Changes in Cardio-Ankle Vascular Index in Smoking Cessation


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**Aim:** To investigate the effect of smoking and smoking cessation on cardio-ankle vascular index (CAVI).

**Methods:** The subjects were 82 smokers (77 men, 64 ± 10 years) and 20 non-smokers (18 men, 61 ± 7 years). CAVI was measured every 3 months and CAVI severity was classified into 3 levels. Decreased, unchanged, and increased CAVI severity levels were coded as “improvement,” “no change,” and “exacerbation,” respectively. Smoking status was coded as “success” for complete abstinence, “partial success” for a reduced number of cigarettes, and “failure” for an unchanging number of cigarettes.

**Results:** Compared with non-smokers, smokers showed a higher CAVI (p < 0.05) prior to smoking cessation. Post-cessation, CAVI improved from 9.4 to 8.6 (p < 0.01) in “success” cases (n = 22), and the significant pre-cessation difference from non-smokers (n = 20, CAVI = 8.8) disappeared. With regard to the change in CAVI severity of each smoking status, “improvement” occurred in 17%, 24%, and 68% of “failure” (n = 35), “partial success” (n = 25), and “success” (n = 22) groups, respectively, and the “success” group was significantly higher than the other two groups.

**Conclusion:** The study showed that CAVI was increased by smoking, and complete smoking cessation improved CAVI.

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Key words: Cardio-ankle vascular index, Smoking cessation, Smoking

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**Introduction**

Recently, a novel arterial stiffness parameter called the cardio-ankle vascular index (CAVI) has been developed. CAVI reflects the stiffness of the aorta, femoral artery, and tibial artery as a whole, and one conspicuous feature is that theoretically CAVI is independent of blood pressure. CAVI is also well correlated with coronary stenosis, diabetes mellitus and metabolic syndrome.

Smoking has become a major social problem, given its harmful effects not only on smokers themselves, and particularly their cardiovascular, respiratory, and digestive systems, but also on people around them. Smoking cessation and continuous abstinence are often difficult to maintain, however, and the “five Rs” (relevance, risk, rewards, roadblocks, and repetition) have been proposed to guide effective smoking cessation. Four of these Rs emphasize the negative aspects of smoking. Rewards, the only positive aspect of non-smoking among the five Rs, is subjective and its effect cannot be assessed objectively.

We had an opportunity to measure the CAVI of people who reported smoking and smoking cessation. The smoking status of a person has been reported to be closely related to the CAVI. As a result, we tried to evaluate the relationship between smoking status and CAVI, and the positive aspect of smoking cessation.

**Case Presentation**

A 54-year-old man with hypertension, hyperlipidemia, and hyperuricemia, and a history of habitual smoking (20 cigarettes/day) attempted to quit smok-
ing in November 2005, but ended up smoking more, with a CAVI of 9.2 in February 2006. He stopped smoking again in March 2006, and this time maintained abstinence over approximately 3 months, with an improved CAVI of 7.6 in June. He resumed smoking in September, although he smoked fewer cigarettes; his CAVI in January 2007 had risen to 8.6 (Fig. 1). This case presentation shows that CAVI changed according to smoking status. This case shows a close connection between smoking status and CAVI.

**Aim**

The aim of this study was to investigate the effect of smoking and smoking cessation on CAVI.

**Methods**

The following subjects were excluded because these conditions can affect CAVI independently: ankle/brachial blood pressure ratio ≤ 0.9, arrhythmia, recent medication changes, untreated angina pectoris, acute myocardial infarction, valvular disease, renal failure, heart failure (ejection fraction <50%) and age over 80 years. The purpose of this study was explained to the subjects, and consent was obtained for participation in the study and also for release of the study data. The study was conducted in accordance with the Declaration of Helsinki guidelines.

**Measurement of CAVI**

CAVI was measured by the methods described previously. Briefly, cuffs were applied to bilateral upper arms and ankles, with the subject lying supine and the head held in the midline position. After resting for 10 min, the examinations were performed. To detect brachial and ankle pulse waves with cuffs, a low cuff pressure from 30 to 50 mmHg was used to ensure the minimal effect of cuff pressure on hemodynamics. Furthermore, blood pressure was measured thereafter. Finally, for the convenience of comparing with pulse wave velocity (PWV), scale conversion was performed. CAVI was calculated by the following formula:

\[
CAVI = \ln \left( \frac{P_s}{P_d} \right) \frac{\text{PWV}^2}{2\rho/\Delta P}
\]

where \(\ln\) is natural logarithm, \(P_s\) is systolic pressure, \(P_d\) is diastolic pressure, \(\Delta P\) is \(P_s-P_d\), and \(\rho\) is blood density. Blood pressure is obtained using a cuff on the upper arm, and PWV is obtained by dividing vascular length by the time for which the pulse wave is propagated from the aortic valve to the ankle, and is measured using cuffs on the upper arms and ankles. All measurements were automatically calculated using the VaSere VS-1000 (Fukuda Denshi Co Ltd, Tokyo, Japan). CAVI was calculated when there had been no change in smoking status and medications for 3 months, and there was a higher CAVI on the right or left.

As a method to evaluate age-dependent CAVI, we classified CAVI severity into the following 3 levels based on the mean and standard deviation (SD) in each age group (Fig. 2):

- Level I: CAVI < (−SD)
- Level II: (−SD) ≤ CAVI < (+SD)
- Level III: CAVI ≥ (+SD)

CAVI severity level II (mean ± SD) was deemed as within the normal range. Decreased, unchanged, and increased CAVI severity levels were coded as “improve-
Characteristics. Comparison of groups 3 months after smoking cessation

<table>
<thead>
<tr>
<th></th>
<th>Smokers</th>
<th>Non-smokers</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>35</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>172 ± 33</td>
<td>189 ± 41</td>
<td>197 ± 42</td>
</tr>
<tr>
<td>After</td>
<td>169 ± 25</td>
<td>181 ± 40</td>
<td>196 ± 42</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>148 ± 41</td>
<td>136 ± 61</td>
<td>146 ± 98</td>
</tr>
<tr>
<td>After</td>
<td>144 ± 56</td>
<td>136 ± 40</td>
<td>144 ± 99</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>45 ± 9</td>
<td>43 ± 18</td>
<td>51 ± 11</td>
</tr>
<tr>
<td>After</td>
<td>48 ± 10</td>
<td>49 ± 18</td>
<td>53 ± 12</td>
</tr>
<tr>
<td>Blood Sugar (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>116 ± 16</td>
<td>118 ± 30</td>
<td>111 ± 48</td>
</tr>
<tr>
<td>After</td>
<td>111 ± 21</td>
<td>112 ± 48</td>
<td>115 ± 35</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>6.1 ± 1.2</td>
<td>5.5 ± 1.4</td>
<td>5.9 ± 1.2</td>
</tr>
<tr>
<td>After</td>
<td>5.9 ± 1.9</td>
<td>5.4 ± 0.7</td>
<td>6.1 ± 1.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>23 ± 3</td>
<td>24 ± 3</td>
<td>23 ± 4</td>
</tr>
<tr>
<td>After</td>
<td>23 ± 4</td>
<td>24 ± 3</td>
<td>24 ± 5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>133 ± 20</td>
<td>134 ± 14</td>
<td>138 ± 14</td>
</tr>
<tr>
<td>After</td>
<td>136 ± 17</td>
<td>132 ± 19</td>
<td>134 ± 13</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>77 ± 15</td>
<td>79 ± 9</td>
<td>83 ± 10</td>
</tr>
<tr>
<td>After</td>
<td>75 ± 11</td>
<td>80 ± 11</td>
<td>84 ± 12</td>
</tr>
<tr>
<td>Pulse rate (beat per minutes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>65 ± 10</td>
<td>64 ± 12</td>
<td>67 ± 18</td>
</tr>
<tr>
<td>After</td>
<td>67 ± 11</td>
<td>61 ± 10</td>
<td>64 ± 19</td>
</tr>
</tbody>
</table>

Results

Of 102 subjects, 82 were smokers (77 cases [94%] men, 64 ± 10 years) and 20 were non-smokers (18 cases [90%] men, 61 ± 7 years). No smokers had used nicotine-replacement therapy of nicotine patches or nicotine gum.

Patient Characteristics

There was no difference in age, gender, clinical diagnoses, and oral medications between smoker and non-smoker groups (Table 1A).

Changes in the serum lipid profile, body mass index, blood pressure and pulse rate before and after smoking cessation were shown in Table 1B. Parameters did not shown any significant change during the present study (Table 1B).
CAVI of Smokers and Non-Smokers

Among smokers, although there were no group differences in the number of cigarettes consumed prior to smoking cessation, the number of cigarettes had actually increased in the “failure” group ($n=35$), had decreased to about half in the “partial success” group ($n=25$), and naturally was 0 in the “success” group ($n=22$) (Table 1C).

Although the “failure” group had a longer history of smoking than the “partial success” group, there was no difference on the Brinkman index.

There were no significant differences in the actual CAVI value before smoking cessation among the “failure”, “partial success”, and “success” groups, although they were all higher than in non-smokers. This suggests that the actual CAVI value is higher among smokers than non-smokers.

In terms of CAVI severity, there was no difference among levels I, II and III.

Effect of Smoking Cessation on Change in Actual CAVI Value (Fig. 3)

**Comparisons between Before and After Smoking Cessation**

Compared with the pre-cessation value, the actual CAVI value at 3 months post-cessation had decreased for the “partial success” and “success” groups; in particular, the decrease in the “success” group was significant.

**Comparisons After Smoking Cessation**

The actual CAVI value decreased gradually in the order of “failure” > “partial success” > “success” groups, and the actual CAVI value in the “success” group was significantly lower than that in the “failure” group ($p<0.01$). In the “partial success” and “success” groups, the significant pre-cessation difference from
non-smokers disappeared at post-cessation. These results suggest that the actual CAVI value may be improved by smoking cessation.

**Effect of Smoking Status on Change in CAVI Severity**

“Exacerbation” of CAVI severity occurred in 20% of both “failure” and “partial success” groups and there was no “exacerbation” in the “success” group (Table 2). CAVI severity did not change in about 60% of both “failure” and “partial success” groups and 32% of the “success” group, which was significantly lower than the “failure” group ($p < 0.05$).

The rate of “improvement” increased in the order of the “failure” (17%) < “partial success” (24%) < “success” (68%) groups, with the “success” group being significantly higher than the “failure” group ($p < 0.01$) and the “partial success” group ($p < 0.01$). These results indicate that positive effects can be expected by smoking cessation.

In the non-smoking sample, “no change” accounted for the majority (90%), while “exacerbation” and “improvement” each accounted for 5%. These results indicate that CAVI severity in non-smokers is not changed easily in 3 months.

**Factors Influencing the Rate of CAVI Change**

**Smoking Status**

The improvement in the rate of CAVI change was highest in the “success” group, with a rate significantly different from the “partial success” ($p < 0.05$) and “failure” ($p < 0.01$) groups. The difference between “partial success” and “failure” groups was not significant (Fig. 4). These results indicate that complete abstinence is the key to improving the rate of CAVI change, while reduced cigarette consumption may have little effect.

**Effect of Cigarette Consumption**

When the rate of CAVI change was compared among the four groups based on cigarette consumption, “0” group (i.e., “success” cases) had the highest rate, which was significantly different from any other group (Fig. 5A). These results indicate that complete abstinence is the key to improving the rate of CAVI change, while reduced cigarette consumption may have little effect.

Limiting the sample to “partial success” cases, we examined the relationship between the rate of CAVI change and cigarette consumption. The rate of “improvement” increased in the order of the “failure” (17%) < “partial success” (24%) < “success” (68%) groups, with the “success” group being significantly higher than the “failure” group ($p < 0.01$) and the “partial success” group ($p < 0.01$). These results indicate that complete abstinence is the key to improving the rate of CAVI change, while reduced cigarette consumption may have little effect.

### Table 2. Effect of smoking cessation on change in cardio-ankle vascular index severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Smokers (n=35)</th>
<th>Partial success (n=25)</th>
<th>Success (n=22)</th>
<th>Non-smokers (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level I</td>
<td>Level II</td>
<td>Level III</td>
<td>Level I</td>
</tr>
<tr>
<td>Exacerbation</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>No change</td>
<td>23</td>
<td>20%</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Improvement</td>
<td>0</td>
<td>0%</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01

### Fig. 4. Comparison of the rate of cardio-ankle vascular index (CAVI) change according to smoking state.
change by cigarette consumption and CAVI and found no significant correlation (Fig. 5B). Incidentally, in the 5 “partial success” cases that reduced cigarette consumption by half (i.e., −50%) compared with precessation, the rate of CAVI change was similar for “improvement” and “exacerbation,” with no fixed trend (Fig. 5B). These results suggest that definite effects of reduced cigarette consumption on the rate of CAVI change cannot be expected.

**Factor that Correlates to the Rate of CAVI Change**

In the “success” cases of smoking cessation (Fig. 6), there was a negative correlation between age and the rate of CAVI change; that is, younger age was associated with greater improvement in the CAVI. There was a negative correlation between the number of cigarettes consumed before smoking cessation and the rate of CAVI change; that is, the fewer cigarettes consumed prior to quitting, the better the improvement in the CAVI. There was a negative correlation between the history of smoking and the rate of CAVI change, where a shorter history of smoking was associated with greater improvement in the CAVI. There was a negative correlation between the Brinkman Index and the rate of CAVI change in that the smaller the Brinkman Index, the better the improvement in the CAVI. To summarize, in “success” samples, the rate of CAVI change was negatively correlated with age, the number of cigarettes consumed prior to quitting, a history of smoking, and the Brinkman Index.

With the rate of CAVI change as the dependent variable, multivariate analysis was performed to examine its explanatory variables. The most robust predictor was smoking history, followed by CAVI severity, and age; however, the number of cigarettes consumed before smoking cessation and the Brinkman index were not significant predictors (Table 3).

**Discussion**

In the case presentation, the possibility was shown that the smoking status relates to CAVI. For this clinical study, we evaluated the relationship between CAVI and the smoking status.

CAVI has been developed as a novel blood pressure-independent arterial wall stiffness parameter, which reflects the stiffness of the aorta, femoral artery, and tibial artery\(^1\), \(2\), \(11\)). CAVI measurement involves not only the elastic but also muscular artery. Then, it is suppressed to reflect the contraction of the smooth muscle cells, which is influenced by various vasoconstrictor factors, such as sympathetic nerves, stimulation by endothelium-derived contracting factors (e.g. angiotensin II, thromboxane A2, prostaglandin H2), a lack of endothelium-derived relaxing factors (e.g., nitrogen monooxide, prostacycline, natriuretic peptide) and also some stress from environmental factors.

In this study, we examined the relationship between CAVI and the smoking status. CAVI could reflect the smoking status, but is age-dependent. Thus, we defined CAVI severity according to 3 levels based on the mean and standard deviation in each age group. Even with this analysis, CAVI severity also reflected the smoking status. In non-smokers, “no
“change” accounted for the majority (90%); therefore, CAVI severity could be a reliable indicator, and reflected the effect of various environmental factors and stress. Our study showed that the improvement in the rate of CAVI change depends on the smoking status, but the difference between “partial success” and “failure” groups was not significant, indicating that reduced cigarette consumption may have little effect

Table 3. Multivariate analysis with rate of cardio-ankle vascular index change as a dependent variable

<table>
<thead>
<tr>
<th></th>
<th>RC</th>
<th>SE</th>
<th>SRC</th>
<th>t</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking history</td>
<td>1.347</td>
<td>0.349</td>
<td>1.493</td>
<td>3.858</td>
<td>0.0020</td>
</tr>
<tr>
<td>CAVI severity</td>
<td>-3.108</td>
<td>1.104</td>
<td>-0.415</td>
<td>-2.814</td>
<td>0.0146</td>
</tr>
<tr>
<td>Age</td>
<td>-1.245</td>
<td>0.490</td>
<td>-1.167</td>
<td>-2.543</td>
<td>0.0245</td>
</tr>
<tr>
<td>Cigarettes before</td>
<td>1.070</td>
<td>0.752</td>
<td>1.396</td>
<td>1.423</td>
<td>0.1782</td>
</tr>
<tr>
<td>Brinkman index</td>
<td>-0.012</td>
<td>0.016</td>
<td>-0.818</td>
<td>-0.728</td>
<td>0.4793</td>
</tr>
</tbody>
</table>

$r = 0.927; p = 0.0001$

RC: regression coefficient; SE: standard error; SRC: standard regression coefficient; CAVI: cardio-ankle vascular index
on the rate of CAVI change.

The effect of so-called light cigarettes that contain less nicotine and tar does not necessarily reduce nicotine concentration, but could instead raise it, and the blood concentration of nicotine and blood carboxyhemoglobin do not correlate, but are rather increased. The presumed mechanism for this is that even when the number of cigarettes consumed stays the same, upon switching to light cigarettes people may also alter their smoking style, such as smoking to a shorter butt length and inhaling more deeply; therefore, the health effects of light cigarettes should be anticipated to fall below expectations. In this study, there were improvement cases (17%) in the “failure” group and exacerbation cases (20%) in the “partial success” group. The mechanism of this result is also thought to result from a different smoking style.

In “success” cases, the rate of CAVI change showed strong associations with age and the smoking status, such as the number of cigarettes consumed prior to quitting, the history of smoking, and the Brinkman Index. Also, the incidence and mortality of coronary artery disease among smokers can be lowered to the levels of non-smokers within 1–5 years from smoking cessation. Furthermore, Meyer et al. reported an increase in cerebral blood flow 3 months after smoking cessation. We therefore measured the CAVI every 3 months as a yardstick. The effects of smoking cessation reportedly are not limited by age and gender; in addition, unlike other arteriosclerotic risk factors that cannot be controlled (e.g. age, gender, family history) or over which people have limited control due to strong genetic factors (e.g. hypertension, diabetes, dyslipidemia), smoking is one of the few risk factors allowing self-management. This is an aspect of the rewards that should be emphasized in motivating smokers to quit, and maintain abstinence from smoking.

Cigarettes contain various toxic substances. Nicotine, in particular, is quickly absorbed and has strong toxicity. Mediated by the adrenal gland, this acute action induces sympathomimetic actions including elevated blood pressure, increased heart rate, elevated arterial wall stiffness, and peripheral artery spasm. In the vascular wall, reduced prostacyclin synthesis leads to artery shrinkage, decreased vasoconstrictor reactivity, and decreased anticoagulative action; thromboxane A2 synthesis, however, does not become inhibited, resulting in increased coagulability and thus accelerated blood clot formation. In addition, large amounts of free radicals in cigarette smoke lower the activation of nitrogen monoxide, which in turn may obstruct the vasodilatation reaction in vascular wall cells. These are some of the examples of the many proposed mechanisms of cigarette smoke toxicity. Unlike other arteriosclerotic risk factors, these acute actions by nicotine show rapid emergence upon smoking and rapid alleviation upon cessation of smoking. These acute actions (especially arterial wall stiffness and/or spasm), we believe, are reflected in the CAVI after three months.

According to a research report investigating the effect of smoking on baPWV, a type of PWV, baPWV is not a very reliable measure for early detection of the effect of smoking. Clinically speaking, various arteriosclerotic risk factors interact to various degrees; therefore, it is a matter of course that measures of PWV, including the CAVI, cannot isolate the effect of smoking among all risk factors. Lastly, regarding the utility of the CAVI, we would like to emphasize the importance of taking advantage of its simplicity and high reproducibility, repeating measurements over time, and capturing the change over time.

**Study Limitations**

Our study has some limitations. First, there were very few subjects in this study, excluding failed smoking cessation. This result shows that smoking cessation is extremely difficult. Second, data on smoking characteristics in our study were collected via self-report and lacked objectivity; therefore, comparative studies using objective measures (e.g. nicotine concentration and blood carboxyhemoglobin at the time of the CAVI measurement) are needed. Third, our study was able to establish the effect of smoking cessation on the CAVI; however, its mechanisms must be elucidated via a multi-angled approach.

**Conclusions**

The CAVI is a simple and convenient, sensitive measure of the effect of smoking. Repeated CAVI measurements over time provide richer information than a single measurement. According to the evaluation based on the CAVI, few effects can be expected from reduced cigarette consumption as the effects manifest only with complete abstinence, and the effects of smoking cessation are determined by the past history of smoking. Our findings also suggest that the effect of smoking cessation may manifest itself relatively quickly, which would be a reward to motivate those who wish to quit, and maintain abstinence from smoking.
References