Diabetes mellitus (DM) is a major risk factor among typical coronary risk factors that must be considered in the primary and secondary prevention of coronary artery disease (CAD). The prognosis of diabetic patients without known CAD is reportedly similar to those with previous myocardial infarction. The diagnostic limitation for CAD in this high-risk group is that clinical symptoms are atypical or even absent, and routine screening tests such as stress myocardial perfusion imaging (MPI) are not effective. In contrast, the development of simultaneous brachial and ankle blood pressure measurements enables the easy evaluation of the ankle-brachial pressure index (ABI), which is reported to be a diagnostic and prognostic marker of atherosclerosis.

We hypothesized that if this simple marker can increase the likelihood of diagnosing CAD in diabetic patients, the diagnostic yields of MPI might be improved with a combined approach using ABI and MPI. Accordingly, we retrospectively evaluated patients with suspected CAD who underwent both simultaneous brachial and ankle blood pressure measurements and stress MPI to evaluate the diagnostic value of ABI in diabetic patients.

**Methods**

**Patients**

We retrospectively evaluated 2,381 consecutive patients with suspected CAD who had undergone both simultaneous brachial and ankle blood pressure measurements and stress MPI between May 2001 and August 2007. The indication for measurements of brachial-ankle pulse wave velocity/ankle-brachial pressure index was based on patients’ profile indicating suspected atherosclerosis. Stress MPI was indicated to patients who were suspected of having CAD. Clinical grounds for suspected CAD were based on medical history, coronary risk profiles, electrocardiographic findings, and associated vascular diseases. We excluded 1,146 patients who did not undergo both simultaneous brachial and ankle blood pressure measurements and stress MPI.

**Methods and Results**

A total of 407 consecutive patients (319 men and 88 women, age range 68±11 years) with suspected CAD, who were not complaining of anginal pain, were evaluated. Among these patients, 170 had diabetes. Stress myocardial perfusion imaging and simultaneous brachial and ankle blood pressure measurements were performed to obtain the ischemic total perfusion deficit (TPD) and ankle-brachial pressure index (ABI), respectively. Ischemic TPD was not significantly different between men and women, whereas ischemic TPD was significantly greater in diabetic patients than in non-diabetic patients (6.9±7.7% vs. 4.9±6.1%; P=0.005). In diabetic patients, ischemic TPD was not significantly different between men and women. However, women with ABI<0.9 showed significantly greater ischemic TPD than those with ABI≥0.9 (12.1±10.8% vs. 5.1±5.9%; P=0.04), whereas no difference in ABI was observed in men.

**Conclusions**

ABI was useful in evaluating CAD in asymptomatic women with diabetes to detect a high-risk subset showing the ischemic TPD of >10%, which is regarded as a scintigraphic indicator for coronary revascularization.

(Circ J 2011; 75: 2206-2212)

**Key Words:** Ankle-brachial pressure index; Coronary artery disease; Diabetes mellitus; Myocardial perfusion imaging; Women

**Background:** Clinical symptoms of coronary artery disease (CAD) are often atypical in women, particularly in those with diabetes mellitus. Therefore, a simple diagnostic test to identify a high-risk subset of women with diabetes who are likely to have CAD is important.

**Methods and Results:** A total of 407 consecutive patients (319 men and 88 women, age range 68±11 years) with suspected CAD, who were not complaining of anginal pain, were evaluated. Among these patients, 170 had diabetes. Stress myocardial perfusion imaging and simultaneous brachial and ankle blood pressure measurements were performed to obtain the ischemic total perfusion deficit (TPD) and ankle-brachial pressure index (ABI), respectively. Ischemic TPD was not significantly different between men and women, whereas ischemic TPD was significantly greater in diabetic patients than in non-diabetic patients (6.9±7.7% vs. 4.9±6.1%; P=0.005). In diabetic patients, ischemic TPD was not significantly different between men and women. However, women with ABI<0.9 showed significantly greater ischemic TPD than those with ABI≥0.9 (12.1±10.8% vs. 5.1±5.9%; P=0.04), whereas no difference in ABI was observed in men.

**Conclusions:** ABI was useful in evaluating CAD in asymptomatic women with diabetes to detect a high-risk subset showing the ischemic TPD of >10%, which is regarded as a scintigraphic indicator for coronary revascularization.

(Circ J 2011; 75: 2206-2212)

**Key Words:** Ankle-brachial pressure index; Coronary artery disease; Diabetes mellitus; Myocardial perfusion imaging; Women
with known CAD such as those with previous myocardial infarction or a history of coronary revascularization. Patients with acute coronary syndrome were not included because stress MPI was considered inappropriate to such patients. In addition, 828 patients who had complained of anginal chest pain were also excluded. Among the remaining 407 patients, 170 (127 men and 43 women; age range, 68±10 years) had DM. The study protocol was approved by the Ethics Committee of Tokyo Medical University (No. 1323).

**Assessment of Coronary Risk Factors**

Risk factors included in the assessment were hypertension, hypercholesterolemia, DM, and cigarette smoking. Hypertension was defined as a history of systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, or documented hypertension on at least 2 occasions in outpatient clinics. Hypercholesterolemia was defined as a fasting serum total cholesterol level ≥220 mg/dL. DM was diagnosed using criteria proposed by the Japanese Diabetes Society.

**Measurements of Ankle-Brachial Pressure Indexes**

Brachial-ankle pulse wave velocity was measured using volume-plethymographic apparatus (Form/ABI, Colin Co Ltd, Komaki, Japan) with the patient in a supine position after resting in the same position for at least 5 min, as described previously. This instrument simultaneously records the brachial and ankle blood pressures on the left and right sides, and also records the electrocardiogram (ECG) and heart sounds. The electrocardiographic electrodes were placed on both wrists, and cuffs were wrapped around both brachia and ankles. Pulse volume waveforms at the brachium and ankle were recorded using a semiconductor pressure sensor. The ABI was defined as the lowest value for both sides as described previously, and peripheral artery disease (PAD) was defined as an ABI <0.9. All recordings were performed while the patients were taking their regular medication, but were not receiving other intravenous drugs at the time of the study.

**Stress MPI**

Stress MPI with ⁹⁹ᵐTc-sestamibi was performed using a 1-day program.

### Table 1. Baseline Characteristics of Men With and Without DM

<table>
<thead>
<tr>
<th></th>
<th>DM (+) (n=127)</th>
<th>DM (–) (n=192)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±11</td>
<td>68±10</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>89 (70%)</td>
<td>107 (56%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>75 (59%)</td>
<td>81 (42%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking</td>
<td>97 (76%)</td>
<td>52 (27%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECG abnormality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>108 (85%)</td>
<td>154 (80%)</td>
<td>NS</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>19 (15%)</td>
<td>38 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>ABI</td>
<td>0.76±0.33</td>
<td>0.79±0.33</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>85 (67%)</td>
<td>118 (61%)</td>
<td>NS</td>
</tr>
<tr>
<td>MPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress TPD</td>
<td>12.0±12.2</td>
<td>8.9±9.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Fixed TPD</td>
<td>5.4±7.9</td>
<td>4.5±7.1</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic TPD</td>
<td>6.8±7.5</td>
<td>4.9±6.0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; ECG, electrocardiogram; ABI, ankle-brachial pressure index; MPI, myocardial perfusion imaging; TPD, total perfusion deficit.

### Table 2. Baseline Characteristics of Women With and Without Diabetes

<table>
<thead>
<tr>
<th></th>
<th>DM (+) (n=43)</th>
<th>DM (–) (n=45)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>669</td>
<td>72±10</td>
<td>0.0005</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (79%)</td>
<td>22 (49%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>32 (74%)</td>
<td>18 (40%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (30%)</td>
<td>3 (7%)</td>
<td>0.004</td>
</tr>
<tr>
<td>ECG abnormality</td>
<td>26 (60%)</td>
<td>25 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Symptom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>22 (51%)</td>
<td>35 (78%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>21 (49%)</td>
<td>10 (22%)</td>
<td>0.007</td>
</tr>
<tr>
<td>ABI</td>
<td>0.98±0.28</td>
<td>0.92±0.29</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>14 (33%)</td>
<td>16 (36%)</td>
<td>NS</td>
</tr>
<tr>
<td>MPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress TPD</td>
<td>11.4±12.9</td>
<td>6.9±9.0</td>
<td>NS</td>
</tr>
<tr>
<td>Fixed TPD</td>
<td>4.6±7.2</td>
<td>2.2±3.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Ischemic TPD</td>
<td>7.4±8.4</td>
<td>4.8±6.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations see in Table 1.
protocol\textsuperscript{18} in 60 patients. Symptom-limited multistep exercise using a bicycle ergometer was undertaken by 13 patients.\textsuperscript{15} $^{99}$Tc-sestamibi (259 MBq) was administered when submaximal heart rate, chest pain, an ST-segment depression $\geq 0.1$ mV or leg fatigue developed, and the exercise was then continued for 1 min at the same level. Image acquisition was started 30 min after the last exercise session. In the remaining 47 patients, adenosine triphosphate disodium (0.16 mg $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$) was administered intravenously for 6 min,\textsuperscript{17} and 3 min later, $^{99}$Tc-sestamibi (259 MBq) was given intravenously. Image acquisition was started 30 min later. On the same day, patients were given $^{99}$Tc-sestamibi (777 MBq) while at rest and 30 min later, quantitative-gated myocardial single-photon emission computed tomography (SPECT) images were acquired.

Using $^{201}$Tl (111 MBq), myocardial SPECT was performed in 347 patients; SPECT was carried out during exercise in 57 patients, and the remaining 290 patients underwent adenosine triphosphate-loading myocardial SPECT. The protocols used to induce stress to these patients were similar to previously reported methods.\textsuperscript{16,18} Delayed images were acquired 4 h later using an ECG gate program.

Data were acquired with a 2- or 3-detector gamma camera (Prism 2000XP or Prism 3000XP, Picker, Cleveland, OH, USA) for 180- or 360-degree arcs. For both radioisotopes, a low-energy, high-resolution parallel multihole collimator was used. ECG-gated SPECT images were reconstructed from the data by a data processor (Odyssey VP, Picker) combined with a Butterworth filter (order 8; cut-off frequency, 0.25 cycle/cm for $^{99}$Tc-sestamibi and 0.2 cycle/cm for $^{201}$Tl) and a ramp filter.

According to a previously reported method,\textsuperscript{19} each SPECT image was divided into 20 segments. The accumulation of radioisotopes in the myocardium was visually evaluated by 2 cardiologists using a 5-grade scale: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake) or 4 (absence of uptake). Disagreements in image interpretation were resolved by consensus. The total of the scores for all the segments during exercise and at rest was designated the summed stress score and the summed rest score, respectively. The summed difference score was defined as a summed stress score minus the summed rest score.\textsuperscript{18} In addition, these indices were converted to a percentage of the total left ventricular (LV) myocardium involved with stress, ischemic, or fixed defects, by dividing the summed scores by 80 (the maximum potential score [4$\times$20]), and multiplying it by 100.\textsuperscript{20} These indices were named as stress, ischemic, or fixed total perfusion deficit (TPD). Abnormal MPI results were defined as a summed stress score of $\geq 4$ and/or a summed difference score of $\geq 2$.\textsuperscript{21}

**Statistical Analysis**

Results are expressed as mean$\pm$SD. A Student’s t-test was used to compare the means of the continuous variables, and contingency tables were analyzed using the chi-square test. A P value $<0.05$ was regarded as denoting statistical significance. The computations were performed using the SPSS-PC+ computer program (Version 11.0; SPSS, Chicago, IL, USA).

**Results**

**Clinical Risk Factors and Symptoms**

In the 407 patients, hypertension in 252 (62%), hypercholesterolemia in 206 (51%), DM in 170 (42%), and smoking in 165 (41%) were found to be coronary risk factors. In addition, ECG abnormality was observed in 195 patients (48%). We examined the clinical characteristics of 319 men, and compared 127 men with DM and 192 men without DM (Table 1). The percentage of men with DM who had hypertension, hypercholesterolemia, and who smoked cigarettes was significantly larger than the percentage of men without DM (P=0.007, P=0.002, and P<0.0001, respectively). The clinical characteristics of 88 women (43 with DM and 45 without DM) are also shown in Table 2. The percentage of women with DM who had hypertension, hypercholesterolemia, and who smoked cigarettes was significantly larger than the percentage of women without DM (P=0.003, P=0.001, and P=0.004, respectively).

Of the 407 patients, 319 (78%) were asymptomatic. The number of asymptomatic patients with DM was significantly less than the number without DM for women (51% vs. 78%; P=0.008), whereas there was no significant difference
between patients with DM and patients without DM for men (Tables 1, 2). There were 88 patients (22%) with breathlessness. Breathlessness was present in more patients with DM than in those without DM for women (49% vs. 22%; P=0.007) (Table 2).

**Measurements of Ankle-Brachial Pressure Indexes**

The mean ABI in all patients was 0.81±0.33. ABI was not significantly different between patients with DM and those without DM for both men and women. The number of patients with PAD was not significantly different between patients with DM and those without DM for both men and women (67% vs. 61% and 33% vs. 36%, respectively; P=NS) (Tables 1, 2).

**Scintigraphic Findings**

Abnormal MPI results were observed in 266 of the 407 patients (65%) and in 121 of the 170 diabetic patients (71%). In the 407 patients, the mean stress TPD, fixed TPD, and ischemic TPD were 10.2±10.9, 4.5±6.7, and 6.0±7.0%, respectively. Furthermore, extensive myocardial ischemia, defined as ischemic TPD ≥10%, was found in 97 (24%) and 50 (29%) of all patients and diabetic patients, respectively.

Ischemic TPD was not significantly different between men and women (5.7±6.7% vs. 6.1±6.5%; P=NS) (Figure 1). Mean ischemic TPD was greater in patients with DM than in those without DM (6.9±7.7% vs. 4.9±6.1; P=0.005) (Figure 2). Ischemic TPD was greater in patients with ABI<0.9 than in those with ABI≥0.9 (6.5±7.3 vs. 4.8±6.1%; P=0.01) (Figure 3A). In men, stress TPD and ischemic TPD
were greater in patients with DM than in those without DM (12.0±12.2 vs. 8.9±9.7, P=0.02; 6.8±7.5 vs. 4.9±6.0, P=0.02) (Table 1). In female patients with DM, stress TPD and ischemic TPD were not significantly different between patients with DM and those without DM (Table 2).

**Relationship Between ABI and Scintigraphic Findings in Patients With DM**

In the 170 patients with DM, ischemic TPD was not significantly different between men and women (6.8±7.5% vs. 7.4±8.4%; P=NS), while ischemic TPD was also not statistically different between 99 patients with an ABI<0.9 and 71 patients with an ABI≥0.9 (7.8±8.2% vs. 5.8±6.9%; P=NS). However, 14 female patients with DM with an ABI<0.9 showed significantly greater ischemic TPD than 29 female patients with DM with an ABI≥0.9 (12.1±10.8% vs. 5.1±5.9%; P=0.04), whereas no such difference was observed in male patients with DM (7.0±7.5% vs. 6.2±7.5%; P=NS) (Figures 3B, C).

In 127 men with DM, the intermediate- (5–9% ischemic TPD) and high-risk (ischemic TPD≥10%) groups were not significantly different between 85 patients with an ABI<0.9 and 42 patients with an ABI≥0.9 (24% vs. 21%, and 31% vs. 24%, respectively; P=NS for both). However, in 43 women with DM, the high-risk group was significantly greater in 14 patients with an ABI<0.9 than in 29 patients with an ABI≥0.9 (57% vs. 21%; P=0.02) (Figure 4). In 5 of the 8 PAD patients in the high-risk group, coronary angiography was performed, revealing 3-vessel disease in 4 patients and 1-vessel disease with a 99% stenosis of the large lateral branch in the remaining patient.

**Discussion**

In this study, we set to determine the importance of the ABI in the diagnosis of CAD in patients without anginal pain. The identification of diabetic patients who might require intensive treatment for CAD before the occurrence of catastrophic cardiac events is often difficult, due partly to the lack of typical chest pain. Furthermore, recent efforts to diagnose high-risk diabetic patients with the use of stress MPI have been unsuccessful, because asymptomatic patients with DM fell into a low-risk category. Thus, initial risk stratification of an asymptomatic or minimally symptomatic diabetic population using a simple and inexpensive test is mandatory, before applying sophisticated diagnostic modalities such as stress MPI or coronary computed tomography.

In the present study, 407 patients without anginal pain, including 170 diabetic patients, were initially evaluated by simultaneous brachial and ankle blood pressure measurements to obtain ABI. In addition, the presence or absence of myocardial ischemia, as well as the extent of inducible ischemia, was assessed by stress MPI. In patients with an ABI<0.9, which is regarded as a marker for PAD, the extent of inducible ischemia was greater than in those with an ABI≥0.9. In diabetic patients, the extent of inducible ischemia was similar in men and women. However, women with an ABI<0.9 showed a greater extent of inducible ischemia than those with an ABI≥0.9, whereas no such increase in ABI was observed in men (Figure 3). In the current study, if women with diabetes had an ABI<0.9, the likelihood of them having extensive myocardial ischemia in ≥10% of the LV exceeded 50% (Figure 4). Because inducible myocar-
dial ischemia in ≥10% of the LV is regarded as a threshold for coronary revascularization, risk stratification combining ABI with stress MPI appears important for women with diabetes without anginal pain.

The ideal method of screening asymptomatic diabetic patients for CAD has not yet been elucidated. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study prospectively investigated 1123 asymptomatic diabetic patients, and found abnormal MPI findings in 16% and extensive myocardial ischemia in ≥10% of the LV in only 1% of patients. As a result, the cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischemia over 4.8 years. A higher incidence of abnormal MPI findings (38%) was reported in the Japanese Assessment of Cardiac Events and Survival Studies by quantitative gated SPECT (J-ACCESS-2) study, which included 513 diabetic patients with thickened carotid artery walls and greater intima-media thickness and metabolic syndrome. The final outcome of this 3-year study is not yet known. In contrast, Rajagopalan et al found abnormal MPI findings in 58% and high-risk findings in 18% of 1,427 asymptomatic diabetic patients from the nuclear cardiology database of the Mayo Clinic. Overall, 9% of the study patients were shown to have angiographic high-risk CAD. In the present study, abnormal MPI results were observed in 59% and 63% of all patients and in those with diabetes, respectively; extensive myocardial ischemia in ≥10% of the LV was also demonstrated in 24% and 29%, respectively. The aforementioned observation underscores the importance of risk profiles in each study population. The risk levels of our patients were similar to those presented by Rajagopalan et al and were higher than that of the J-ACCESS-2 study, although the patients in the present study did not have metabolic syndrome or a thickened carotid artery wall and greater intima-media thickness. These differences in patient characteristics might explain the high diagnostic performance of stress MPI in this study.

A recent international registry, which included 5,073 Japanese patients, demonstrated a higher occurrence of myocardial infarction or stroke in patients with atherosclerosis such as PAD than in patients without. One of the 2 most important variables that were related to a high-risk finding in the study by Rajagopalan et al was the presence of PAD. Even in the DIAD study, cardiac death or non-fatal myocardial infarction was significantly related to PAD. In the present study, the extent of myocardial ischemia was significantly greater in patients with PAD. However, a higher prevalence of PAD in men with diabetes decreased the predictive value of this marker for CAD. In contrast, the low prevalence of PAD made this simple marker valuable to detect a high-risk MPI finding in women with diabetes. Thus, simultaneous measurements of the brachial and ankle blood pressures on the left and right sides are useful not only to diagnose PAD, but also to initially stratify the risk of CAD, particularly in women.

Study Limitations
The present study was performed retrospectively, and therefore, a prospective approach that applies ABI measurements and stress MPI in a large patient population is necessary. In particular, we previously reported a mean ischemic TPD of 7.9% in 113 subjects with 3 or more coronary risk factors, whereas in the current study, we obtained an average ischemic TPD of 7.0% in 85 asymptomatic male patients with both DM and PAD. Although the effect of the number of risk factors and/or the presence of PAD on the development of myocardial ischemia might differ in patients with or without DM, the results based on a small number of patients require further confirmation by data accumulation. In addition, coronary angiography was not performed in all patients because it is ethically difficult to perform invasive coronary angiography in asymptomatic patients whose MPI findings are normal. Rather, recent evidence indicates that inducible myocardial ischemia in ≥10% of the LV is an important indicator for coronary revascularization to improve the prognosis of patients. Thus, the assessment of CAD by the use of stress MPI is considered appropriate in this group of patients without anginal pain.

Conclusions
ABI measurements were useful for evaluating a high-risk subset for CAD in women with DM. If such women had an ABI of <0.9, the likelihood of having myocardial ischemia in ≥10% of the LV, which is a scintigraphic indicator for coronary revascularization, exceeded 50%.

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Disclosures
Conflicts of interest: none declared.

References


