Original Article

Impact of Cardiovascular Risk Factors on Progression of Arteriosclerosis in Younger Patients: Evaluation by Carotid Duplex Ultrasonography and Cardio-Ankle Vascular Index (CAVI)

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Aim: To evaluate progression of arteriosclerosis using cardio-ankle vascular index (CAVI) and carotid duplex ultrasonography (DUS) in young and adolescent patients considered to be at risk of cardiovascular disease.

Methods: We evaluated the progression of arteriosclerosis using CAVI and carotid DUS in 240 young and adolescent patients. Dyslipidemia (DL), hypertension (HT), and diabetes mellitus (DM) were major cardiovascular risk factors. Patients were divided to 4 groups according to number of risk factors.

Results: In terms of risk factors, CAVI and CAVI difference (CAVI-D) were elevated only in the HT group (p=0.0290, p=0.0243 vs. no risk respectively). CAVI-D was positively associated with diastolic blood pressure (DBP). Mean intima-media thickness (IMT) was positively associated with LDL-C or systolic blood pressure, and negatively with HDL-C. Plaque score was associated with LDL-C or DBP. In patients with the 3 risk factors, CAVI, CAVI-D and mean IMT were significantly higher than in those without risk (p=0.0009, p=0.0042 and p=0.0151 respectively), and CAVI and CAVI-D were higher than in those with 1 risk (p=0.0204 and p=0.0231). Carotid plaque develops from around 30 years of age in Japan. Despite numbers of risk factors, there were no differences in CAVI, CAVI-D, mean IMT or plaque score between smoker and non-smoker groups.

Conclusion: In conclusion, an increase in the number of risk factors also results in progression of arteriosclerosis in young and adolescent patients. HT was the most important risk factor for arteriosclerosis in these patients.


Key words: Cardio-ankle vascular index (CAVI), Carotid duplex ultrasonography, Arteriosclerosis, Risk factor, Young and adolescent

Introduction

Arteriosclerosis is a major cause of cardiovascular events, and is associated with several adult diseases such as hypertension (HT), diabetes mellitus (DM), dyslipidemia (DL), obesity and metabolic syndrome. For direct evaluation of arteriosclerosis, carotid plaque and/or pulse wave velocity have been used widely in patients with these major risk factors.

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Accepted: July 18, 2013

Accepted for publication: December 8, 2013

In middle-aged and/or aged patients, carotid arteriosclerosis evaluated by carotid duplex ultrasonography (DUS) or pulse wave velocity (PWV) has been associated with the above disease states, and an increase in the number of such so-called ‘risk diseases’ may result in progression of arteriosclerosis. There are many published reports on the evaluation of arteriosclerosis using DUS and/or PWV and on the association between risk diseases and arteriosclerosis. However, the association between progression of arteriosclerosis and risk diseases has been poorly elucidated in young or adolescent patients.

However, PWV is unstable and appears to be influenced by blood pressure. Consequently cardio-ankle vascular index (CAVI) has been developed for
Arteriosclerosis in Young and Adolescent

Medical records and patient data were evaluated retrospectively. All patients underwent CAVI, carotid DUS, and blood testing within a 3-month period during the study. The 240-patient group comprised 161 males aged from 20 to 44 years of age (median age 38.0 and interquartile range 35.0-41.0 years old), and 79 females also aged from 20 to 44 years of age (median age 38.0 and interquartile range 31.0-41.8 years old); overall median age and interquartile range were 38.0 and 33.0-41.0 years old respectively.

We evaluated major cardiovascular risk factors such as DL, HT, and DM. DL was defined as low-density lipoprotein-cholesterol (LDL-C) ≥ 140 mg/dL, high-density lipoprotein-cholesterol (HDL-C) < 40 mg/dL, triglyceride (TG) ≥ 150 mg/dL and/or serum total cholesterol (TC) ≥ 220 mg/dL. DM was defined as fasting blood glucose (FBS) ≥ 126 mg/dL and/or glycosylated hemoglobin (HbA1c) (NGSP) ≥ 6.5%.

### Methods

#### Subjects

This study was comprised of patients who were examined from 2007.6 to 2010.12 at Toho University Medical Center Sakura Hospital. Most of these patients came to this hospital for evaluation of cardiovascular diseases and/or cardiovascular risk factors.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Number of Risk Factors</th>
<th>Risk 0</th>
<th>Risk 1</th>
<th>Risk 2</th>
<th>Risk 3</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (M/F)</td>
<td>21 (10/11)</td>
<td>86 (58/28)</td>
<td>85 (54/31)</td>
<td>48 (39/9)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36.0 (31.3-41.0)</td>
<td>39.0 (34.0-41.0)</td>
<td>38.0 (31.0-42.0)</td>
<td>38.0 (35.5-40.5)</td>
<td>N.S.</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 (23.3-30.8)</td>
<td>26.1 (24.0-29.7)</td>
<td>29.3 (26.4-33.3)</td>
<td>29.4 (25.7-37.4)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Risk Factor, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL</td>
<td>0 (0%)</td>
<td>57 (66%)</td>
<td>75 (88%)</td>
<td>48 (100%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DM</td>
<td>0 (0%)</td>
<td>17 (20%)</td>
<td>62 (73%)</td>
<td>48 (100%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HT</td>
<td>0 (0%)</td>
<td>12 (14%)</td>
<td>33 (39%)</td>
<td>48 (100%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>190 (169-201)</td>
<td>204 (173-239)</td>
<td>214 (180-242)</td>
<td>218 (192-253)</td>
<td>0.0053</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>55 (48-65)</td>
<td>48 (41-57)</td>
<td>43 (36-52)</td>
<td>42 (35-48)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>119 (87-135)</td>
<td>124 (102-150)</td>
<td>139 (104-155)</td>
<td>138 (108-165)</td>
<td>0.0159</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>106 (76-114)</td>
<td>132 (92-187)</td>
<td>177 (119-234)</td>
<td>183 (125-244)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>101 (91-103)</td>
<td>100 (94-110)</td>
<td>148 (113-217)</td>
<td>155 (127-202)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HbA1c (NGSP) (%)</td>
<td>5.5 (5.4-5.8)</td>
<td>5.6 (5.5-6.2)</td>
<td>7.6 (6.1-10.8)</td>
<td>8.4 (7.0-10.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114 (105-123)</td>
<td>122 (116-130)</td>
<td>130 (121-144)</td>
<td>152 (146-164)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>67 (65-72)</td>
<td>76 (70-81)</td>
<td>81 (73-92)</td>
<td>99 (91-106)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>creatinine (mg/dL)</td>
<td>0.71 (0.62-0.81)</td>
<td>0.78 (0.63-0.88)</td>
<td>0.75 (0.57-0.89)</td>
<td>0.80 (0.69-0.96)</td>
<td>N.S.</td>
</tr>
<tr>
<td>uric acid (mg/dL)</td>
<td>5.2 (4.4-6.3)</td>
<td>5.9 (4.4-7.1)</td>
<td>5.9 (4.6-7.2)</td>
<td>6.7 (5.5-7.5)</td>
<td>N.S.</td>
</tr>
<tr>
<td>white blood cells (μL)</td>
<td>5,850 (5,370-7,280)</td>
<td>6,790 (5,710-8,180)</td>
<td>7,180 (5,750-8,720)</td>
<td>7,130 (6,120-8,970)</td>
<td>N.S.</td>
</tr>
<tr>
<td>pulse pressure (mmHg)</td>
<td>48 (41-53)</td>
<td>48 (43-53)</td>
<td>51 (44-58)</td>
<td>58 (51-67)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Ankle SBP (mmHg)</td>
<td>125 (114-130)</td>
<td>142 (130-152)</td>
<td>149 (135-165)</td>
<td>182 (166-201)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Ankle DBP (mmHg)</td>
<td>67 (63-72)</td>
<td>77 (70-82)</td>
<td>82 (71-90)</td>
<td>95 (89-104)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ABI</td>
<td>1.09 (0.99-1.12)</td>
<td>1.13 (1.06-1.19)</td>
<td>1.11 (1.05-1.15)</td>
<td>1.14 (1.09-1.18)</td>
<td>0.0095</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64 (55-74)</td>
<td>65 (57-73)</td>
<td>71 (66-79)</td>
<td>75 (68-88)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>smoking, n (%)</td>
<td>7 (33.3%)</td>
<td>45 (52.3%)</td>
<td>44 (51.8%)</td>
<td>30 (62.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as median and interquartile range or number (%) of subjects.


evaluation of arterial stiffness, and this technique is considered to be a powerful index of arterial stiffness and arteriosclerosis. Although CAVI derives from PWV, this is not influenced to the same extent by blood pressure4).

We have evaluated progression of arteriosclerosis using CAVI and carotid DUS in young and adolescent patients considered to be at risk of cardiovascular disease.
sure on hemodynamics. Blood pressure was obtained with the cuff applied to the upper arm. PWV was obtained by dividing the vascular length by the time taken for the pulse wave to be propagated from the aortic valve to the ankle. This was measured by cuffs applied to the upper arms and ankles. To be compatible with the aortic PWV method, scale conversion constants \( a, b \) were determined to match CAVI with the aortic PWV method. Using the scale conversion constants, PWV data were converted to CAVI values. All these measurements and calculation systems were equipped together and automatically calculated in the VaSera. The average coefficient of variation of CAVI was <5%.

CAVI increases with age, and is higher in males than in females. The VaSera system incorporates standard CAVI values for each age and gender. CAVI-D is then calculated as follows: CAVI-D = calculated CAVI - standard CAVI for each age and gender.

HT was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg. Patients were divided into 4 groups according to number of risk factors.

This study was approved by the Ethics Committee of Toho University Medical Center Sakura Hospital.

**Measurement of CAVI**

We measured CAVI with a VaSera CAVI instrument (Fukuda Denshi Inc, Tokyo, Japan) as described previously. CAVI was calculated by the following formula: 

\[
CAVI = a \left( \frac{2\rho}{P_d - P_s} \right) \ln \left( \frac{P_s}{P_d} \right) \text{PWV}^2 + b,
\]

where \( P_s \) is systolic blood pressure, \( P_d \) is diastolic blood pressure, \( \text{PWV} \) is pulse wave velocity, \( \Delta P = P_s - P_d \), \( \rho \) is blood density, and \( a \) and \( b \) are constants. cuffs were applied bilaterally to upper arms and ankles, with the subject lying supine and the head held in midline position. After resting for 10 min., the measurement was started. To detect brachial and ankle pulse waves with cuffs, a low cuff pressure of 30 to 50 mmHg was used to ensure minimal effect of cuff pressure on hemodynamics. Blood pressure was obtained with the cuff applied to the upper arm. PWV was obtained by dividing the vascular length by the time taken for the pulse wave to be propagated from the aortic valve to the ankle. This was measured by cuffs applied to the upper arms and ankles. To be compatible with the aortic PWV method, scale conversion constants \( a, b \) were determined to match CAVI with the aortic PWV method. Using the scale conversion constants, PWV data were converted to CAVI values. All these measurements and calculation systems were equipped together and automatically calculated in the VaSera. The average coefficient of variation of CAVI was <5%.

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**Fig. 1.** Univariate regression analysis demonstrates association between CAVI-D, mean IMT, and Plaque score.

IMT: Intima-media thickness. CAVI-D indicates deviation of CAVI from mean for that age.
Carotid Duplex Ultrasonography (DUS)

Carotid DUS was performed with linear-array 7.5-MHz transducers (iU22, Philips Healthcare, Netherlands; SSA-700A, SSA-790A, Toshiba Medical Systems Corp. Toshiba, Inc, Tokyo, Japan).

Intima-media thickness (IMT) and plaque were evaluated by carotid DUS and the mean IMT and plaque score (PS) were calculated.

IMT was measured as reported previously. A region of approximately 1.5 cm proximal to the flow divider in the common carotid artery was identified, and far-wall IMT was evaluated as the distance between the luminal-intimal interface and the medial adventitial interface. The optimal image was frozen in the end-diastolic phase to minimize variability during the cardiac cycle. IMT was twice measured bilaterally from 4 contiguous sites approximately 5 mm and 10 mm proximal to the dilatation of the common carotid artery. Mean IMT values were used in this study. PS was calculated as reported previously. Plaques (localized increases in IMT ≥1.1 mm) were detected by cross-sectional and longitudinal scanning of bilateral common and internal carotid arteries. PS was computed by summing the maximum thickness (in mm) of each plaque located in the bilateral carotid arteries.

Statistical Analysis

Continuous variables are expressed as the mean ± SD or median and interquartile range.

Correlations between CAVI-D, mean IMT and PS were assessed by linear regression analysis. One-way ANOVA with Scheffe’s F test or Kruskal-Wallis test was used for analysis of differences between groups. Independent Student t tests were used to compare continuous quantitative parameters between 2 groups. Linear regression analysis was used for correlation efficiency between risk factors and CAVI-D, mean IMT or plaque score. Multiple stepwise regression analysis was performed to identify any independent predictor of CAVI-D, mean IMT or PS from all risk factors.

A p value < 0.05 was considered significant. Windows (SAS institute INC, Cary, NC, USA) Stat View 5.0 Package was used.

Results

Patient backgrounds are summarized in Table 1. Patients were divided into 4 groups according to number of risk factors. There were no significant differences between groups in age, creatinine, uric acid, or white blood cell count.

Associations Among CAVI, Mean IMT and PS

There was significant association between CAVI-D and mean IMT (r = 0.193, p = 0.0027), CAVI-D and PS (r = 0.225, p = 0.0005), and mean IMT and PS (r = 0.558, p < 0.0001) (Fig. 1). When PS or mean IMT was increased, CAVI-D was also increased.

Carotid plaque was observed from 27 years of age in males and from 28 years of age in females.

CAVI and Risk Factors

The results of stepwise regression analysis are
shown in Table 2. DBP was independently associated with CAVI-D. Mean IMT was independently associated with LDL-C or SBP, and negatively associated with HDL-C. Plaque score was independently associated with LDL-C, DBP.

In terms of risk factors, CAVI and CAVI-D were elevated only in the HT group ($p=0.0290$, $p=0.0243$ vs. no risk respectively) (Fig. 2).

In patients with 3 risk factors, CAVI, CAVI-D and mean IMT were significantly higher than in those without risk ($p=0.0009$, $p=0.0042$ and $p=0.0151$ respectively), and CAVI and CAVI-D were higher than in those with 1 risk ($p=0.0204$ and $p=0.0231$) (Fig. 3). Carotid plaque developed from around 30 years of age (Fig. 4).

Despite numbers of risk factors there was no difference in CAVI, CAVI-D, mean IMT, or plaque score between smoker and non-smoker groups (Table 3).

**Discussion**

PWV\(^{11}\) or stiffness parameter $\beta \^{12}$ have been long utilized to evaluate arteriosclerosis. However, these modalities are dependent on blood pressure and are complex to use clinically. Recently, CAVI has been developed and has been reported to be independent of blood pressure\(^4,1^{3}\).

In addition, carotid arteriosclerosis can be visualized by DUS, and the degree of carotid arteriosclerosis can be evaluated by mean IMT and PS. Carotid arteriosclerosis has been shown to be associated with systemic arteriosclerosis and cardiovascular events\(^9,1^{4}-1^{6}\). Carotid arteriosclerosis may be associated with high CAVI values\(^7\). This is consistent with previous reports\(^1^8\) which revealed that high CAVI values are associated with smoking\(^1^9,2^0\), DM\(^2^1\), coronary artery disease\(^2^2\), and stroke\(^2^3\).
Although many reports on arteriosclerosis in middle-aged or aged patients have been published, there have been few studies on arteriosclerosis in younger patients. This is the first study on progression of arteriosclerosis evaluated by both carotid DUS and CAVI.

There was significant association between CAVI-D and mean IMT, CAVI and PS, and mean IMT and PS.

In terms of risk factors, CAVI and CAVI-D was elevated only in the HT group. Stepwise regression analysis demonstrated that HT is an independent predictor of CAVI-D, mean IMT and PS. Previous studies using other diagnostic methodologies have reported that SBP in childhood or blood pressure can influence progression of arteriosclerosis. In very young patients, DBP has been reported to be associated with progression of carotid arteriosclerosis. Our results are consistent with the previous reports in terms of importance of HT in progression of arteriosclerosis.

Atherosclerosis has been shown to be associated with high cholesterol levels. This may be the reason why the present stepwise analysis demonstrated an association between mean IMT or PS and HDL-C or LDL-C.

As CAVI reflects systemic arterial stiffness, the association of CAVI with dyslipidemia may be different from that of carotid arteriosclerosis.

In patients with 3 risk factors, CAVI, CAVI-D and mean IMT were significantly higher than in those without risk; also, CAVI and CAVI-D were higher than in those with 1 risk. In younger Japanese patients, arteriosclerosis may develop gradually, and CAVI may be more sensitive to carotid DUS for early detection of arteriosclerosis. In young and adolescent patients, increase in numbers of risks also results in progression...
Fig. 4. Association between carotid arteriosclerosis and age.

Carotid arteriosclerosis was evaluated by plaque score or IMT. In upper panels, patients were classified by number of risk factors. In lower panels, patients were classified by gender.

Risk 0: no risk factor, Risk 1: one risk, Risk 2: 2 risks, Risk 3: 3 risks.

Table 3. Comparisons between the smoking and non-smoking patients with no risk and 3 risks

<table>
<thead>
<tr>
<th></th>
<th>Risk 0</th>
<th></th>
<th></th>
<th>Risk 3</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no smoking</td>
<td>smoking</td>
<td>p value</td>
<td>no smoking</td>
<td>smoking</td>
<td>p value</td>
</tr>
<tr>
<td>n (%)</td>
<td>14 (66.7%)</td>
<td>7 (33.3%)</td>
<td></td>
<td>18 (37.5%)</td>
<td>30 (62.5%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.0 (26.0-41.0)</td>
<td>38.0 (35.5-41.3)</td>
<td>N.S.</td>
<td>38.5 (32.0-40.0)</td>
<td>38.0 (37.0-41.0)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Number of cigarettes smoked per day</td>
<td>15.0 (15.0-18.8)</td>
<td></td>
<td></td>
<td>20.0 (15.0-30.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAVI</td>
<td>6.7 ± 0.9</td>
<td>7.5 ± 0.8</td>
<td>N.S.</td>
<td>8.0 ± 0.9</td>
<td>7.9 ± 1.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>CAVI-D</td>
<td>-0.18 ± 0.70</td>
<td>0.18 ± 0.81</td>
<td>N.S.</td>
<td>0.88 ± 0.82</td>
<td>0.63 ± 1.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>mean IMT</td>
<td>0.64 ± 0.10</td>
<td>0.66 ± 0.11</td>
<td>N.S.</td>
<td>0.78 ± 0.24</td>
<td>0.82 ± 0.16</td>
<td>N.S.</td>
</tr>
<tr>
<td>Plaque score</td>
<td>0.16 ± 0.42</td>
<td>0.36 ± 0.95</td>
<td>N.S.</td>
<td>1.52 ± 2.12</td>
<td>1.54 ± 2.42</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Data are presented as the median and interquartile range, the mean ± SD or number (%) of subjects.

Risk 0: no risk, Risk 3: 3 risks, IMT: intima-media thickness, N.S.: not significant
CAVI-D indicates deviation of CAVI from mean for that age.
of arteriosclerosis. This study also demonstrated that plaque may develop at around 30 years of age in young patients with risk factors.

Smoking may accelerate progression of arteriosclerosis with age. In our patients with no risk or 3 risks, there was no difference in arteriosclerosis between smoker and non-smoker groups. Most of our younger smokers were light smoker and short periods of smoking. This may be the reason why smoking had little influence on arteriosclerosis in the present study.

In young and adolescent patients with risk factors for arteriosclerosis, carotid DUS and CAVI tests should be required to detect progression of arteriosclerosis and thereby prevent cardiovascular events.

Conclusions

The progression of arteriosclerosis in young and adolescent patients was evaluated by use of carotid DUS and CAVI. Increases in risk factors for arteriosclerosis resulted in progression of arteriosclerosis and increases in CAVI values. Carotid plaque develops from 27 years of age in young Japanese patients with risk factors. HT was the most important risk factor for arteriosclerosis in these patients. Evaluation of arteriosclerosis by carotid DUS and CAVI in young and adolescent patients at high risk should be required for prevention of cardiovascular events.

Acknowledgements

We thank Ms. Carol Ann Matsubara for her assistance in this manuscript.

Conflicts of Interest

None.

References


