Radial Arterial Wave Reflection is Associated with the MEGA Risk Prediction Score, an Indicator of Coronary Heart Disease Risk, in Middle-Aged Men with Mild to Moderate Hypercholesterolemia

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Aim: The present study examined the association between the radial augmentation index (AI), a marker of arterial wave reflection, and the MEGA risk prediction score (MEGA score), an indicator of coronary heart disease (CHD) risk, in middle-aged men with mild to moderate hypercholesterolemia.

Methods: Radial AI was measured during a company health examination in 266 men (age: 47 ± 5 years) with total cholesterol levels ranging 220–270 mg/dL who were not taking antihypertensive, lipid-lowering, or antidiabetic agents. The MEGA score was calculated based on sex, age, low- and high-density lipoprotein cholesterol, blood pressure, glucose level, and smoking status. The higher MEGA score indicates increased CHD risk. A MEGA score ≥ 22 corresponds to a 5-year CHD risk ≥ 2.5% and we defined a MEGA score ≥ 22 as a high estimated CHD risk.

Results: The mean AI was 74.4 ± 12.6%. A high estimated CHD risk was seen in 32 subjects (12.0%). After adjusting for height and heart rate, the AI was higher in subjects with a high estimated CHD risk (81.5 ± 10.6%) than in those without (73.4 ± 10.4%, p < 0.001). The odds ratio for high estimated CHD risk in the highest tertile of AI was 8.14 (p = 0.002) in comparison to the lowest tertile, after adjusting for multiple potential confounders which did not constitute the MEGA score.

Conclusion: The radial AI was positively associated with the estimated risk of CHD. These results suggest the usefulness of radial AI as a risk marker for future onset of CHD in middle-aged men with mild to moderate hypercholesterolemia.


Key words: Augmentation index, Hypercholesterolemia, Coronary heart disease, MEGA risk prediction score, Risk factors

Introduction

Pulse wave analysis provides a variety of information on arterial properties1. Arterial wave reflection represents the timing and intensity of the backward wave from the periphery, which is determined by large elastic arterial stiffness, as well as a small muscular arteriole and arteriolar tone2. Augmented arterial wave reflection therefore indicates the deterioration of functional and structural properties of the systemic arterial tree. Arterial wave reflection is mainly expressed by the augmentation index (AI), defined as a ratio of the late to early systolic peak on the waveform1, 2. While the AI is influenced by sex, height, and heart rate2, it has been reported to be significantly associated with the established risk factors for cardiovascular disease (CVD), such as age2-9, blood pressure (BP)2-9, lipid profile5, 9, glucose intolerance10, and smoking status5, 6, 9, 11. Previous studies conducted in the US and Europe reported a positive relationship between AI and several...
risk prediction scores for CVD\textsuperscript{6, 7, 12}, which were calculated based on the severity of cardiovascular risk factors; however, this relationship remains to be fully understood in the Japanese population, despite understanding that it could contribute to advances in the field of cardiovascular preventive medicine.

In Japan, hypercholesterolemia is expected to play a key role in increasing mortality and morbidity from CVD in the future\textsuperscript{13}. The MEGA study is a large-scale, prospective, randomized controlled trial that elucidated the primary preventive effect of pravastatin against CVD in Japanese persons with mild to moderate hypercholesterolemia\textsuperscript{14}. Based on these data, the MEGA risk prediction score (MEGA score) was recently developed as a risk prediction tool for coronary heart disease (CHD)\textsuperscript{15}. The aim of the present study was to examine the association between radial AI and the MEGA score in middle-aged men with mild to moderate hypercholesterolemia.

\section*{Methods}

\subsection*{Study population}

This study was conducted during the annual health examination at a company in Kanagawa, Japan, 2007. A total of 944 male workers, between 40 and 62 years of age, received the complete health examination. All workers were engaged in daytime desk work. Among them, any subjects who met the exclusion criteria in the original MEGA study\textsuperscript{16} were excluded; namely, serum total cholesterol levels < 220 mg/dL \((n = 608)\) or > 270 mg/dL \((n = 30)\), a history or presence of CVD \((n = 4)\), and active liver disease \((n = 2)\). No subjects who fulfilled any other exclusion criteria in the MEGA study. Any subjects on antihypertensive, lipid-lowering, or antidiabetic medications \((n = 34)\) were further excluded to avoid the effect of these medications on arterial wave reflection. Finally, 266 subjects participated in the present study. All participants had been directed to follow a cholesterol-restricted diet by company nursing staff after undergoing the examination. This study was approved by the institutional review committee, and all participants gave informed consent.

\subsection*{Lifestyle and biochemical data}

A self-reported questionnaire was used to collect data on the smoking status, family history of CVD, and medical information, including prescribed drugs. Blood samples were obtained from the antecubital vein after an overnight fast. Standard enzymatic methods were used to measure serum total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and plasma glucose levels. Serum high-density lipoprotein (HDL) cholesterol was measured using a direct method. White blood cell count was measured using an automatic cell counter. Glucose abnormality was defined as plasma glucose levels \(\geq 110 \text{ mg/dL}\). Current smoking was defined as regular smoking.

\subsection*{BP measurement and pulse wave analysis}

All hemodynamic measurements were conducted in a temperature-controlled room maintained at 22 ± 2°C. The brachial BP and radial pulse wave were measured simultaneously, after at least 5 minutes of rest in the sitting position, using the HEM-9000AI device (Omron Healthcare Co., Kyoto, Japan). This device consists of a main unit, a cuff for measuring BP by the oscillometric method, and a wristwatch-shaped tonometer sensor unit. Right brachial BP was automatically measured twice. The average of two readings was used to determine systolic and diastolic BP. The mean BP was calculated as: (systolic BP – diastolic BP)/3 + diastolic BP. Hypertension was defined as systolic BP \(\geq 140 \text{ mmHg}\) and/or diastolic BP \(\geq 90 \text{ mmHg}\). The left radial arterial pressure waveform was obtained by the automated applanation tonometric method. The methodology for measuring radial pulse waveform by the device has been described in detail elsewhere\textsuperscript{3, 17}.

In brief, the tonometry sensor unit has a pressure sensor consisting of an array of 40 microtransducer elements. When the sensor unit is placed on the subject’s wrist, one of these 40 sensor elements is automatically selected to obtain optimal radial arterial pressure waveforms. Continuous steady-state 15-second data were recorded for each subject. The AI was determined for each pulse using the main unit and the following formula: ((late systolic peak – diastolic trough) / (early systolic peak – diastolic trough)) \times 100 (%) \textsuperscript{(Fig. 1)}. A late systolic peak was detected from the second maximum of the fourth derivative of pulse waveform, using the software program incorporated into the HEM-9000AI device\textsuperscript{18}. The mean AI value for all pulses assessed during a 15-second time period was used in subsequent analysis. The intra-observer coefficient of variation of AI was 3.4% in the present study. Radial AI was previously reported to show a close linear correlation with central AI \((r = 0.81 \text{ to } 0.96)\)\textsuperscript{5, 8, 17, 19}, thus suggesting a similar clinical utility between central and radial AI.

\subsection*{Estimation of the CHD risk}

The MEGA score was calculated based on the original report to estimate the 5-year CHD risk \textsuperscript{(Fig. 2)}\textsuperscript{15}. Briefly, seven factors (sex, age, HDL and LDL cholesterol levels, smoking status, hypertension,
and glucose abnormality) were used to calculate the MEGA score. This score increases as cardiovascular risk factors accumulate and become severe, and an increase in this score indicates an increased CHD risk. As shown in Fig. 2, Step 3, the 5-year predicted CHD risk with a MEGA score ≥ 22 in the diet (control) group is more than 2.5%. Recent observational studies conducted either at a work site or in the community in Japan reported that the incidence of CHD per 1,000 person-years in men was approximately 0.5 to 2.0(20), thus indicating the 5-year CHD risk to be 0.25 to 1.0%. We therefore defined a MEGA score ≥ 22 as a high estimated CHD risk in the present study.

**Statistical analysis**

Continuous variables were expressed as the mean ± SD. Categorical data were expressed as the percent of the total. All statistical tests were performed using the SPSS software program version 11.0.1 (SPSS Inc., Chicago, USA). Differences in the characteristics of study subjects among groups categorized by the MEGA score were tested by either analysis of variance or the Chi-square test, as appropriate. Pearson's moment correlation coefficient was used to evaluate the simple correlation. A partial correlation coefficient was used to assess the correlation between AI and various clinical parameters after controlling for height and heart rate. Analysis of covariance, with height and heart rate as covariates, was used to compare mean AI values among groups categorized by the MEGA score, followed by multiple comparisons with the Bonferroni correction. Multiple logistic regression analysis was performed to determine the odds ratio for high estimated CHD risk in the middle and highest tertile of AI in comparison to the lowest tertile. All statistical tests were two-sided and a p value of less than 0.05 was considered significant.

**Fig. 1.** A representative radial arterial pressure waveform in a 43-year-old man in the present study

The augmentation index is calculated as: P2/P1 × 100 (%), where P1 and P2 indicate the height of the early and late systolic peak, respectively.

**Fig. 2.** The calculation form of the MEGA risk prediction score

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Table 1. Characteristics of the study participants, according to the MEGA score category

<table>
<thead>
<tr>
<th>MEGA score</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Body mass index (kg/m²)</th>
<th>Heart rate (bpm)</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>Mean BP (mmHg)</th>
<th>Total cholesterol (mg/dL)</th>
<th>LDL cholesterol (mg/dL)</th>
<th>HDL cholesterol (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
<th>Fasting plasma glucose (mg/dL)</th>
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</thead>
<tbody>
<tr>
<td>≤ 9 (n=65)</td>
<td>47±4</td>
<td>170±6</td>
<td>22.6±2.0</td>
<td>67±9</td>
<td>117±10</td>
<td>72±8</td>
<td>87±8</td>
<td>236±12</td>
<td>148±14</td>
<td>74±14</td>
<td>90±43</td>
<td>91±6</td>
</tr>
<tr>
<td>10–15 (n=105)</td>
<td>46±4</td>
<td>171±6</td>
<td>23.8±2.6</td>
<td>71±9</td>
<td>116±10</td>
<td>74±8</td>
<td>88±8</td>
<td>236±13</td>
<td>163±16</td>
<td>54±9</td>
<td>125±52</td>
<td>90±6</td>
</tr>
<tr>
<td>16–21 (n=64)</td>
<td>49±6</td>
<td>170±5</td>
<td>24.3±3.4</td>
<td>71±11</td>
<td>125±17</td>
<td>79±12</td>
<td>94±13</td>
<td>239±12</td>
<td>162±17</td>
<td>53±11</td>
<td>142±66</td>
<td>91±7</td>
</tr>
<tr>
<td>≥ 22 (n=32)</td>
<td>49±5</td>
<td>170±6</td>
<td>24.9±2.3</td>
<td>75±9</td>
<td>134±14</td>
<td>87±9</td>
<td>103±10</td>
<td>239±16</td>
<td>160±27</td>
<td>50±9</td>
<td>186±154</td>
<td>109±33</td>
</tr>
</tbody>
</table>

Values are the mean ± SD or the percent of total study participants. BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVD, cardiovascular disease. *Analysis of variance or the Chi-square test, as appropriate.

Table 2. Correlation coefficient between AI and various clinical parameters

<table>
<thead>
<tr>
<th></th>
<th>Correlation coefficient</th>
<th>Partial correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.28***</td>
<td>0.25***</td>
</tr>
<tr>
<td>Height</td>
<td>-0.37***</td>
<td>-</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.42***</td>
<td>-</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.17**</td>
<td>0.35***</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.16**</td>
<td>0.42***</td>
</tr>
<tr>
<td>Mean BP</td>
<td>0.17**</td>
<td>0.41***</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.02</td>
<td>-0.02</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>-0.04</td>
<td>-0.08</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.00</td>
<td>0.11</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>0.01</td>
<td>0.19**</td>
</tr>
<tr>
<td>Family history of CVD (Yes=1)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Current smoking (Yes=1)</td>
<td>0.13*</td>
<td>0.18**</td>
</tr>
<tr>
<td>MEGA score</td>
<td>0.16**</td>
<td>0.30***</td>
</tr>
</tbody>
</table>

*Adjusted for height and heart rate. **p<0.05, ***p<0.01, and ****p<0.001. Abbreviations shown in Table 1.

Results

In the entire study population, the mean age was 47±5 years old and the mean AI was 74.4±12.6%. A high estimated CHD risk (MEGA score ≥ 22) was seen in 32 (12.0%) subjects. The characteristics of the study participants, according to the MEGA score category, are summarized in Table 1. Age, body mass index, heart rate, BP, lipid profile (with the exception of total cholesterol levels), fasting plasma glucose levels, and white blood cell count all significantly differed among the groups. The prevalence of hypertension, glucose abnormality, and current smoking also significantly differed among the groups.

The correlation coefficients between AI and various clinical parameters are shown in Table 2. The AI correlated significantly with several cardiovascular risk factors, such as age, BP, and current smoking, as well as the MEGA score. The AI also correlated significantly with both height and heart rate, thus suggesting that these are potential confounding factors for the association of AI with cardiovascular risk factors and the MEGA score. The partial correlation coefficient adjusted for height and heart rate was therefore analyzed, as shown in Table 2. The partial correlation coefficient of AI with BP, current smoking, white blood cell
count, and the MEGA score rose in comparison to the simple correlation coefficient.

**Fig. 3** shows the differences in height and heart rate-adjusted mean AI according to the classification of the MEGA score. The AI was significantly higher in groups with a MEGA score of 16–21 and ≥22 (78.7 ± 10.0% and 81.7 ± 10.2%, respectively) than in those with a score of ≤9 and 10–15 (70.6 ± 10.1% and 71.8 ± 10.1%, respectively, all p < 0.001). When subjects were dichotomized according to a MEGA score of ≥22 and ≤21 (either with or without a high estimated CHD risk), the AI was significantly higher in the group with a MEGA score ≥22 (81.5 ± 10.6%) than in those with a score ≤21 (73.4 ± 10.4%, p < 0.001).

**Table 3** denotes the results of multiple logistic regression analysis for the association between the tertile of AI and high estimated CHD risk. The highest tertile of AI (≥80%) showed a significantly increased odds ratio for high estimated CHD risk in comparison to the lowest tertile of AI (≤68%) both in Model 1 (adjusted for height and heart rate) and Model 2 (further adjusted for body mass index, family history of CVD, serum triglycerides levels, and white blood cell count, which were all potential confounders that did not constitute the MEGA score). In order to examine whether age and BP are the main contributing factors to the association between AI and the MEGA score, we further adjusted the analysis for age and BP. The odds ratio decreased, but remained significant after further adjusting for age and systolic BP (Model 3); however, when mean or diastolic BP was substituted for systolic BP in the analysis, the odds ratio further decreased and a significant level was no longer maintained (data not shown).

**Discussion**

In the present cross-sectional study, the radial AI correlated significantly with the MEGA score. This study also demonstrated the radial AI to be significantly higher in the group with subjects at high estimated CHD risk than in the group without. Moreover, when setting the lowest tertile of AI as a reference, the highest tertile of AI had a significantly increased odds ratio for high estimated CHD risk, after controlling for potential confounders that did not constitute the MEGA score. The MEGA score increases as cardiovascular risk factors accumulate and become severe, and an increase in this score indicates an increased CHD risk. The present findings therefore suggest that an augmented radial arterial wave reflection is associated both with the severity of cardiovascular risk factors and with the estimated risk of the future onset of CHD in middle-aged, Japanese men with mild to moderate hypercholesterolemia. These findings are consistent with those of several earlier studies conducted in the US and Europe that showed a significant relationship between AI and several risk prediction tools for CVD, such as the Framingham risk score and the coronary risk chart of the European Society of Cardiology.6, 7, 12

An augmented arterial wave reflection increases left ventricular afterload, which may induce left ventricular hypertrophy and may increase myocardial

![Fig. 3](image-url)
oxygen consumption \(^\text{23}\); therefore, AI is thought to not only be a marker of arterial properties but also be a potential cause of the development of CVD. These notions support the results of earlier prospective studies conducted in Western countries which demonstrated AI to be predictive of cardiovascular mortality and morbidity in high-risk patients, such as those with end-stage renal disease \(^\text{24}\) and those with CHD \(^\text{25, 26}\). In contrast, a geriatric population-based study in Italy failed to show the prognostic utility of AI \(^\text{27}\); however, it remains unclear whether AI can be used as a prognostic marker in a non-hospital-based, Japanese population. In this regard, the present results that radial AI was associated with the risk prediction scores for CHD suggest the potential utility of AI as a predictor for CVD, particularly of CHD, at least in middle-aged Japanese men with mild to moderate hypercholesterolemia. Since the present study cannot determine a causal relationship because of its cross-sectional nature, longitudinal studies will be required to clarify the predictive value of AI for a cardiovascular prognosis.

Among the factors that constitute the MEGA score, age, BP, and current smoking significantly correlated with AI in the present study. In particular, age and BP moderately correlated with AI. Moreover, the odds ratio for high-estimated CHD risk in the highest tertile of AI either decreased or did not maintain a significant level after adjusting for age and BP. These findings suggest that these factors may predominantly contribute to the positive association between AI and the MEGA score in this study population. A number of previous studies demonstrated AI to be significantly associated with age, BP, and smoking status \(^\text{2-4, 6-9, 11}\).

The present findings are therefore consistent with those of previous studies. Recently, Tomiyama et al. reported \(^\text{3}\) that radial AI obtained using the prototype of the present device was significantly associated with mean BP and current smoking in a large Japanese population (including over 6,500 subjects) without overt CVD, which further supports our present results. In contrast, there were no significant correlations between AI and LDL or HDL cholesterol levels in the present study. This lack of association may be partially explained by the characteristics of the present population that all subjects had hypercholesterolemia. In fact, a significant relationship between AI and the lipid profile was demonstrated in our earlier report conducted in the original population of the present study that included both hyper- and normocholesterolemic subjects \(^\text{28}\), as well as in those from other investigators \(^\text{5, 9}\).

There are some potential limitations to the present study. First, the MEGA score was developed for Japanese subjects with hypercholesterolemia in whom total cholesterol levels ranged from 220 to 270 mg/dL, and the present study adopted the same inclusion criteria. Moreover, the present population only included middle-aged men; therefore, the results may not accurately extrapolate to subjects not showing the aforementioned total cholesterol levels as well as to the elderly, women or other ethnic groups. Second, the number of study participants was somewhat small for an epidemiological study. This limitation may thus have affected our findings due to the small number of participants with high estimated CHD risk. Further studies including a larger number of participants are needed to support our present findings.

In conclusion, the present study showed a significant association between the radial AI and the MEGA score—an indicator of CHD risk— in middle-aged Japanese men with mild to moderate hypercholesterolemia. These results suggest that an augmented arterial wave reflection, which indicates the deterioration of arterial properties, is related to the severity of cardiovascular risk factors and the estimated CHD risk in such subjects. From a clinical perspective, the present findings raise the possibility that the radial AI predicts cardiovascular mortality and morbidity. Further prospective studies are thus required to examine whether the radial AI is a useful predictor of the future onset of CVD, including CHD.

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