Associations Between Augmentation Index and Severity of Atheroma or Aortic Stiffness of the Descending Thoracic Aorta by Transesophageal Echocardiography

Hideto Sako, MD*,**; Shin-ichiro Miura, MD*; Koichiro Kumagai, MD*; Keijiro Saku, MD*

Background: Although the aortic augmentation index (AI) is an attractive tool as an index of the vascular system, the association between radial AI or brachial-ankle pulse wave velocity (PWV) and severity of atheroma or arterial stiffness of the morphological central artery is unclear.

Methods and Results: Severity of atheroma and aortic stiffness of the descending thoracic aorta (DTA) by transesophageal echography in 96 patients with paroxysmal atrial fibrillation was assessed. The relationship between radial AI or brachial-ankle PWV and atherosclerotic lesions was also investigated. The DTA was divided into 3 equal longitudinal portions, and the atheromatous lesions of each portion of the DTA were scored according to their character and extension. Instantaneous dimensional changes in the DTA was measured, and the aortic stiffness index \( \beta \) was calculated. Radial AI was significantly correlated with age, plasma low-density lipoprotein-cholesterol concentrations, systolic blood pressure, pulse pressure, the mean atheromatous score and the mean aortic stiffness index. However, brachial-ankle PWV was not associated with central arterial stiffness. Multivariate logistic regression analysis showed that radial AI was most closely correlated with the mean atheromatous score.

Conclusions: Radial AI might be a novel tool for determining the severity of central aortic atheromatous lesions.

(Circ J 2009; 73: 1151 – 1156)

Key Words: Augmentation index; Central arterial stiffness; Transesophageal echocardiography

Central arterial stiffness has been shown under numerous conditions to be associated with increased cardiovascular events in the general population\(^1,2\) in association with hypertension (HT)\(^3\), diabetes mellitus (DM)\(^4\), hypercholesterolemia\(^5\), end-stage renal disease (ESRD)\(^6\) and advanced age\(^7\). Central arterial stiffening or reduced arterial compliance leads to augmented central blood pressure (BP) and increased cardiac afterload and is an independent predictor of cardiac events\(^8,9\). One of the more useful parameters of pressure wave analysis is the aortic augmentation index (AI), which is an index of wave reflection and a manifestation of systemic arterial stiffness. The entire arterial system contributes to the timing and amplitude of wave reflection and aortic AI. An increased aortic AI has been associated with atherosclerosis of the aorta and other sites, including the coronary arteries\(^10,11\).

Aortic AI, determined non-invasively, has been shown to be associated with angiographic coronary artery disease (CAD)\(^12\) and to be predictive of mortality in patients with ESRD, even after adjusting for pulse wave velocity (PWV)\(^13\). Aortic AI has been found to be correlated with risk factors for CAD, coronary atherosclerosis and cardiovascular outcome. A further age-related increase in arterial stiffness is observed in the presence of CAD\(^14\). This presumably reflects the widespread nature of the atherosclerotic process. Thus, conversely, an increase in arterial stiffness could be an early predictor of coronary risk and might be useful in screening. These observations suggest that increased aortic stiffness or aortic AI could be a marker of generalized atherosclerosis\(^9,12,15\). Carotid-femoral PWV, determined non-invasively, is also widely measured as an indicator of large arterial stiffness and has been shown to predict adverse cardiovascular events in hypertensive and elderly individuals\(^9,15\). Some previous studies regarding the relationship between aortic AI and carotid-femoral PWV have been reported\(^16-18\). Aortic AI and carotid-femoral PWV have been proposed as convenient and robust alternative indicators of central arterial stiffness. Recently, studies have shown that radial AI could be also a useful marker or predictor of CAD\(^19,20\). However, the relationship between AI measured at the radial artery or PWV measured at the peripheral artery and central arterial stiffness is still unclear.

The aim of the present study was to determine the association between radial AI and severity of atheroma and arterial stiffness of the central artery using transesophageal echography (TEE). We also studied the associations between brachial-ankle PWV and central arterial stiffness.

Methods

Study Participants

The participants included 100 consecutive patients with paroxysmal atrial fibrillation (PAF) who had normal sinus rhythm as defined by electrocardiogram (ECG). The ethics committee of Fukuoka University Hospital approved this study and written informed consent was obtained from each patient. Baseline demographic, medical history and lifestyle
data were collected for all participants. Height, weight, and body mass index were measured. A resting ECG was performed, and sitting brachial systolic and diastolic BP (SBP and DBP) and heart rate were measured as the average of 3 readings by use of an automatic oscillometric sphygmomanometer (HEM-907; Omron Healthcare, Kyoto, Japan). Blood samples were obtained by venipuncture after an overnight fast. Standard enzymatic methods were used to measure total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride (TG), plasma glucose, and hemoglobin (Hb) A1c. Patients with LDL-cholesterol ≥160 mg/dl or TG ≥150 mg/dl were diagnosed as hyperlipidemia (HL). Patients with SBP ≥140 mmHg or DBP ≥90 mmHg or who were receiving antihypertensive treatment were considered to have HT. Patients who were treated for DM or who showed a fasting glucose concentration ≥126 mg/dl were considered to have DM. Otherwise, the results of a 75-g oral glucose tolerance test were used to diagnose DM. None of the patients were receiving hormone replacement therapy. In addition, patients who had persistent atrial fibrillation, severe valvular heart disease, aortic dissection, aortitis, permanent pacemaker implantation, or post-operative prosthetic valve replacement, or who were receiving hemodialysis, were excluded.

Pulse Wave Analysis
Radial AI was measured in a quiet room kept at a constant temperature. After 5 min of rest and with the subject seated, brachial BP in the right upper arm was measured using an automatic cuff oscillometric sphygmomanometer after an overnight fast and 24 h off any antihypertensive medications. An arterial waveform was recorded by using automated applanation tonometry of the left radial artery (HEM-9000AI; Omron Healthcare). The radial AI was calculated as follows: (second peak SBP [SBP2] – DBP [DBP])/(first peak SBP [SBP1] – DBP) × 100 (%). This calculation was performed automatically using a fourth-order differential equation for the radial arterial waveform.

After radial AI recording was done, the individual was allowed to rest in the supine position for 5 min and brachial-ankle PWV was measured with a volume-plethysmographic apparatus (FORM/ABI, Colin Co Ltd, Komaki, Japan) while the participant remained in the same position. This instrument simultaneously records the brachial-ankle PWV and the brachial and ankle BP on the bilateral side, produces an ECG, and records heart sounds.

Evaluation of Atheromatous Lesions
This study was performed with Sonos 5500 (Phillips) ultrasound equipment with a multiplane probe transducer at 5 MHz. We examined the distal half of the circular TEE image of the descending thoracic aorta (DTA) when assessing atherosclerosis in this study. To assess atherosclerosis semi-quantitatively, we divided the DTA into three 5 cm-long segments (D1, D2 and D3) that extended from a point 25 cm from the incisor to the diaphragm (approximately 40 cm from the incisor), and continuously assessed the severity of atherosclerosis using transverse and longitudinal images from each area.

Furthermore, we classified atheromatous lesions of the
DTA into 4 categories and scored each segment on a 4-point scale (from 0 to 3) according to the severity of the atheromatous lesions on 2D images. An atheromatous score of 0 indicated a fine and smooth intima-media complex (Figure 1A). An atheromatous score of 1 indicated diffuse intima thickness of intima-media complex <3 mm (Figure 1B). An atheromatous score of 2 indicated the presence of significant raised plaque and the thickness of intima-media complex ≥3 mm (Figure 1C). An atheromatous score of 3 indicated calcified plaque that produced a marked increase in echo intensity together with acoustic shadowing behind the lesion (Figure 1D). Atheromatous lesions of the DTA were scored for each of the 3 equal portions of the DTA (D1 through D3).

Measurement of Aortic Stiffness
To assess the aortic stiffness index $\beta$, we simultaneously measured 3 equal portions of the DTA using TEE-guided M-mode images and BP by cuff sphygmomanometer. The maximum aortic lumen diameter during the ejection period ($D_{\text{max}}$) and the minimum aortic lumen diameter during the pre-ejection period ($D_{\text{min}}$) were measured (Figure 2). The aortic stiffness index $\beta$ was then calculated as follows: $\beta = \ln (\text{SBP/DBP})/(D_{\text{max}}-D_{\text{min}})/D_{\text{min}}$, where $\ln$ indicates the natural logarithm.

Statistical Analysis
Statistical analysis was carried out using the Stat View statistical software package (Stat View 5; SAS Institute, Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Data are shown as the mean±standard deviation. Categorical and continuous variables were compared between groups by a chi-square analysis and analysis of variance, respectively. A value of $P<0.05$ was considered significant. Multivariable analysis was performed by a logistic regression analysis for independent variables that were related to the radial AI.

Results
Baseline Characteristics of the Participants
The baseline characteristics of the participants are shown in Table 1. The study consisted of 76 men and 20 women with a mean age of 60±11 years (range, 31 to 84 years). Four patients who were suspected to have asymptomatic peripheral arterial disease, which presented ankle-brachial pressure index (ABI) <0.9 were excluded. Fifty-five participants had HT, and 50 of these were treated with an antihypertensive agent. HL was present in 44 participants, and 22 were treated with statins. Overall, the average radial AI was 83±10% (range, 54 to 104%), and average brachial-ankle PWV was 1,701±401 cm/s (range, 1,147 to 2,842).

Mean Atheromatous Score and Stiffness Index $\beta$ of the DTA
Table 2 shows the atheromatous score for each segment of the DTA. The mean atheromatous score was 1.26±0.61.

Table 1. Clinical Characteristics of the Participants

<table>
<thead>
<tr>
<th>Age, years</th>
<th>60±11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women, n</td>
<td>76/20</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.8±3.1</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>200±34</td>
</tr>
<tr>
<td>LDL-cholesterol, mg/dl</td>
<td>120±32</td>
</tr>
<tr>
<td>HDL-cholesterol, mg/dl</td>
<td>52±15</td>
</tr>
<tr>
<td>Triglyceride, mg/dl</td>
<td>139±100</td>
</tr>
<tr>
<td>Hemoglobin A₁c, %</td>
<td>5.6±0.7</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>55 (57%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>17 (18%)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>44 (46%)</td>
</tr>
</tbody>
</table>
| Medications, n (%) | \[\text{ACEI} \quad 9 \text{ (9%)}]
| \[\text{ARB} \quad 26 \text{ (27%)}]
| \[\text{CCB} \quad 18 \text{ (19%)}]
| \[\beta\text{-blocker} \quad 12 \text{ (13%)}]
| \[\text{Statin} \quad 22 \text{ (23%)}]
| \[\text{Radial AI, %} \quad 83±10]
| \[\text{baPWV, cm/s} \quad 1,701±401]

Data were mean±SD.

Table 2. Mean Atheromatous Scores and Stiffness Index $\beta$ of the DTA

<table>
<thead>
<tr>
<th>Atheromatous score</th>
<th>1.23±0.69</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTA (D1)</td>
<td>1.31±0.73</td>
</tr>
<tr>
<td>DTA (D2)</td>
<td>1.28±0.66</td>
</tr>
<tr>
<td>DTA (D3)</td>
<td>1.26±0.61</td>
</tr>
<tr>
<td>Mean atheromatous score</td>
<td>1.26±0.61</td>
</tr>
<tr>
<td>Mean stiffness index $\beta$</td>
<td>3.28±1.70</td>
</tr>
</tbody>
</table>

Data were mean±SD.

DTA, descending thoracic aorta.
In addition, each dimension calculated from M-mode images of the DTA, and the stiffness index $\beta$ was measured for that area (data not shown.) The mean stiffness index $\beta$ was $3.28 \pm 1.70$.

**Correlations Between AI and Other Parameters**

As shown in Figure 3, we found significant relationships between radial AI and age ($r=0.372$, $P<0.0005$), LDL-cholesterol concentrations ($r=0.219$, $P<0.05$), SBP ($r=0.350$, $P<0.0001$) and pulse pressure ($r=0.394$, $P<0.0001$). However, radial AI was not associated with HDL-cholesterol, TG, and HbA1c concentrations. In addition, there was a significant positive correlation between radial AI and the mean atheromatous score ($r=0.580$, $P<0.0001$) and the mean aortic stiffness index $\beta$ ($r=0.463$, $P<0.0001$). In contrast, there was no significant relationship between brachial-ankle PWV and the mean atheromatous score or the mean aortic stiffness index $\beta$. Furthermore, although brachial-ankle PWV was positively correlated with age ($r=0.246$, $P<0.05$), brachial-ankle PWV was not associated with radial AI.
AI and Atheromatous Score

(r=0.185, P=0.136).

Contribution of Radial AI as Assessed by Logistic Regression Analysis

Because there were significant relationships between radial AI and age, LDL-cholesterol concentrations, SBP, pulse pressure, mean atheromatous score and the mean aortic stiffness index $\beta$, a multivariate logistic regression analysis was done for independent variables (age, LDL-cholesterol concentrations, SBP, pulse pressure, mean atheromatous score and mean aortic stiffness index $\beta$) that were related to radial AI. This analysis showed that radial AI was most closely correlated with the mean atheromatous score (P<0.0001).

Discussion

In the present study, rAI was significantly and closely associated with the mean atheromatous score and mean aortic stiffness index $\beta$ assessed by TEE, whereas there was no relationship between brachial-ankle PWV and morphological central arterial stiffness. This study also indicated that the radial AI was most closely correlated with the mean atheromatous score. Furthermore, as shown in previous studies using aortic AI, the present study showed that radial AI was correlated with age and LDL-cholesterol concentrations.

There was no relationship between radial AI and brachial-ankle PWV in this study. Some studies investigating the relationship between AI and PWV have previously been conducted. Brachial-ankle PWV correlated well with aortic PWV. The validity and reproducibility of brachial-ankle PWV measurements are considerably high, and this method seems to be an acceptable marker reflecting vascular damages. However, there seems to be some methodological limitations. AI was derived non-invasively from the aortic pressure waveform obtained by applying a transfer function to the radial pressure wave form. The rationale for the use of peripheral AI was shown a strong linear correlation between radial AI and central AI estimated by a generalized transfer function. The brachial-ankle PWV measurements might not lead to true aortic PWV, because these measurements are based on spatial segments. Furthermore, there might also be some errors in the estimated path length used to calculate PWV from surface markings. AI is influenced by ventricular ejection and the tone of muscular arteries. In contrast, brachial-ankle PWV is seemed to be mostly related to changes in elastic arteries. Both indexes radial AI and brachial-ankle PWV are influenced by functional factors (cardiac function and BP/autonomic nerve) and organic factors (arterial sclerosis and mural attribute change). In this study, radial AI might be an index that reflected a more organic factor.

The TEE method is accurate for measuring aortic stiffness because it provides high-quality images of the thoracic aorta. The index $\beta$ characterizes the entire deformation behavior of the vascular wall and is independent of the intramural pressure within the physiological range. This parameter has been used in TEE studies that have estimated aortic vascular stiffness in humans. In the present study, a good correlation was seen between radial AI and mean aortic stiffness index $\beta$ (Figure 3D), which indicated that radial AI was an accurate tool for evaluating arterial stiffness and a reasonably good parameter.

Radial AI was also significantly correlated with the mean atheromatous score and LDL-cholesterol (Figure 3C). Elevation of LDL-cholesterol might predict the progression of carotid stenosis and LDL-cholesterol is a major risk factor for CAD. Interestingly, the results of a multivariate logistic regression analysis showed that radial AI was most closely correlated with the mean atheromatous score rather than the mean aortic stiffness index $\beta$. This was because participants in the present study were from a specific population; they clinically showed PAF, had multiple risk factors for atherosclerosis, were older (60±11 years), and had a high prevalence of HT (57%) and HL (46%). AI was also significantly higher in patients with hypercholesterolemia, compared with healthy controls. These results suggest that radial AI is a good and simple index of the severity of atherosclerosis.

Brachial-ankle PWV increases proportionally with age. In the present study, although there was no relationship between radial AI and brachial-ankle PWV, radial AI and brachial-ankle PWV each showed a significant correlation with age. Some previous studies have investigated the relationship between aortic AI and carotid-femoral PWV. Kelly et al reported that vasoactive drugs influence aortic AI independently of carotid-femoral PWV in healthy men. Carotid-femoral PWV is not associated with an elevated radial AI in patients with diabetes. Our results indicated that brachial-ankle PWV is also not associated with radial AI. Moreover, McEniery et al reported that while aortic AI might be a more sensitive marker of arterial stiffness and risk in younger individuals, carotid-femoral PWV is likely to be a better measure in older individuals. As the participants in this study were aged 60±11 years, we should not compare brachial-ankle PWV with radial AI.

Study Limitations

The present study had several potential limitations. These include a cross-sectional study design, advanced age, medication, and PAF. Furthermore, we only included a specific population of participants who had PAF because we needed to perform TEE in the present study. They showed sinus rhythm detected by TEE.

Conclusion

Radial AI is closely correlated to the central aortic atheromatous score and central arterial stiffness in patients with PAF assessed by TEE. In addition, there was no relationship between radial AI and brachial-ankle PWV. Therefore, radial AI and brachial-ankle PWV cannot be used interchangeably as an index for arterial stiffness in the clinical setting. Finally, because radial AI was most closely correlated with the mean atheromatous score, radial AI might be a novel tool for determining the severity of atherosclerosis.

Table 3. Contribution of AI as Assessed by Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.254</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>0.509</td>
</tr>
<tr>
<td>SBP</td>
<td>0.697</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.792</td>
</tr>
<tr>
<td>Mean aortic stiffness index $\beta$</td>
<td>0.389</td>
</tr>
<tr>
<td>Mean atheromatous score</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure. Other abbreviations see in Table 1.
Disclosure

The authors declared no conflict of interest.

References