BP have been demonstrated to result from activation of the sympathetic nervous system (12, 13). Indeed, both oral (14) and transdermal (15) administration of nicotine has been demonstrated to increase HR and MBP in healthy volunteers and to mimic smoking-induced endothelial dysfunction. Nicotine also has been shown to result in a marked inhibition of nitric oxide release leading to reduced endothelial arteriolar dilatation (16), which was preventable with superoxide dismutase (17). These data suggest that both sympathetic nerve activation, and nitric oxide related endothelial dysfunction, are involved in smoking-induced hemodynamic effects.

In the present study, HR, MBP, SBP, DBP and baPWV increases were of short duration, although the HR increase was sustained for a longer period compared to the other parameters. These data suggest that HR might be regulated differently from the other parameters. Vitamin C treatment significantly inhibited the smoking-induced increase in baPWV, but did not affect HR, MBP, SBP or DBP. Vitamin C has been reported to prevent smoking-and/or nicotine-induced endothelial dysfunction indicated by forearm blood flow responses (8). baPWV mainly reflects large artery stiffness but also has been reported to reflect endothelium-dependent peripheral vasodilatation (18). Furthermore, Failla et al. has demonstrated cigarette smoking reduces distensibility not only in the radial artery but also in the carotid artery (19), causing a systemic artery stiffening. Vlachopoulos et al. has recently demonstrated that cigarette smoking increases PWV more greatly in the radial artery than in the aortic artery of young male smokers, and the increase remained significant after adjustment for blood pressure suggesting a direct effect on aortic wall possibly mediated through endothelial dysfunction (20). Together with these findings, endothelial function might play at least in part a role in the mechanisms of vitamin C inhibition of the baPWV elevation induced by smoking, though further studies are needed to clarify this.

Although the short-term effect of vitamin C to prevent endothelial dysfunction, as seen in this study, has been reported, long-term effects of the compound are controversial (8, 21). Therefore, our data cannot be extrapolated as showing a beneficial effect of daily use of vitamin C for vascular protection in chronic smokers with established endothelial dysfunction. Cessation of smoking should be strongly encouraged in such individuals.

In conclusion, the oral administration of vitamin C significantly inhibited smoking induced acceleration in arterial stiffness indicated by baPWV, which was independent of HR and BP, suggesting that an antioxidant effect on endothelial dysfunction might play at least in part in this situation.

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**References**


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