Values of Cardio-Ankle Vascular Index (CAVI) between Amami Islands and Kagoshima Mainland Among Health Checkup Examinees

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Aim: To investigate the prevalence and geographical variation of high arterial stiffness in groups from the Amami islands (Amami) and Kagoshima mainland (mainland), Japan, using the cardio-ankle vascular index (CAVI) as a surrogate marker of arterial stiffness.

Methods: We recruited 4,523 health checkup examinees from Amami and 440 examinees from the mainland, with an age range of 40-69 years. The frequency of high arterial stiffness (CAVI ≥9.0) was geographically compared between the regions, and both mean CAVI values were compared with those of the healthy Japanese population with less risk factors for coronary artery disease. Clinical, lifestyle, and regional factors for increased CAVI values were estimated by the multiple linear regression model.

Results: The frequency of high arterial stiffness on Amami was significantly lower than on the mainland. Mean CAVI values on Amami were similar in males and lower in females than in the healthy Japanese population, but those on the mainland were higher for both sexes. Age, systolic blood pressure, triglycerides, fasting blood glucose, and a history of hypertension and diabetes mellitus were positively related to increased CAVI values on Amami. The regional factor of Amami, compared with the mainland, was negatively related to increased CAVI values in both sexes after adjusting for traditional cardiovascular risk factors.

Conclusion: CAVI values in Amami residents were significantly lower than in mainland residents, suggesting that environmental or genetic factors might have improved arterial stiffness in the Amami population.


Key words: Arterial stiffness, Cardio-ankle vascular index, Geographical variation

Introduction

Ischemic heart disease and stroke are major causes of death in Japan¹ and Western countries². High arterial stiffness is reported to be a risk factor for the development of these diseases³-⁶, as well as peripheral arterial disease⁷ and disorders of the kidney and retinopathy⁸,⁹; therefore, evaluation of high arterial stiffness could be an effective control tool for these diseases.

High arterial stiffness is caused by thickening of the intimal layer due to cholesterol deposition, smooth muscle cell proliferation, and the proliferation of con-
nective tissue; calcification of the arterial lumen due to cholesterol deposits and macrophage infiltration; and loss of arterial wall flexibility due to thickness, calcification, and narrowing. Risk factors are dyslipidemia\textsuperscript{10}, hypertension\textsuperscript{11}, diabetes mellitus\textsuperscript{8,9}, smoking habits\textsuperscript{12}, family history\textsuperscript{13, 14}, male gender, and advanced age\textsuperscript{15-17}.

Arterial stiffness can be evaluated by various methods: stiffness parameter-$
\beta$, pulse wave velocity (PWV)\textsuperscript{18}, carotid-femoral pulse wave velocity (cfPWV)\textsuperscript{19}, heart-femoral pulse wave velocity (hfPWV)\textsuperscript{20}, and brachial-ankle pulse wave velocity (baPWV)\textsuperscript{21, 22} are used as common noninvasive clinical indices, but these methods are limited because PWV is dependent on blood pressure at the measurement time. Cardio-ankle vascular index (CAVI) is a recently developed method that uses PWV in the aorta, femoral artery, and tibial artery, and it is less dependent on blood pressure than other PWV methods\textsuperscript{23-25}. Indeed, a recent study has demonstrated that CAVI is independent of blood pressure at the time of measurement, while the previous PWV was an influence\textsuperscript{26}. Furthermore, CAVI is more easily conducted for a large number of subjects in the epidemiological field. The validity and reproducibility of CAVI have already been successfully evaluated\textsuperscript{27, 28}. CAVI values are correlated with carotid intima-media thickness\textsuperscript{24, 25, 29, 30}, Several studies have revealed a significant relationship between CAVI and the presence and severity of patients with coronary artery disease\textsuperscript{31}, hemodialysis\textsuperscript{32, 33}, and chronic kidney disease\textsuperscript{34}. Changes in arterial stiffness following cessation of smoking and application of CAVI have been reported recently\textsuperscript{28}; however, there is little information on the prevalence and geographical variation of high arterial stiffness evaluated by CAVI among the general population.

We have been conducting a genome-cohort study in a remote region of Amami of Kagoshima Prefecture, Japan, as a member of the Japan Multi-Institutional Collaborative Cohort Study (J-MICC Study) since 2005\textsuperscript{36, 37}. The Amami islands are located in the southern part of Kagoshima and Japan, and neighbor Okinawa. We conducted a cross-sectional study using the baseline data obtained in this genome-cohort study and compared it with that obtained on the mainland of Kagoshima.

**Aim**

The aim of the present study was to investigate the prevalence and geographical variation of high arterial stiffness in groups from the Amami islands (Amami) and the Kagoshima mainland (mainland) in Kagoshima, Japan, using CAVI as a surrogate marker of arterial stiffness.

**Methods**

**Study Subjects**

We conducted a baseline survey in 1 city and 9 towns located on 5 islands in the Amami region from 2005 to 2008. After obtaining written informed consent (response rate: 65.4%), we recruited 5,154 subjects aged 40-69 years from the general population, who had routine health checkups conducted by the local government or private companies. The baseline survey consisted of a questionnaire survey, blood collection using serum, plasma, buffy coat, urine collection, and examination of arterial stiffness using CAVI. Results of the routine health checkups were also obtained after informed consent. We excluded subjects who withdrew their participation before February 2010 ($n=15$); whose questionnaire ($n=98$), health checkup ($n=350$), or CAVI ($n=54$) data were not available; and whose CAVI data quality were insufficient due to arrhythmia, such as atrial fibrillation or undetectable pulse wave ($n=49$). We also excluded subjects who had a low ankle-brachial index (ABI < 0.9) ($n=65$) because such cases had inaccurate CAVI values due to decreased blood flow\textsuperscript{23}. Ultimately, 4,523 subjects (1,853 males and 2,670 females) were eligible for analysis.

We also used the stored data of examinees who had health checkups, questionnaires, and CAVI assessments completed at JA Kagoshima Kouseiren Medical Health Care Center located on the mainland from 2004 to 2007, after deleting personal information. We were able to obtain data for 1,033 subjects aged 18-82 years. Excluded subjects were under 40 years or over 69 years old ($n=330$), who lived on Amami or at an unknown residence ($n=231$), who had no health checkup data ($n=29$), and who had low ABI values ($n=3$). The eligible number of subjects aged 40-69 years in the mainland group was 440 (240 males and 200 females).

The present study was approved by the ethics committee on Life Sciences and Genetic Analysis, Kagoshima University Graduate School of Medical and Dental Sciences.

**Questionnaire**

We collected information about the lifestyle and medical history of subjects on Amami using a structured questionnaire standardized by the J-MICC Study\textsuperscript{36}. Information about subjects on the mainland...
was collected by another structured questionnaire. Both self-administrative questionnaires were checked by trained health professionals after the subjects had been interviewed. We used information that was common to both questionnaires.

Health Checkup

We obtained health checkup data from JA Kagoshima Kouseiren Medical Health Care Center and Oshima Medical Association, with which local governments on Amami had contracts for health checkups. Health checkups on the mainland were also conducted by JA Kagoshima Kouseiren Medical Health Care Center.

Blood samples were obtained after fasting. The health checkups included assessments of total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), fasting blood sugar (FBS), blood urea nitrogen (BUN), creatinine (Cr), and uric acid (UA).

Since LDL-C was not examined at JA Kagoshima Kouseiren Medical Health Care Center, the LDL-C values were estimated using the Friedewald formula:

\[ \text{LDL-C} = \text{TC} - \text{HDL-C} - \text{VLDL} \]

Where a and b are constant and \( \rho \) is blood density. The right CAVI value was used for analysis.

Measurement of CAVI

CAVI was measured by the standardized method using a Vasera VS-1000 or VS-1500 (Fukuda Denshi Co., Ltd, Tokyo, Japan) for the Amami and mainland groups, as described previously. In brief, a cuff was placed on the right and left ankles and the brachium; electrodes for electrocardiography were attached to both upper arms, and a microphone was placed on the sternal angle for phonocardiography. CAVI was measured in the supine position. PWV was calculated by dividing the distance from the aortic valve to the artery of the ankle by the sum of the time between the closing sound of the aortic valve and the ankle pulse wave. To minimize cuff inflation effects on blood flow dynamics, pulse waves were measured with the cuff inflated to lower than diastolic blood pressure (DBP: 50 mmHg). Blood pressure (BP) was measured with an oscillometer. Systolic blood pressure (SBP), DBP, and pulse pressure (PP) were measured by the BP of the right brachial artery. CAVI was calculated by the following equation:

\[
\text{CAVI} = \left[ \frac{2 \rho \times 1}{\text{SBP} - \text{DBP}} \right] \times \left[ \ln\left(\frac{\text{SBP}}{\text{DBP}}\right) \times \text{PWV}^2 \right] + b
\]

where a and b are constant and \( \rho \) is blood density. The right CAVI value was used for analysis.

Healthy Japanese Population with Less Risk Factors for Coronary Artery Disease

Suzuki et al. showed the mean and standard deviation (SD) of CAVI by sex in every 5-year and 10-year age group using data on 5,969 healthy subjects (2,239 males and 3,730 females) of 32,627 Japanese subjects aged 20-74 years after excluding subjects with established risk factors of high arterial stiffness, such as hypertension, dyslipidemia, hyperglycemia, and renal dysfunction. They also excluded subjects with abnormal WBC, electrocardiography, or fundus examination results or a history of hypertension, dyslipidemia, heart diseases, stroke, diabetes mellitus, renal diseases, or gout. These subjects were recruited from the participants and their family members in 42 prefectures of Japan, who had received the standard health checkup for workers in Japan from 2005 to 2007. They were asked to add a CAVI examination for use in this survey after oral explanation with documents. We used these data for the healthy Japanese population with less risk factors for coronary artery disease.

Definition

We defined the group with high arterial stiffness as having CAVI ≥ 9.0. The definition of related factors other than clinical characteristics are as follows: smoking: never smokers vs. ex-smokers and current smokers; drinking: nondrinkers and ex-drinkers vs. current drinkers of < 20 g alcohol/day vs. 20-40 g alcohol/day vs. > 40 g alcohol/day; exercise: < 1 time/month vs. ≥ 1 time/month and < 3 times/week vs. ≥ 3 times/week; and a history of hypertension, coronary artery disease, diabetes mellitus, or dyslipidemia. Information with respect to their diagnosis or medication for these diseases was obtained from the questionnaire. TC was not included in this model because HDL-C and LDL-C were used.

Statistical Analysis

We compared the clinical characteristics of subjects in the Amami and mainland groups using the mean and SD of the examination values. Differences between the 2 groups were examined using an unpaired t-test. The prevalence of high arterial stiffness was compared between regions by sex and age groups using the chi-square test and Fisher’s exact test. We also used multiple linear regression analysis to examine the relationship between CAVI and clinical characteristics, lifestyles, and a history of clinical status, and regional factors. Differences in the mean CAVI values between the Amami subjects and the mainland subjects, and the healthy Japanese popula-
Comparison of age, body mass index, clinical values, smoking and drinking habits, history of related diseases, and CAVI between the subjects on the Amami islands and the Kagoshima mainland by sex

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Amami islands (n=1,853)</th>
<th>Kagoshima mainland (n=240)</th>
<th>p-value</th>
<th>Amami islands (n=2,670)</th>
<th>Kagoshima mainland (n=200)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.55 ± 8.14</td>
<td>53.95 ± 8.60</td>
<td>0.004</td>
<td>55.72 ± 7.91</td>
<td>55.11 ± 7.95</td>
<td>0.287</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.92 ± 3.18</td>
<td>23.83 ± 2.89</td>
<td>&lt;0.001</td>
<td>24.12 ± 3.47</td>
<td>22.55 ± 3.23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>208.08 ± 36.21</td>
<td>205.81 ± 34.31</td>
<td>0.036</td>
<td>216.20 ± 35.37</td>
<td>213.56 ± 29.69</td>
<td>0.306</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>161.90 ± 149.13</td>
<td>129.73 ± 77.52</td>
<td>0.001</td>
<td>103.69 ± 63.60</td>
<td>95.69 ± 56.80</td>
<td>0.084</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>57.54 ± 14.50</td>
<td>53.27 ± 13.02</td>
<td>&lt;0.001</td>
<td>63.61 ± 14.02</td>
<td>62.04 ± 13.06</td>
<td>0.125</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>120.83 ± 32.72</td>
<td>126.47 ± 32.08</td>
<td>0.013</td>
<td>131.58 ± 32.37</td>
<td>132.27 ± 27.13</td>
<td>0.768</td>
</tr>
<tr>
<td>FBS (mg/dL)</td>
<td>104.80 ± 25.24</td>
<td>107.61 ± 21.19</td>
<td>0.099</td>
<td>96.22 ± 18.11</td>
<td>101.13 ± 25.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>15.57 ± 4.06</td>
<td>16.24 ± 3.95</td>
<td>0.018</td>
<td>14.62 ± 3.57</td>
<td>14.94 ± 3.76</td>
<td>0.234</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.80 ± 0.21</td>
<td>0.85 ± 0.21</td>
<td>&lt;0.001</td>
<td>0.60 ± 0.13</td>
<td>0.60 ± 0.10</td>
<td>0.810</td>
</tr>
<tr>
<td>UA (mg/dL)</td>
<td>6.15 ± 1.36</td>
<td>5.99 ± 1.17</td>
<td>0.070</td>
<td>4.57 ± 1.03</td>
<td>4.26 ± 0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beat/min)</td>
<td>63.22 ± 11.62</td>
<td>71.38 ± 11.78</td>
<td>&lt;0.001</td>
<td>65.82 ± 9.89</td>
<td>71.97 ± 9.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>133.94 ± 17.52</td>
<td>128.48 ± 15.34</td>
<td>&lt;0.001</td>
<td>127.15 ± 18.13</td>
<td>125.46 ± 17.40</td>
<td>0.201</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83.19 ± 10.96</td>
<td>84.93 ± 10.65</td>
<td>0.020</td>
<td>77.46 ± 11.11</td>
<td>80.70 ± 10.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>100.95 ± 14.92</td>
<td>100.94 ± 13.60</td>
<td>0.989</td>
<td>95.56 ± 15.20</td>
<td>98.09 ± 14.60</td>
<td>0.023</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>50.75 ± 10.72</td>
<td>43.55 ± 9.01              &lt;0.001</td>
<td>49.69 ± 10.93</td>
<td>44.76 ± 11.01              &lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>36.27</td>
<td>35.42</td>
<td>0.847</td>
<td>92.55</td>
<td>93.50</td>
<td>0.858</td>
</tr>
<tr>
<td>Ex-smoker (%)</td>
<td>32.38</td>
<td>35.00</td>
<td>0.636</td>
<td>2.40</td>
<td>3.50</td>
<td>0.603</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>31.25</td>
<td>29.58</td>
<td>0.761</td>
<td>5.02</td>
<td>3.00</td>
<td>0.425</td>
</tr>
<tr>
<td>Current drinker (%)</td>
<td>85.70</td>
<td>85.83</td>
<td>0.227</td>
<td>31.35</td>
<td>41.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of HT (%)</td>
<td>28.12</td>
<td>18.33</td>
<td>0.002</td>
<td>22.40</td>
<td>14.00</td>
<td>0.008</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>1.83</td>
<td>2.08</td>
<td>0.299</td>
<td>0.90</td>
<td>0.50</td>
<td>0.182</td>
</tr>
<tr>
<td>History of CAD (%)</td>
<td>2.32</td>
<td>1.25</td>
<td>0.171</td>
<td>1.99</td>
<td>1.50</td>
<td>0.252</td>
</tr>
<tr>
<td>History of diabetes mellitus (%)</td>
<td>8.36</td>
<td>8.33</td>
<td>0.375</td>
<td>4.08</td>
<td>1.50</td>
<td>0.056</td>
</tr>
<tr>
<td>History of dislipidemia (%)</td>
<td>10.31</td>
<td>6.67</td>
<td>0.063</td>
<td>10.19</td>
<td>11.50</td>
<td>0.164</td>
</tr>
<tr>
<td>CAVI</td>
<td>8.15 ± 0.99</td>
<td>8.63 ± 1.20               &lt;0.001</td>
<td>7.78 ± 0.97</td>
<td>8.52 ± 1.03               &lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBS, fasting blood sugar; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; HT, hypertension; CAD, coronary artery disease; CAVI, cardio-ankle vascular index. Values are mean ± SD, or percentages.

...tion with less risk factors for coronary artery disease were examined using an unpaired t-test. Statistical analysis was performed with Stata, Version 8.0 for Windows (StataCorp LP, College Station, Tx).

Results

The clinical and lifestyle characteristics of the subjects differed between the Amami and mainland groups. Body mass index (BMI), TC, TG, HDL-C, SBP, and PP were higher, and LDL-C, BUN, Cr, heart rate (HR), DBP, and CAVI were lower in males in the Amami group than in the mainland group; these differences were statistically significant (Table 1). BMI, UA, and PP were significantly higher, while FBS, HR, DBP, MBP, and CAVI were significantly lower in females in the Amami group than in the mainland group. Males and females in the Amami group had a significantly higher prevalence of a history of hypertension. Current smoking and drinking habits were not geographically different except for a higher frequency of drinking in females in the mainland group.

A positive relationship was observed between CAVI values and age, although CAVI values varied widely by subject at each age (Fig. 1A, 1B). CAVI values in the mainland group were distributed at higher values than in the Amami group for both sexes. The correlation coefficients were 0.489 in Amami males, 0.547 in mainland males, 0.494 in Amami females, and 0.547 in mainland females.

The frequency of high arterial stiffness (CAVI...
Fig. 1A. Distribution of cardio-ankle vascular index (CAVI) by age in males. The black circle and solid line show each CAVI value and regression line, respectively, on the Amami islands. The dark diamond and broken line show each CAVI value and regression line, respectively, on the Kagoshima mainland. The relation between CAVI and age is expressed as $\text{CAVI} = 0.06 \times \text{age} + 4.86$ for the Amami islands and $\text{CAVI} = 0.08 \times \text{age} + 4.53$ for the Kagoshima mainland.

Fig. 1B. Distribution of cardio-ankle vascular index (CAVI) by age in females. The black circle and solid line show each CAVI value and regression line, respectively, on the Amami islands. The dark diamond and broken line show each CAVI value and regression line, respectively, on the Kagoshima mainland. The relation between CAVI and age is expressed as $\text{CAVI} = 0.06 \times \text{age} + 4.41$ for the Amami islands and $\text{CAVI} = 0.07 \times \text{age} + 4.60$ for the Kagoshima mainland.
≥9.0) was compared by sex, age group, and region (Fig. 2). Its frequency increased with age in both sexes and regions. Males showed a higher frequency of high arterial stiffness than females in each age group and region. Amami residents also had lower percentages of high arterial stiffness than the mainland in each sex and age group. The frequency of high arterial stiffness in the Amami and mainland groups was 5.6% vs. 13.3% (p=0.009), 15.4% vs. 37.2% (p<0.001), and 37.9% vs. 76.1% (p<0.001) in males aged 40-49, 50-59, and 60-69 years, respectively, and 1.0% vs. 13.8% (p<0.001), 7.6% vs. 28.4% (p<0.001), and 23.0% vs. 63.2% (p<0.001) in females in the same respective age groups.

We examined the relationship between CAVI values and clinical characteristics: smoking, drinking, and exercise habits; and a history of clinical status, using multiple linear regression analysis (Table 2). A positive relationship was observed for the following: age, SBP, TG, FBS, and history of hypertension and diabetes mellitus in males on Amami; age in males on the mainland; age, SBP, TG, FBS, UA, and history of hypertension in females on Amami; age and history of hypertension in females on the mainland. In contrast, a negative relationship was observed for BUN in males on Amami. The regional effect for differences in CAVI values was also examined using this model after adjusting for traditional cardiovascular risk factors (Table 3). The regional factor of Amami, compared with the mainland, was negatively and significantly related to increased CAVI values in both sexes (p<0.001 in males and p<0.001 in females).

Mean CAVI values of Amami subjects and the healthy Japanese population were similar in all male age groups and were lower in Amami females in their 40s and 50s (Fig. 3A, 3B). In contrast, mean CAVI values of the mainland subjects were higher than those of Amami subjects and the healthy Japanese population in all age groups of both genders.

**Discussion**

The present study investigated high arterial stiffness using CAVI in relatively large subject groups and compared its distribution and related factors between the Amami islands and the mainland of Japan. We found geographical differences in the mean CAVI values: residents of Amami had lower CAVI values than those of mainland residents. CAVI values in Amami residents were almost equivalent to the healthy Japanese population with less risk factors for coronary arterial diseases; however, differences in lifestyle and clinical characteristics could not explain these geographical variations.
The present study is the first to investigate the geographical variation of high arterial stiffness by CAVI in the same ethnic group of the Japanese general population. A regional difference in aging changes in aortic PWV has been reported by Ávolo et al. who found that aortic PWV in the residents of an urban Chinese town increased with age to a similar degree as people in Western countries; in contrast, increases in aortic PWV with age in a rural Chinese town was much slower. They reported that salt intake was the main contributor to the regional difference of PWV. Compared with this study, differences in CAVI values in the present study are small, which may be partially due to the different impact of lifestyle and genetic differences between the Japanese and Chinese populations, in addition to methodological differences. The CAVI values of patients with hypertension and diabetes mellitus have been compared between Mongolian and Japanese populations, and the Mongolian CAVI values were higher than those of the Japanese. In the present study, mean CAVI values of the Amami subjects were similar to those of the healthy Japanese population in males, and lower in females. In contrast, those of the mainland subjects were higher in both sexes. These results suggest that Amami subjects have a similar or lower distribution of high arterial stiffness compared with the healthy Japanese population.

Because CAVI is one of the methods to measure high arterial stiffness, its related factors are common to previous risk factors for coronary artery disease. The present study revealed that CAVI was positively correlated with age, SBP, TG, BUN, FBS, and a history of hypertension and diabetes mellitus in Amami males after adjusting for related factors. These results, except for BUN, were concordant with those of previous studies; however, significant findings were not...
apparent in the mainland subjects. The major reason for this small contribution may be the low statistical power in the mainland subjects, but the values of multiple coefficients on the mainland were similar to those on Amami. The regional factor of Amami showed a significant negative relation to increased CAVI values after adjusting for traditional cardiovascular risk factors in the combined analysis of the 2 regions. As BMI in Amami residents was higher than in the mainland group, BMI was also included in this analysis. These results suggest that the geographical variation of high arterial stiffness was independently observed in the present study after controlling for related factors of high arterial stiffness.

We found lower CAVI values in the Amami population than in the mainland population, although established risk factors of coronary artery disease\textsuperscript{28, 30}, such as BMI, TG, SBP, and a history of hypertension, were more prevalent on Amami. This paradoxical finding requires further consideration. One possible explanation is a birth cohort effect of previous lifestyle. The serum TC level among the general population in 1987 was much lower on Amami than on the mainland according to a report of health checkups by the local government, and the magnitude of each change from 1987 to 2007 was much larger on Amami, although these differences were not apparent for TG, HDL-C, or hypertension\textsuperscript{42, 43}. This report suggests that the Amami population ingested more low-cholesterol food than the mainland population 20 years ago, but that they are currently ingesting as much high-cholesterol food as the mainland population. Another potential explanation is the different genetic backgrounds of susceptibility to developing arterial stiffness. Several gene polymorphisms are reported to be associated with the risk of high arterial stiffness\textsuperscript{44-46}, but only one report has examined the geographical distribution of these polymorphisms in

| Table 3. Correlation coefficient (coef) for the region, clinical characteristics and lifestyle with CAVI values in multiple linear regression analysis by sex |
|----------------------------------|-------------------------------|-------------------------------|
|                                  | Males                         | Females                      |
|                                  | Multiple coef | p-value                      | Multiple coef | p-value                      |
| Region (Amami islands)           | -0.518            | <0.001                        | -0.712        | <0.001                        |
| Age (years)                     | 0.057             | <0.001                        | 0.056         | <0.001                        |
| Height (cm)                     | 0.039             | 0.122                         | 0.015         | 0.438                         |
| Weight (kg)                     | -0.037            | 0.228                         | 0.001         | 0.957                         |
| BMI (kg/m\(^2\))                | 0.028             | 0.738                         | -0.067        | 0.270                         |
| SBP (mmHg)                      | 0.007             | 0.004                         | 0.007         | <0.001                        |
| DBP (mmHg)                      | 0.002             | 0.545                         | -0.001        | 0.816                         |
| HR (beat/min)                   | 0.001             | 0.653                         | 0.001         | 0.509                         |
| TG (mg/dL)                      | 0.001             | <0.001                        | 0.001         | 0.009                         |
| HDL-C (mg/dL)                   | 0.001             | 0.508                         | 0.000         | 0.988                         |
| LDL-C (mg/dL)                   | 0.001             | 0.032                         | 0.001         | 0.187                         |
| FBS (mg/dL)                     | 0.003             | 0.001                         | 0.004         | <0.001                        |
| BUN (mg/dL)                     | -0.013            | 0.023                         | -0.003        | 0.604                         |
| Cr (mg/dL)                      | 0.248             | 0.060                         | -0.096        | 0.497                         |
| UA (mg/dL)                      | 0.018             | 0.318                         | 0.062         | 0.002                         |
| Smoking                         | 0.086             | 0.060                         | 0.062         | 0.396                         |
| Drinking                        | 0.022             | 0.321                         | -0.025        | 0.380                         |
| Exercise                        | 0.006             | 0.808                         | 0.030         | 0.190                         |
| History of HT                   | 0.272             | <0.001                        | 0.291         | <0.001                        |
| History of stroke               | 0.033             | 0.845                         | 0.249         | 0.234                         |
| History of CAD                  | 0.163             | 0.293                         | -0.243        | 0.065                         |
| History of diabetes mellitus    | 0.365             | <0.001                        | 0.141         | 0.218                         |
| History of dislipidemia         | -0.058            | 0.463                         | 0.115         | 0.087                         |

Region, Kagoshima mainland=0, Amami islands=1; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; FBS, fasting blood sugar; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; HT, hypertension; CAD, coronary artery disease.
Fig. 3A. Comparison of the mean and 95% confidence interval of the cardio-ankle vascular index (CAVI) among the Amami island subjects (I), the Kagoshima mainland subjects (M), and the healthy population (H) by age group in males. *p<0.05, **p<0.01.

Fig. 3B. Comparison of the mean and 95% confidence interval of the cardio-ankle vascular index (CAVI) among the Amami island subjects (I), the Kagoshima mainland subjects (M), and the healthy population (H) by age group in females. *p<0.05, **p<0.01.
this study region. SNP genotypes with frequency differences between the Hondo and Ryukyu clusters among 7003 Japanese have been reported. The Amami islands neighbor Okinawa, which includes the Ryukyu cluster. Further studies are needed to clarify the role of environmental and genetic factors in the observed geographical variation. A methodological issue should also be discussed with regard to the geographical variation. We used the same equipment to examine the CAVI in both study regions. Quality control for the biochemical examination was also conducted, and the results were found to be appropriate.

Several limitations have to be considered. First, the present subjects may not be completely representative of the general population, but were comparable between the 2 studied regions because subjects in both groups were recruited from health checkup examinees in the general population. The present study may still include some selection bias because the Amami subjects were recruited through a routine health checkup program at the local governmental level, whereas the mainland subjects were recruited at a health checkup center that they visited. This selection bias, however, may not be large and can be controlled since both subject groups were recruited from the general population and the prevalence of a history of stroke, coronary artery disease, and diabetes mellitus did not differ between them. Since some health status markers, such as SBP, LDL-C, and FBS levels, differed by region, we also adjusted for these factors to evaluate geographical variation. Second, the CAVI data quality was not compared between the 2 regions; however, we used the same method to examine CAVI, and those with potential misclassification due to arrhythmias and low ABI were excluded. Third, the number of subjects on the mainland was not large compared with those on Amami, but the statistical power was enough to clarify the difference in the mean CAVI values and the regional factor between regions. Fourth, for calculating CAVI values, the CAVI system uses estimated aortic path length by height, not the real distance, and several researchers have proposed concerns about the use of this estimation. Finally, no studies have reported the ability of CAVI to predict cardiovascular end points in prospective observation studies or interventional trials. These limitations should be evaluated in the future.

**Conclusion**

CAVI values in Amami residents were significantly lower than in mainland residents; however, differences in lifestyle and clinical characteristics could not explain these geographical variations. It is suggested that other environmental or genetic factors might improve the arterial stiffness of people on Amami. Further molecular epidemiological studies are required to clarify these factors.

**Conflict of Interest**

The authors declare no conflicts of interest.

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