Acute and Chronic Effects of Smoking on Arterial Stiffness

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Background: The brachial–ankle pulse wave velocity (baPWV) and cardio-ankle vascular index (CAVI) are used to evaluate arterial distensibility. The purpose of this study was to elucidate the acute and chronic effects of smoking on arterial stiffness as measured by baPWV and CAVI.

Methods and Results: Ten male smokers were studied to evaluate the acute effect of smoking on arterial stiffness. To elucidate the chronic effect of smoking on arterial stiffness, 160 male active smokers were analyzed. CAVI and baPWV were calculated by measuring the pulse volume record, blood pressure (BP), and vascular length from heart to ankle. CAVI and baPWV were measured using a VaSera VS-1000. In the acute study, baPWV and CAVI increased immediately after smoking 1 cigarette. In the chronic study, baPWV and CAVI significantly correlated with mean BP (MBP) and the Brinkman index. In multiple regression analysis, baPWV independently correlated with MBP, and CAVI independently correlated with the Brinkman index, but not with MBP. Receiver-operating characteristics (ROC) curves of baPWV and CAVI to predict Brinkman index ≥500 demonstrated that the area under the ROC curve of CAVI was higher than that of baPWV.

Conclusions: Smoking causes a significant increase in arterial stiffness as measured by baPWV and CAVI. CAVI correlated with the Brinkman index, which suggests that CAVI is a useful index of the degree of arterial stiffness caused by smoking. (Circ J 2011; 75: 696–702)

Key Words: Arterial stiffness; Brachial–ankle pulse wave velocity (baPWV); Cardio-ankle vascular index (CAVI); Smoking

Cigarette smoking is a major risk factor for cardiovascular disease.5–5 Smoking alters arterial function through several mechanisms, including endothelial dysfunction, unfavorable changes in the lipid profile, and abnormal thrombohemostasis.6 Flow-mediated dilatation in subjects with systolic blood pressure (SBP) <120 mmHg appears to be impaired by cigarette smoking.7 Smoking has been reported to reduce arterial distensibility in both medium and large arteries.8 Carotid–femoral pulse wave velocity (PWV) has been used as a noninvasive clinical index of aortic stiffness9,10 and smoking causes a significant increase in this index.11,12 Cigarette smoking induces global changes in both peripheral and central vascular function, even in young smokers.13

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A simple, noninvasive, and automatic method of measuring brachial–ankle PWV (baPWV) has been developed, and a close correlation between baPWV and aortic PWV has been reported.14 We previously reported that baPWV correlated with age in healthy subjects, suggesting that it reflects age-related changes in vascular stiffness.15 Although baPWV is a useful index of arterial stiffness, the drawback is that the result is affected by changes in blood pressure (BP) during measurement of PWV.16–17

Recently, an atherosclerotic index, the cardio-ankle vascular index (CAVI), was developed for measuring PWV and BP.17–19 CAVI is adjusted for BP based on the stiffness parameter β and measures arterial stiffness independent of BP. We have previously reported that the correlation of CAVI with SBP was weaker than the correlation of baPWV with SBP, and CAVI was not affected by changes in BP during measurement.19 CAVI has been associated with the presence and severity of coronary atherosclerosis.20 Furthermore, high CAVI implies progression of carotid and coronary atherosclerosis, and CAVI may be more closely linked with arteriosclerosis than baPWV.21

It has been reported that active smokers, as confirmed by cotinine levels, have worse arterial stiffness than nonsmokers, and long-term smoking can markedly increase arterial stiffness.22 However, to the best of our knowledge, there...
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have been no reports on the comparative effect of smoking on baPWV and CAVI. Thus, the purpose of this study was to elucidate the acute and chronic effects of smoking on arterial stiffness as measured by baPWV and CAVI.

### Methods

**Acute Effect of Smoking**

We studied 10 male active smokers (mean age, 35±6 years) to evaluate the acute effect of smoking on arterial stiffness. None of the participants had hypertension, diabetes mellitus, hypercholesterolemia or cardiac disease, and they were not taking any medications.

First, baPWV and CAVI were measured using a Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan) after a 5-min rest. Next, all subjects smoked 1 cigarette for 5 min while supine, and baPWV and CAVI were measured after smoking.

**Chronic Effect of Smoking**

We enrolled 160 male active smokers undergoing routine health checkups at JA Kagoshima Kouseiren Medical Health Care Center. From the personal interviews it was ascertained that 8 subjects were receiving treatment for hypertension, 4 for diabetes mellitus, and one for hyperlipidemia. One subject had a history of ischemic heart disease, and one had a history of stroke. Information on smoking history was obtained from a self-administered questionnaire. This study included 5 subjects with low estimated glomerular filtration rate (eGFR <60 ml·min⁻¹·1.73 m⁻²). eGFR was calculated by the equation of the Japanese Society of Nephrology: eGFR = 194 × Cr⁻¹.094 × age⁻⁰.₂⁸⁷ (ml·min⁻¹·1.73 m⁻²).

Blood samples were collected after the subjects fasted overnight. The serum concentrations of total cholesterol, triglycerides (TG) and high-density lipoprotein-cholesterol were measured by standard laboratory procedures, and that of low density lipoprotein-cholesterol (LDL-C) was calculated by the Friedewald equation. Eight subjects with a serum TG concentration of 400 mg/dl or higher did not have their LDL-C calculated because the Friedewald equation is unsuitable for TG values above this level.

All subjects underwent measurements of baPWV and CAVI using a Vasera VS-1000 after 5 min at rest.

### CAVI and baPWV Measurements

CAVI and baPWV were measured using a Vasera VS-1000 (Fukuda Denshi, Tokyo, Japan) as reported previously. In brief, cuffs were applied to the 4 extremities and electrocardiographic electrodes attached to the upper arm. A microphone was placed on the sternal angle for phonocardiography. The subjects then rested supine for 5 min. PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same waves were transmitted to the ankle, and

### Table 1. Changes in BP and Heart Rate After Smoking 1 Cigarette

<table>
<thead>
<tr>
<th></th>
<th>Before smoking</th>
<th>After smoking</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>120±9</td>
<td>124±11</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>75±9</td>
<td>77±9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>92±9</td>
<td>94±10</td>
<td>0.30</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>63±9</td>
<td>74±8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BP, blood pressure.
the time difference between the second heart sound on the phonocardiogram and the notch of the brachial pulse wave.\textsuperscript{17,19,23} To minimize cuff inflation effects on blood flow dynamics, pulse waves were measured with the cuffs inflated to less than the diastolic BP (DBP) (50 mmHg). The extremity BP was then measured by oscillometry. SBP, DBP and pulse pressure (PP) were obtained by measuring BP at the right brachial artery.

CAVI was calculated by the following equation: CAVI = \( a \times \frac{1}{\text{SBP}_1} \times \frac{1}{\text{DBP}_1} \times \frac{\ln (\text{SBP}_2/\text{DBP}_2)}{\text{PWV}_2} + b \) (\( \rho \) density of blood, a and b: constants).\textsuperscript{18,19,23}

In this study, there were no subjects with peripheral artery disease as documented by an ankle–brachial index less than 0.9. The protocol used for the present study was approved by the institutional review board of Kagoshima University. Informed consent was given by all the volunteers.

**Statistical Analysis**

Data are expressed as the mean±SD. Differences between the mean values at 2 time points of measurement were analyzed by a paired t-test. The relationship between continuous variables was analyzed by linear regression analysis. The independence of the association between variables was tested with multiple regression analysis. Statistical analyses were performed with Stat View, version 5.0, and receiver-operating characteristics (ROC) curve analysis was performed with JMP version 5.1.1. P values less than 0.05 were considered statistically significant.

**Results**

**Acute Effect of Smoking on baPWV and CAVI**

We analyzed the acute effect of smoking on baPWV and CAVI in 10 male active smokers. The mean age was 35±6 years, mean height was 172±5 cm and mean body weight was 68±8 kg. Table 1 demonstrates the changes in BP and heart rate (HR) after smoking 1 cigarette. HR and DBP significantly increased immediately after smoking 1 cigarette (HR: 63±8 to 74±8 beats/min, P<0.001; DBP: 75±9 to 77±9 mmHg, P<0.05), and SBP tended to increase immediately after smoking. Figure 1 shows the changes of baPWV and CAVI immediately after smoking 1 cigarette. Both baPWV and CAVI significantly increased after smoking (baPWV: 1.17±1.15 to 1.22±1.12 cm/s; CAVI: 7.0±0.9 to 7.3±0.7, P<0.01).

**Chronic Effect of Smoking on baPWV and CAVI**

The clinical characteristics of the 160 male smokers are summarized in Table 2. The mean age was 46±12 years, and the mean BP (MBP) was 99±13 mmHg. The mean baPWV value was 1,327±239 cm/s and the mean CAVI value was 8.3±1.3. Table 3 shows the relationship between baPWV or CAVI and the other clinical variables. baPWV significantly correlated with age, TG, fasting blood sugar, uric acid (UA), MBP and the Brinkman index. In contrast, CAVI significantly correlated with age, TG, blood urea nitrogen, UA, MBP and the Brinkman index.

Multiple regression analysis was performed using baPWV
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or CAVI as an objective variable, and conventional atherosclerotic risk factors, such as age, TG, fasting blood sugar, UA, MBP and Brinkman index, as explanatory variables. This analysis revealed that baPWV independently correlated with age, UA and MBP. In contrast, CAVI independently correlated with age, TG, UA and the Brinkman index, but not with MBP (Table 4).

Figure 2 demonstrates the ROC curves of baPWV and CAVI to predict the median value of the Brinkman index (≥500). The area under the ROC curve (AUC) for baPWV was 0.63, with the highest discriminating sensitivity and specificity being 0.59 and 0.65, respectively at baPWV =1,276 cm/s. In contrast, the AUC for CAVI was 0.69 and the highest discriminating sensitivity and specificity were 0.60 and 0.72, respectively at CAVI =8.2. The AUC, sensitivity and specificity of CAVI were demonstrably higher than the values for baPWV.

Discussion

We have shown acute and chronic effects of smoking on arterial stiffness as measured by baPWV and CAVI. In the acute study, HR, DBP, baPWV and CAVI significantly increased after smoking just 1 cigarette. In the chronic study, baPWV and CAVI significantly correlated with age, the Brinkman index and MBP. In multiple regression analysis, baPWV independently correlated with age and MBP, but not with the Brinkman index, whereas CAVI independently correlated with age and the Brinkman index, but not with MBP. Furthermore, the ROC curves of baPWV and CAVI to predict the median value of the Brinkman index (≥500) demonstrated that AUC of CAVI was higher than that of baPWV. These results suggest that CAVI is a useful index that is independent of BP for evaluating the degree of arterial stiffness caused by smoking.

Therefore, our message for clinicians is that CAVI is a useful index of the arterial stiffness caused by smoking. We recommend measuring CAVI in current smokers and using the result to advise smoking cessation.

Acute Effect of Smoking on Arterial Stiffness

Previous studies have reported that smoking 1 cigarette increased carotid–femoral PWV.\(^{11,12}\) Similarly, we showed in this study that baPWV and CAVI significantly increased after smoking 1 cigarette. Acute cigarette smoking reduces distensibility not only in medium-sized but also in large elastic arteries.\(^8\) There are several mechanisms for the acute increase in arterial stiffness, including an increase in both circulating and local catecholamine levels caused by nicotine stimulating the sympathetic ganglia and increasing the central nervous system sympathetic neural discharge, and impaired nitric oxide (NO) production resulting in endothelial dysfunction.\(^11\) Plasma catecholamines are maximal at the end of a 10-min period of smoking and return to baseline levels 30 min after the start of smoking.\(^{24}\) Lekakis et al showed that endothelial dysfunction persisted for 90 min after smoking.\(^{25}\) These are possible mechanisms for the acute effects of smoking on the baPWV and CAVI.

Chronic Effect of Smoking on Arterial Stiffness

In the present study, baPWV and CAVI correlated with the Brinkman index in our linear regression analysis. Vascular dysfunction has been implicated as an early event in atherogenesis. A particularly important aspect of vascular function is the integrity of the L-arginine–NO–cyclic guanosine monophosphate pathway.\(^{26}\) Cigarette smoking is shown to be associated with reduced endothelial-dependent vasodilation, NO generation, and endothelial NO synthase activity.\(^{27}\) Flow-mediated dilatation (FMD) of the brachial artery has been demonstrated to reflect endothelium-dependent vasodilation. Yufu et al\(^{28}\) reported that FMD was independently predicted by baPWV in their smoking group, but not in their non-smoking group, and they suggested that the increased baPWV in the smokers was associated with a reduction in endothelium-dependent vasodilation.

In addition, it has been reported that smoking status relates to CAVI and that smoking cessation might improve CAVI.\(^{29}\)
Comparison of baPWV and CAVI

Although linear regression analysis demonstrated that both baPWV and CAVI correlated with the Brinkman index, multiple regression analysis showed that only CAVI independently correlated with the Brinkman index. We have already reported that the correlation between baPWV and SBP is closer than the correlation between CAVI and SBP,19 which is why baPWV correlated with SBP, but not with the Brinkman index, in multiple regression analysis in the present study. In addition, the ROC curves of baPWV and CAVI to predict the Brinkman index ≥500 demonstrated that the AUC of CAVI was higher than that of baPWV.

These results suggest that CAVI is superior than baPWV in evaluating the hemodynamic effect of smoking.

Study Limitations

Some limitations of this study should be considered when interpreting the results. First, we analyzed the effect of smoking on baPWV and CAVI in almost healthy subjects. Although we could evaluate the pure effect of smoking in these subjects, our results should be useful in relation to patients with atherosclerotic risk factors. Second, a small number of subjects was used to evaluate the acute effect of smoking. Additional studies in a larger population should be conducted. Third, the subjects included in the present study were only men, because the rate of women smokers was very low (4%). For this reason, the results of this analysis may not be applicable to women.

Conclusion

Smoking caused a significant increase in arterial stiffness as measured by baPWV and CAVI. Because it is independent of BP, CAVI may be a useful clinical method of evaluating the degree of the arterial stiffness caused by smoking.

References

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