The Correlation Between Coronary Stenosis Index and Flow-Mediated Dilation of the Brachial Artery

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We examined the relationship between flow-mediated dilation (FMD) of the brachial artery and the extent and severity of coronary artery disease (CAD). Using high-resolution ultrasonography, we measured FMD and nitroglycerin-induced brachial artery dilation. We studied 121 patients (77 men, 44 women; mean age 64±11 years, range 25–79 years) who underwent coronary arteriography. The extent and severity of CAD were assessed by the coronary stenosis index (CSI). The adjusted FMD correlated inversely with CSI ($r = -0.63, p<0.0001$). Multivariate analysis demonstrated that the adjusted FMD was an independent predictor of CSI. The adjusted FMD was 10.2±4.9% in patients without CAD (n=32), 7.7±6.0% in patients with single-vessel disease (n=31), 5.2±5.5% in patients with double-vessel disease (n=29), and 2.0±3.9% in patients with triple-vessel disease (n=29). The adjusted FMD was significantly lower in the double-vessel (p<0.01) and triple-vessel (p<0.0001) disease groups than in patients without CAD. The adjusted FMD was significantly lower in the triple-vessel disease group than in the single-vessel disease group (p<0.001). Based on our results, as coronary atherosclerosis becomes more severe, the adjusted brachial artery FMD becomes more severely impaired. *(Jpn Circ J 1998; 62: 425–430)*

Key Words: Flow-mediated dilation; Coronary artery disease; Coronary stenosis index

Clermajer et al. recently developed a non-invasive method of measuring endothelial function based on the measurement of flow-mediated dilation (FMD), which is the same as endothelium-dependent vasodilation in systemic arteries using high-resolution ultrasonography. Other studies using this method have confirmed that a change of 0.1–0.2 mm in arterial diameter can be detected accurately. It has been shown by this method that the vasodilator response of the brachial artery to reactive hyperemia is significantly reduced in patients with coronary artery disease (CAD) compared with normal subjects. Endothelial dysfunction is an early physiologic event in atherogenesis. Further, endothelial dysfunction has also been demonstrated in adults with established atherosclerosis involving the coronary arteries. Femoral arteries or brachial arteries. Atherosclerosis is a diffuse process. Most investigators have demonstrated that endothelial dysfunction is a diffuse disorder that may affect the brachial, femoral, and coronary circulation. This is consistent with the systemic effects of risk factors such as hypercholesterolemia (HC), diabetes mellitus (DM), hypertension (HT), and smoking. Sorensen et al. have reported that atherosclerosis in the human brachial artery is common and correlated with atherosclerosis of the left anterior descending coronary artery. Anderson et al. reported a strong correlation between endothelial dysfunction in the brachial and coronary circulations. However, the relationship between brachial arterial function and the extent and severity of CAD has not been determined. Based on these findings, there may be a correlation between FMD of the brachial artery and the extent and severity of atherosclerosis of the coronary arteries. The objective of this study was therefore to examine the relationship between the endothelium-dependent vasodilator function of the brachial artery and the extent and severity of CAD in humans.

**Methods**

**Patients**

The study included 121 patients (77 men, 44 women; mean (±SD) age 64±11 years; range 25–77 years) of 132 consecutive patients who underwent coronary arteriography for the assessment of ischemic heart disease at our hospital. Significant CAD (>75% stenosis) was present in 89 patients: 31 patients had single-vessel disease, 29 patients had double-vessel disease, and 29 patients had triple-vessel disease. The remaining 43 patients did not have significant coronary atherosclerosis. Coronary artery vasospasm was elicited in 11 of these 43 patients by an acetylcholine provocation test. Because Motoyama et al. have reported that endothelium-dependent vasodilation is impaired in the peripheral arteries of patients with vasospastic angina pectoris, these 11 patients were excluded from this study. Patients were considered to have HT if they were already receiving therapy for HT or if their blood pressure was greater than 160/95 mmHg. Blood pressure was measured at the left forearm just before measurement of FMD. Patients were considered to have HC if they were already receiving therapy for HC or if their serum total cholesterol concentration was greater than 240 mg/dl. Blood samples for the serum lipid determination were obtained on admission. Patients were considered to have DM if they were already receiving drug therapy or dietary treatment for DM or if they were...

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Table 1 Clinical Characteristics of Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th></th>
<th>No stenoses (n=32)</th>
<th>Single-vessel disease (n=31)</th>
<th>Double-vessel disease (n=29)</th>
<th>Triple-vessel disease (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59±15</td>
<td>64±8</td>
<td>69±7</td>
<td>65±9</td>
</tr>
<tr>
<td>Female gender</td>
<td>44%</td>
<td>39%</td>
<td>38%</td>
<td>24%</td>
</tr>
<tr>
<td>Cigarette smokers</td>
<td>34%</td>
<td>29%</td>
<td>14%</td>
<td>31%</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>178±33</td>
<td>193±35</td>
<td>189±41</td>
<td>182±29</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>53±18</td>
<td>47±14</td>
<td>44±14</td>
<td>40±11</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>104±27</td>
<td>119±33</td>
<td>123±39</td>
<td>113±20</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>115±75</td>
<td>132±60</td>
<td>106±38</td>
<td>132±68</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122±17</td>
<td>125±14</td>
<td>140±25</td>
<td>135±18</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>74±11</td>
<td>71±9</td>
<td>75±12</td>
<td>77±10</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>108±30</td>
<td>108±25</td>
<td>122±48</td>
<td>118±24</td>
</tr>
</tbody>
</table>

0, no stenoses; 1, single-vessel disease; 2, double-vessel disease; 3, triple-vessel disease.

diagnosed with DM after admission based on a 75-g oral glucose tolerance test. Obesity was defined as a body mass index (BMI) greater than 25 (kg/m²). Cigarette smokers were defined as those patients who had smoked at least 1 cigarette daily for >1 year. The extent of smoking was quantified as follows: 0, non-smoker or former smoker; 1, <20 cigarettes/day; 2, 20–40 cigarettes/day; 3, >40 cigarettes/day. Former smokers were defined as those who had not smoked for more than 3 months. A family history of CAD was considered positive if a patient’s parents or siblings had clinical evidence of CAD before the age of 60.

Table 1 summarizes the clinical characteristics of the patients. Total cholesterol, LDL-cholesterol, triglyceride, fasting plasma glucose concentration, and diastolic blood pressure were not significantly different among the 4 groups. The incidence of cigarette smoking and the proportion of women were also not significantly different among the 4 groups. HDL-cholesterol concentration in the patients with double- or triple-vessel disease was significantly lower than in the patients without CAD. The patients without CAD were significantly younger than those with double-vessel disease. The systolic blood pressure in the patients without CAD or with single-vessel disease was significantly lower than in those with double-vessel disease.

All patients gave informed consent, and the study protocol was approved by the local committee on ethical practice.

Study Protocol

All vasoactive medications, including calcium channel-blocking agents, nitrates, angiotensin-converting enzyme inhibitors, alpha-adrenergic blocking agents, and beta-adrenergic blocking agents, were discontinued for at least 20 h before the measurement of FMD and coronary angiography (CAG). If patients were receiving a third-generation calcium channel blocking agent, such as amlodipine, it was discontinued for at least 48 h before the measurement of FMD.

FMD and CAG measurements were performed on the same day. FMD and nitroglycerin (NTG)-induced dilation of the brachial artery were measured by the same investigator, and data analysis of FMD was carried out before CAG. The measurements of FMD were performed at 07.00 h according to the method described by Celermajer et al. The diameter of the brachial artery was determined by 2-dimensional ultrasonography (SSD-2200; Aloka, Tokyo, Japan) with a 7.5-MHz linear transducer. The operating parameters were kept constant during all measurements. The right brachial artery was scanned over a longitudinal section 3–5 cm above the elbow, and the scanned area was marked to allow repeated measurements of the same segment. The vessel diameter was assessed using M-mode echography during the end-diastolic phase and was measured from the anterior to the posterior interface between the media and adventitia (the “m line”) at a fixed distance.

After the baseline measurement was obtained, the right forearm was compressed by inflating a pneumatic tourniquet to a pressure of 300 mmHg for 5 min. Increased flow was then induced by sudden cuff deflation. Repeated echographic scanning was performed 60, 90, and 120 sec after cuff deflation, and the maximal vessel response from the 3 measurements was used to determine the FMD. Because the diameter of the brachial artery affects the FMD, the FMD was corrected for vessel size using the following equation: adjusted FMD = FMD − 2.56 (4.2 – vessel size), where −2.56 is the partial regression coefficient of vessel size in the multiple regression equation described in Table 3 and 4.2 is the mean vessel diameter.

Fifteen minutes was allowed for vessel recovery, and then a second resting scan was obtained. Sublingual NTG spray (300 μg; Myocrol Spray; Toa Eiyo, Tokyo, Japan) was then administered, and 5 min later another echographic scan was obtained. The scans were transferred into a computer, and further measurements were calculated using a software program. In order to determine the reliability of the measurements, 16 patients were randomly selected for repeated assessment of FMD and NTG-induced dilation of the brachial artery. The mean differences between the initial and repeat measurements were 0.27±0.17 mm for the baseline diameter, 2.8±1.6% for the adjusted FMD, and 4.5±1.5% for the NTG-induced dilation.

Coronary Angiography and Interpretation and Scoring of the Coronary Artery

CAG was performed using either the Judkins femoral method or the Sones brachial method. The coronary
artery system was divided into 15 segments based on the classification system of the American Heart Association Grading Committee. The extent and severity of CAD were assessed by assigning stenosis scores to each of the 15 segments. The coronary stenosis index (CSI) was defined as the sum of these scores. No significant stenosis was graded as 0; stenosis of less than 25% as 1; 25–49% stenosis as 2; 50–74% stenosis as 3; and 75% or more stenosis as 4. Thus, the highest possible CSI was 60 (15 segments × 4). The interobserver agreement for the CSI was measured (r = 0.97, p < 0.0001), and the average of 2 measurements for each patient was used as the CSI for data analysis.

**Statistics**

All data are expressed as means ± SD. One-way factorial analysis of variance was used to compare baseline characteristics. When a significant difference was present, intergroup comparisons were performed with Scheffe's multiple comparison test. The incidence of cigarette smoking and the proportion of women in each group were evaluated using the chi-square test. Intergroup differences were analyzed using an unpaired t test. Correlations between the FMD results and the continuous variables of age and baseline brachial arterial diameter were evaluated using Pearson's correlation coefficient. The correlation between the adjusted FMD and the CSI was evaluated using Spearman's rank correlation. This procedure was also used for the percent NTG-induced dilation. Potential predictors of the vasodilator response of the brachial artery to reactive hyperemia or of the CSI were tested using multiple regression analysis. A p value < 0.05 was considered statistically significant.

**Results**

**Coronary Risk Factors and FMD**

The changes in the brachial arterial diameter in response to reactive hyperemia ranged from −7.4% to 28.8% in all patients. Although the FMD correlated inversely with vessel diameter (r = −0.50, p < 0.0001), the adjusted FMD did not correlate with vessel size (r = −0.14, p = 0.11). The adjusted FMD correlated inversely with age (r = −0.19, p < 0.05). Univariate analy-
Fig 1. Correlation between adjusted flow-mediated dilation (FMD) and coronary stenosis index (CSI).

![Graph showing correlation between adjusted FMD and CSI]

Table 4 Multiple Regression Analysis for Determinants of CSI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Partial regression coefficient</th>
<th>Standard regression coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.16</td>
<td>0.12</td>
<td>0.10</td>
</tr>
<tr>
<td>Male gender</td>
<td>3.75</td>
<td>0.13</td>
<td>0.08</td>
</tr>
<tr>
<td>Smoking</td>
<td>−0.31</td>
<td>−0.03</td>
<td>0.62</td>
</tr>
<tr>
<td>Family history</td>
<td>3.89</td>
<td>0.12</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>−0.45</td>
<td>−0.10</td>
<td>0.13</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>0.18</td>
<td>0.26</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>−0.20</td>
<td>−0.17</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.56</td>
<td>0.12</td>
<td>0.04</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>−0.04</td>
<td>−0.10</td>
<td>0.56</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>0.12</td>
<td>0.29</td>
<td>0.09</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>−0.09</td>
<td>−0.10</td>
<td>0.34</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>0.03</td>
<td>0.13</td>
<td>0.16</td>
</tr>
<tr>
<td>Adjusted FMD (%)</td>
<td>−1.03</td>
<td>−0.44</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Multiple r value=0.76, r²=0.58. Smoking was considered a categoric variable (0=no smoking, 1=<20 cigarettes/day, 2=20–40 cigarettes/day, 3=>40 cigarettes/day). BMI, body mass index.

The adjusted FMD was significantly lower in patients with double- and triple-vessel disease than in patients without CAD (2 vs 0, p<0.01; 3 vs 0, p<0.0001), and significantly lower in patients with triple-vessel disease than in patients with single-vessel disease (p<0.001). In contrast, the brachial arterial responses to NTG did not differ in any of the groups.

**Discussion**

In response to increased blood flow occurring after 5 min of ischemia, the diameter of the normal brachial artery increases in a reproducible manner! This flow-mediated dilation has been shown to be endothelium-dependent in animal studies, and the dilation in humans is most likely to be endothelium-dependent as well.

During reactive hyperemia, the increase in shear stress produced by increased flow causes the release of nitric oxide, and this response can be attenuated by inhibiting nitric oxide synthesis with N^6^-monomethyl-L-arginine.

Although FMD may have been correlated with confounding factors in our study, there was a significant inverse relationship between the adjusted FMD and the CSI. The adjusted FMD in patients with multivessel disease was significantly lower than in patients with single-vessel disease or without significant coronary artery stenosis. Thus, this non-invasive and simple test of endothelial function revealed that patients with severe multivessel coronary atherosclerosis had greater impairment of endothelial function in the systemic arteries. Further, this method provides an approximate measurement of the extent and severity of CAD.

In this study, several of the patients with severe coronary atherosclerosis such as triple-vessel disease had negative values for FMD. Although the cause of this paradoxical vasoconstrictor response is not known, Nabel et al observed a vasoconstrictor response to increased coronary blood flow in large human coronary arteries with atherosclerosis. They suggested that the mechanism responsible for this paradoxical response may be endothelial cell dysfunction and blunting of NO release. It is there-
fore possible that our patients with triple- vessel disease also had more severe endothelial cell dysfunction in the brachial arteries than did patients with single- vessel disease.

In the present study, the cholesterol concentration was not predictive of brachial artery dysfunction. Similar results were reported in a previous study\(^5\). Twenty-one percent of our patients were receiving cholesterol-lowering drug therapy, and it is possible that this may have masked the relationship between cholesterol concentration and FMD. Many other factors, including estrogen concentration\(^2,3,24\), age\(^25,26\), smoking\(^27\) and blood pressure\(^28\) influence endothelium-dependent vasodilation. Hashimoto et al\(^24\) have reported that, in premenopausal women, endothelium-dependent vasodilation varies during the menstrual cycle. Because only 2 of the patients in our study were premenopausal women, changes caused by the menstrual cycle would have had little influence on our results. Although Lieberman et al\(^3\) have reported that estrogen replacement therapy augments endothelium-dependent vasodilation in postmenopausal women, none of the postmenopausal women in our study was receiving estrogen supplementation.

We excluded 11 patients from this study who had vasospastic angina pectoris because there is controversy over the endothelium-dependent vasodilator function of the brachial artery in patients with vasospastic angina. Motoyama et al\(^27\) reported that FMD of the brachial arteries was impaired in patients with vasospastic angina, although they did not have apparent atherosclerosis of the coronary arteries. On the other hand, Ito et al\(^29\) reported that FMD of the brachial arteries was not impaired in these patients.

**Study Limitations**

The peak flow in response to reactive hyperemia was not measured in this study. Celermajer et al\(^1\) have reported that peak flow may be decreased by as much as 25% less in patients with CAD than in normal subjects. A decrease of this magnitude in the peak flow may affect the FMD of the brachial artery somewhat, and this point is a major limitation of this study.

Some of the patients in our study were already receiving therapy for ICH, HT, or DM or were receiving antplatelet drugs such as aspirin. It takes several days to 1 week for these drugs to wash out completely. Further, a history of administration of these drugs can influence vasoconstruction and endothelial function, even if the drugs have been washed out. The possible influence of these drugs on our results should be taken into consideration.

Hirooka et al\(^30\) reported that endothelium-dependent vasodilator responses differ between the coronary and forearm vasculature in humans. They hypothesized that this difference occurs because atherosclerotic vascular disease is generally more severe in the coronary vasculature than in the forearm vasculature. The results of Hirooka et al suggest that there may be some limitations of this non-invasive test of endothelial function in patients with CAD.

**Conclusion**

There is a strong inverse correlation between adjusted brachial FMD and the CSI. Specifically, more severe atherosclerosis in the coronary artery is associated with greater impairment in the adjusted brachial artery FMD. Further, the adjusted FMD is an independent predictor of CSI in patients with CAD.

**References**


