Ankle–Arm Index is a Useful Test for Clinical Practice in Outpatients With Suspected Coronary Artery Disease

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Background Although a low ankle–arm index (AAI) has been reported to be associated with increased risk of cardiovascular mortality in several populations, no data exist concerning the impact of AAI for outpatients with suspected coronary artery disease (CAD) in the clinical setting.

Methods and Results The present study enrolled 840 outpatients (age range 35–87 years, mean age 63.9±10.2) with suspected CAD. All patients underwent AAI measurements and coronary angiography, and based on the AAI values, they were divided into group A (AAI <0.9; n=191; CAD positive, 181) and group B (AAI ≥0.9; n=649; CAD positive, 509). Metabolic syndrome (MS), obesity, and level of the inflammatory biomarker high sensitive C-reactive protein (hsCRP) were compared between the 2 groups. The sensitivity, specificity, positive and negative predictive values in predicting CAD with an AAI value <0.9 in all patients were 26.2%, 93.3%, 94.8% and 21.6%, respectively. The patients in group A was significantly older and there was a higher female-to-male ratio than in group B. The presence of hypertension and diabetes mellitus, current smoking status, and levels of low density lipoprotein (LDL)-cholesterol level, uric acid and hsCRP differed significantly between the 2 groups. Group A had a higher percentage of high LDL-cholesterol level, high waist-to-hip ratio and more positive cases of MS than group B. Multivariate logistical regression analysis showed that AAI was related to MS, high levels of hsCRP (>3 mg/L) and uric acid (>7 mg/dl) with odds ratios of 1.769, 3.907 and 2.580, respectively.

Conclusions The AAI test is an effective tool in predicting CAD in outpatients in clinical practise. (Circ J 2006; 70: 686–690)

Key Words: Ankle–arm index; Coronary artery disease; High sensitive C-reactive protein (hsCRP); Metabolic syndrome; Peripheral artery disease

Several population studies have shown that the ankle–arm index (AAI), a quick and effective method of assessing and evaluating the presence of peripheral artery disease (PAD), is a strong predictor of mortality.1–2 It has been demonstrated that subclinical cardiovascular disease in one vascular bed correlates with the presence of clinical disease in another bed.3–5 The natural history of patients with PAD is also affected by coexisting coronary artery disease (CAD) and cerebrovascular disease.6 Consequently, interest is increasing in using the AAI as a non-invasive tool for identifying of subclinical atherosclerosis, including CAD, but the role of AAI in predicting a CAD diagnosis in clinical practice is unknown.

Additionally, metabolic syndrome (MS), which refers to the clustering of diabetes mellitus (DM) or impaired glucose tolerance, hypertension, obesity, and dyslipidemia, is closely associated with cardiovascular morbidity and mortality.7,8 Because PAD is correlated with atherosclerotic ischemic heart disease, PAD has also, predictably, been strongly associated with several CAD classic risk factors, particularly DM, current smoking status and hypertension.9,10 Therefore, a relationship between MS and AAI may exist and was investigated in the present study.

Methods

Between September, 2002 and December, 2004, 858 consecutive outpatients suspected of having CAD were included in a double-blind, prospective study. Informed consent was given by each patient. Eighteen patients meeting the following criteria were excluded: severe cardiac insufficiency (n=8), prior vascular surgery involving the aorto-iliac vessels because of ischemic legs (n=6), and AAI ≥1.5 (n=4) in both legs at baseline because this ratio is associated arterial calcification and increased wall stiffness as reported by previously.11 Thus, a total of 840 patients were enrolled in the study.

All patients underwent coronary angiography. Digital baseline coronary angiograms were quantitatively analyzed off-line with an automated edge detection system (DCI or Integris BH3000, Philips, Eindhoven, The Netherlands) using the dye-filled guiding catheter for reference. Lesion diameter was measured during diastole. The diameter of the reference vessel was measured proximal to the target lesion. Positive CAD was defined as stenosis >50% in a native coronary artery.

Arterial assessments were performed by experienced cardiologists following a standard protocol as previously.
Table 1  Clinical and Biochemical Characteristics of the Patients Suspected of Having CAD

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=191)</th>
<th>Group B (n=649)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>68.7±9.1</td>
<td>62.0±10.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>M/F</td>
<td>120 (62.8%)/71 (37.2%)</td>
<td>489 (75.3%)/160 (24.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>81 (42.4%)</td>
<td>210 (32.4%)</td>
<td>0.012</td>
</tr>
<tr>
<td>Hypertension</td>
<td>113 (59.2%)</td>
<td>315 (48.5%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Smoking</td>
<td>86 (45.0%)</td>
<td>238 (36.7%)</td>
<td>0.042</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>187.3±49.8</td>
<td>181.8±38.7</td>
<td>0.103</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>150.7±130.8</td>
<td>165.2±130.2</td>
<td>0.175</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>42.1±11.4</td>
<td>40.9±10.8</td>
<td>0.208</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>117.4±41.3</td>
<td>109.0±32.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.1±1.8</td>
<td>6.8±1.8</td>
<td>0.021</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>4.7±2.5</td>
<td>2.3±4.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of CVA</td>
<td>16 (8.4%)</td>
<td>39 (4.6%)</td>
<td>0.068</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>63.4±14.5</td>
<td>65.1±11.2</td>
<td>0.084</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; HDL, high density lipoprotein; LDL, low density lipoprotein; hsCRP, high sensitive C-reactive protein; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction.

Patients were examined in the supine position after at least 5 min of rest. Systolic blood pressure was measured in both arms and in the right and left posterior tibial artery. A Doppler stethoscope (8 MHz) and standard blood pressure cuff connected to a random zero manometer were used to detect arterial flow. The resting AAI was the ratio of ankle systolic blood pressure (average of pressures recorded in the posterior and anterior tibial arteries) to the higher of the left or right brachial pressures. The lower AAI value obtained for both legs was used as the gauge of disease in the data analysis.

Patients were assigned to group A (AAI <0.9) or group B (AAI ≥0.9) based on AAI results. Group A comprised 191 patients (120 males, 71 females; age range 44–85 years) and group B comprised 649 patients (489 males, 160 females; age range 35–87 years).

The sensitivity, specificity, positive and negative predictive values (PPV and NPV) in predicting CAD by AAI <0.9 were defined as follows: sensitivity = patients with CAD proved by coronary angiography and AAI <0.9/patients with CAD proved by coronary angiography; specificity = patients without CAD proved by coronary angiography and AAI ≥0.9/patients without CAD proved by coronary angiography; PPV = patients with CAD proved by coronary angiography and AAI <0.9/patients with AAI <0.9; NPV = patients without CAD proved by coronary angiography and AAI ≥0.9/patients with AAI ≥0.9.

The high sensitive C-reactive protein (hsCRP) levels were determined with an ultrasensitive CRP test with a coefficient of variation of less than 5% and a low detection limit of 0.175 mg/L (N Latex CRP; Dade Behring Co, Ltd). Criteria for MS were adopted from the Third Report of the National Cholesterol Education Program Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adults Treatment Panel III, ATP III).22 Subjects who met at least 3 criteria were diagnosed with MS. Waist circumference was measured at a point midway between the lowest rib and the iliac crest while standing. Male patients with a waist circumference >102 cm and female patients with a waist circumference >88 cm were considered to have high WHR. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of body length in meters (kg/m²). A BMI ≥30 kg/m² was defined as obese.

The chi-square test was used to compare the following data: gender; presence of DM, hypertension or MS; current smoking status; history of cerebrovascular accident; and distribution of dyslipidemia or obesity. The non-paired Student's t-test was used to compare age, number of lesions or target vessel involvement from angiography results, left ventricular ejection fraction (LVEF) and clinical laboratory data between the 2 groups. The results are expressed as mean±standard deviation (SD). Multivariate analysis was performed with logistical regression to identify the independent variable. Odds ratios (ORs) were derived from the logistic model and the 95% confidence intervals (CI) of the ORs were computed for the principal results. A p-value <0.05 was considered statistically significant.

Results

The percentage of patients with AAI <0.9 was 22.7% (191/840). Group A consisted of 191 patients, 181 of whom had CAD confirmed by angiography. Group B, which comprised 649 patients, had 509 patients with CAD. The sensitivity, specificity, PPV and NPV in predicting CAD using AAI <0.9 in all patients were 26.2% (181/690), 93.3% (140/150), 94.8% (181/191) and 21.6% (140/649), respectively.

Comparison of the demographic characteristics of the 2 groups revealed no differences for the following data: history of cerebrovascular accident; LVEF; and levels of cholesterol, triglyceride or high density lipoprotein (HDL)-cholesterol. Patients in group A were significantly older than those in group B (68.7±9.1 vs 62.0±10.0 years, p<0.0001). Regarding gender distribution, males were predominant in both groups (62.8% in group A, 75.3% in group B). However, a comparison of gender distribution between the 2 groups showed that females accounted for a higher proportion of group A than of group B (37.2% vs 24.7%, p=0.001). The following significant differences were found between the 2 groups: presence of hypertension (59.2% vs 48.5%, p=0.011); DM (42.4% vs 32.4%, p=0.012); and current smoking status (45.0% vs 36.7%, p=0.042). The low density lipoprotein (LDL)-cholesterol, uric acid and hsCRP levels were significantly higher in group A.
Diabetes mellitus (%) 81 (42.4%) 210 (32.4%) 0.012
Hypertension (%) 113 (59.2%) 315 (48.5%) 0.011
Hyper-triglyceride (%) 73 (38.2%) 263 (40.5%) 0.614
Hyper-cholesterol (%) 66 (34.6%) 191 (29.4%) 0.181
Hyper-LDL-cholesterol (%) 61 (31.9%) 158 (24.3%) 0.039
Low-HDL-cholesterol (%) 110 (57.6%) 385 (59.3%) 0.676
High waist girth (%) 57 (29.8%) 174 (26.8%) 0.408
Waist circumference (cm) 92.0±10.0 92.6±9.6 0.461
High BMI (%) 39 (20.4%) 164 (25.3%) 0.179
BMI (kg/m²) 25.3±4.2 26.4±3.9 0.001
High WHR (%) 145 (75.9%) 439 (67.6%) 0.032
WHR 0.98±0.08 0.97±0.08 0.053
Criteria of metabolic syndrome 2.3±1.3 2.1±1.3 0.017
Number of vessels 1.9±0.9 1.3±0.9 <0.0001
Number of lesions 2.4±1.2 1.5±1.2 <0.0001
LM involvement (%) 16 (8.4%) 36 (5.5%) 0.171

BMI, body mass index; WHR, waist-hip ratio; LM, left main coronary artery. Other abbreviations see in Table 1.

Discussion

Previous studies have recognized that patients with PAD have a higher risk of adverse cardiovascular events, preclinical carotid plaque, strokes and transient ischemic accidents. These studies demonstrated that low AAI values, especially <0.9, are indicative of generalized atherosclerosis.13–15 Furthermore, epidemiological and clinical studies have indicated that low AAI levels are associated with cardiovascular and overall mortality, a fact that makes them potentially useful as independent predictors. An AAI <0.9 has been consistently associated with a 3- to 8-fold increase in cardiovascular death and 2- to 5-fold increase in all-causes death compared with an AAI >0.9.16,17 However, to our knowledge, there is a lack of data for AAI in outpatients suspected of having CAD in clinical practise. In this study, outpatients suspected of having CAD who underwent AAI examinations had high specificity and PPV, although sensitivity and NPV were relatively low, illustrating that low AAI values are an alarm for definite CAD in outpatients suspected of having the disease. Furthermore, in our previous report, AAI was associated with the severity of CAD in patients who had been identified with ischemic heart disease. More complex stenotic lesions (B2 or C) and morphology (calcified, chronic total occlusion, irregular, bifurcation and diffuse) were found in the group with AAI <0.9 than in those with AAI ≥0.9. Therefore, AAI may be a simple, objective and inexpensive technique for identifying persons at high risk of coronary atherosclerotic disease.

As PAD is correlated with atherosclerotic ischemic heart disease, PAD has also, predictably, been closely associated with the classic risk factors for CAD.19–21 As expected, the baseline characteristics in the present study are compatible with these findings, with the exception of no differences in dyslipidemia among groups with and without PAD. In the present study, with the exception LDL-cholesterol, there was no significant difference in serum lipids between the 2 groups. In the 2001 ATP III guidelines, elevated LDL-cholesterol is the principal target of risk reduction therapy. However, LDL-cholesterol has rarely been assessed with PAD. It had been shown to be an independent predictor of the occurrence of intermittent claudication in a Finnish study22 our findings are the first to suggest a positive correlation between LDL-cholesterol and PAD in outpatients suspected of having CAD.

Hyperuricemia as an independent risk factor for atherosclerosis remains controversial. Considerable epidemiological and experimental evidence suggest that serum uric acid is an important independent risk factor for cardiovascular and renal diseases, especially in patients with hypertension, heart failure or DM. The First National Health and Nu-
significant component of MS. Recent reports have shown uric acid levels as a risk factor for heart disease. The World Health Organization recently deemed uric acid levels as a significant component of MS. Recen studies on uric acid as a risk factor for atherosclerosis have assessed its association with heart disease. The World Health Organization recently deemed uric acid levels as a significant component of MS. Recent reports have shown that an elevated uric acid level is a risk factor for PAD in Australian and Taiwanese diabetic populations. However, no study has reported the relationship between serum uric acid levels and patients suspected of having CAD with or without PAD. The present study identified significantly higher uric acid levels in patients with PAD suspected of having CAD in the clinical setting than in those without PAD.

Recently, hsCRP has been considered as a powerful independent risk factor for atherosclerosis and other related complications in healthy individuals and patients with cardiovascular disease, with a predictive power exceeding that of LDL-cholesterol. Furthermore, the relationship between hsCRP level and both insulin resistance and MS has also been reported. A recent review article demonstrated that hsCRP is currently under careful consideration as an addition clinical criterion for MS. However, the relationship between hsCRP and PAD has not yet been established. A recent study showed that the serum hsCRP level is independently associated with PAD in type 2 DM patients. McDermott et al reported that higher circulating D-dimer and hsCRP levels are strongly correlated with greater disability for walking and physical functioning in individuals with PAD. In the present study, hsCRP levels were significantly and positively correlated with patients with PAD suspected of having CAD, which provides further evidence that hsCRP levels are associated with CAD.

Obesity has been proven to be an independent risk factor for CAD. It is now a worldwide concern because of its major role in a constellation of morbidity, including cardiovascular disease, hypertension, DM, and dyslipidemia. Prospective epidemiological studies have revealed that central obesity (determined by waist circumference and WHR) is more relevant to CAD risk than general obesity (determined by body weight and BMI). In the present study, group A had a higher percentage of subjects with high WHR than group B (75.9% vs 67.6%, p = 0.032), which suggests that patients with PAD have a higher CAD risk than those without PAD and is a finding that is compatible with results obtained by previous studies.

Notably, in the general population AAI declined with age, and the presence of DM or hypertension. Patients in group A were older, and as expected had higher percentages of hypertension and DM. Because there were significant differences in these clinical characteristics between the 2 groups in this study, the differences for AAI could have only resulted from differences in these clinical parameters. Multivariate logistic regression analysis was required to determine whether AAI is an independent variable and in this study, a low AAI had a relation to MS, and high levels of hsCRP and uric acid. This is a crucial point supporting the use of AAI rather than other variables.

This study confirmed that in the clinical setting AAI could predict potential hazards in patients suspected of having CAD. Low AAI values indicated high uric acid and hsCRP levels, which are potential risk factors for atherosclerosis and atherosclerosis-related complications such as cardiovascular morbidity and mortality, stroke, and decreased occurrence of MS. Furthermore, because a low AAI value had a high specificity and PPV (93.3% and 94.8%, respectively) in predicting CAD diagnosis in this study, physicians should be aware that patients with a low AAI are at considerable risk for CAD. We conclude that the AAI test can be used to identify patients at high risk for CAD and MS.

Acknowledgment

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