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<tr>
<td>作者</td>
<td>TANAKA, Shinichiro</td>
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Background: Some stable angina patients with significant coronary function have low exercise capacity, whereas some have high exercise capacity. The aim of the present study was to determine whether coronary pressure-derived fractional flow reserve (FFRmyo), a functional index of coronary stenosis, is a better indicator of exercise capacity than angiographic stenosis.

Methods and Results: The 15 male (65.8±8.9 years old) subjects with stable angina and 75% angiographic stenosis underwent a cardiopulmonary exercise test (CPX), and peak oxygen uptake (Peak\(\bar{V}_O_2\)) and oxygen uptake at anaerobic threshold (AT) were measured. The relationship between FFRmyo and CPX values was assessed. The left anterior descending artery was affected in 8 patients, the left circumflex artery in 5, and the right coronary artery in 2. Percent diameter stenosis (%DS) was 61.7±9.1% by quantitative coronary angiography. Mean FFRmyo, Peak\(\bar{V}_O_2\), and AT was 0.84±0.066, 17.1±3.2 ml·kg\(^{-1}\)·min\(^{-1}\), and 11.1±2.0 ml·kg\(^{-1}\)·min\(^{-1}\), respectively. There was no significant correlation between %DS and FFRmyo, Peak\(\bar{V}_O_2\), or AT (\(r=0.12, \, -0.051, \, \text{and} \, -0.013\), respectively; \(P=NS\)), but FFRmyo had a significant positive correlation with Peak\(\bar{V}_O_2\) and AT (\(r=0.534 \, \text{and} \, 0.542\), respectively; \(P<0.05\)).


Key Words: Fractional flow reserve; Functional exercise capacity; Ischemic heart disease

Low peak oxygen uptake (Peak\(\bar{V}_O_2\)) and poor exercise capacity are generally considered to be predictors of mortality in patients with ischemic heart disease.\(^1\)\(^-\)\(^4\) Patients presenting with these symptoms benefit from revascularization via percutaneous coronary intervention (PCI). However, there were some patients with higher functional capacity who already have oxygen consumption at high levels\(^5\) and often get no benefit from PCI.\(^3\)\(^4\) For example, it has been reported that patients with low functional capacity, low peak\(\bar{V}_O_2\), and poor oxygen uptake at the anaerobic threshold (AT) during a cardiopulmonary exercise test (CPX) show significant improvement after PCI, suggesting that myocardial impairment induced by intermittent ischemia is reversible, whereas the functional capacity of those with higher peak\(\bar{V}_O_2\) is not significantly improved after PCI.\(^3\) Thus, it is suggested that the efficacy of PCI is influenced by the baseline condition of the patient.

Although angiographic stenosis is often associated with reduced exercise capacity and functional capacity, the relationship between angiographic stenosis and functionality varies widely.\(^6\)\(^-\)\(^7\) Coronary pressure-derived fractional flow reserve (FFRmyo), which is calculated from coronary pressure measurements, is a reliable index of the functional severity of coronary stenosis, and an FFRmyo value of 0.75 distinguishes stenoses that are associated with inducible ischemia from those that are not.\(^8\)\(^9\) Indeed, in patients with stable chest pain, the most important prognostic factor is the occurrence of myocardial ischemia reflected by an FFRmyo value <0.75. Even after treatment with PCI, the clinical outcomes of such patients are found to be significantly worse than those of patients with functionally insignificant stenoses (FFRmyo ≥0.75).\(^6\)\(^-\)\(^7\) We hypothesized that there is an association between exercise capacity and functional stenosis, as reflected by FFRmyo, in patients with stable coronary heart disease and we tested this hypothesis using pressure wires and CPX tests.

Methods

Study Design and Participants

The present study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Gifu Prefectural General Medical Center. All study participants gave written informed consent prior to enrollment in the study.

Between November 2006 and September 2008, 15 patients were enrolled. All of them showed 75% angiographic stenosis (classified according to the American Heart
Association) in 1 artery, which was amenable to PCI. In addition, the participants had class I–III angina pectoris [classified according to the Canadian Cardiovascular Society (CCS)]. Exclusion criteria were acute coronary syndromes, recent myocardial infarction (<2 months), a history of myocardial infarction, left main coronary artery stenosis >25% or high-grade proximal left anterior descending artery stenosis with significant stenosis (>75%) of other vessels, left ventricular angiography-based detection of abnormal wall motions such as asynery or diffuse hypokinesia, reduced left ventricular function (ejection fraction, <55%), significant valvular heart disease, diabetes mellitus treated with insulin, smoking habit, and occupational, orthopedic or other conditions that precluded exercise. Eligible patients underwent CPX tests during which PeakVO₂ (ml kg⁻¹ min⁻¹) and AT (ml kg⁻¹ min⁻¹) were measured. The correlation between the FFR and CPX values was then assessed.

Exercise Testing
A symptom-limited incremental exercise test was performed using an upright, electromagnetically braked cycle ergometer. Breath-by-breath VO₂, carbon dioxide production (VCO₂), and minute ventilation (VE) were measured throughout the test using an AE-300S AEROMONITOR (Minato Medical Science Co Ltd, Osaka, Japan). A ramp protocol with an exercise regimen of a 3-min warm-up at 10 W at a pedal speed of 50 revolutions/min, followed by a linear increase in the work load at a rate of 1 W every 6 s (10 W/min) was used. 12-lead ECG and heart rate were continuously monitored throughout the test using a stress system ML-9000 (Fukuda Denshi Co Ltd, Tokyo, Japan), and cuff blood pressure was measured every minute using an automatic manometer (FB-300; Fukuda Denshi). The end point of the CPX test was determined as per the guidelines for diagnostic evaluation of patients with chronic ischemic heart disease.

Angiographic Assessment
Angiography was performed in 2 orthogonal views after intracoronary administration of 5.0 mg of isosorbide dinitrate. Digital angiograms were analyzed online using an automated edge-detection system (Good net; Goodman Co Ltd, Nagoya, Japan). Using the guiding catheter as a scaling device, reference diameter, minimal lumen diameter, and percent diameter stenosis (%DS) were calculated. The algorithm of the cardiovascular measurement system interpolated reference vessel diameters from the diameters of apparently normal segments just proximal and distal to the target lesion.

Coronary Pressure Measurement and Calculation of FFRmyo
Coronary pressure was measured using a 0.014-inch sensor-tipped PCI guidewire (PressureWire; Radi Medical Systems, Uppsala, Sweden). The wire was introduced via a 6- or 7-Fr guiding catheter, calibrated, advanced into the coronary artery, and positioned distal to the lesion as described previously.⁸¹¹ Adenosine (140 μg kg⁻¹ min⁻¹) was administered intravenously to induce maximum hyperemia.⁸¹²

FFRmyo was calculated as the ratio of the mean hyperemic distal coronary pressure measured with a pressure wire to the mean aortic pressure measured with a guiding catheter. The measurement was performed twice, and FFRmyo was considered as the average of the 2 measurements.
Antianginal Thrombotic Treatment

All the patients received oral therapy comprising 75 mg of clopidogrel or 200 mg of ticlopidine plus 81 mg of aspirin daily. Anti-ischemic therapy included a long-acting β-blocker, calcium-channel blocker, nitrates and nicorandil, alone or in combination with statins, and either an angiotensin II receptor blocker or an angiotensin-converting enzyme inhibitor for standard secondary prevention.13

Statistical Analysis

All analyses were performed using the intention-to-treat principle. Continuous data are expressed as means±SD and proportions, and categorical data are expressed as frequencies and percentages. Pearson’s correlation coefficient analysis and simple regression analysis were used to assess the relationships between subjects. Values of P<0.05 were considered significant. All analyses were performed using SAS software version 5.0 (SAS Institute, Inc, Cary, NC, USA).

Results

Characteristics of the Patients and their Lesions

The clinical characteristics of the 15 study participants are shown in Table 1. Their mean age was 66 years (range, 54–76); 53% of the patients had hypertension, 47% had hyperlipidemia, and 67% had diabetes. Although 10 patients had angina, all recorded normal ECGs while resting. Ergometry revealed myocardial ischemia (eg, ST-segment depression) in 5 patients, and 6 patients were positive on stress thallium scintigraphy.

Angiographic characteristics are summarized in Table 2. Stenotic lesions were localized in the left anterior descending artery in 8 patients, in the left circumflex artery in 5 patients, and in the right coronary artery in 2 patients. The average reference vessel diameter was 3.04 mm, and the mean minimal lumen diameter was 1.12±0.45 mm and the %DS was 61.8±9.4%. Mean FFRmyo was 0.84 (range, 0.69–0.99).

Functional Capacity Assessed by CPX

Table 3 shows the results of the CPX tests. The average maximal exercise tolerance was 96.3 W, and the PeakVO2 was 16.7±2.9 ml·kg⁻¹·min⁻¹ at 96.3 W. All the VO2 curves were observed to plateau during CPX. PeakVO2 reflected the maximum VO2 value. Mean AT value was 11.1±2.0 ml·kg⁻¹·min⁻¹, and the mean load at that AT level was 53.1 W. The endpoint of the CPX test was shortness of breath in 4 patients and leg fatigue in 6 patients. Target heart rate was nearly achieved in 4 patients: 90% of maximum heart rate. CPX test was terminated in 1 patient because of elevated diastolic blood pressure (>120 mmHg).

Correlations Among Functional Capacity, Angiographic Stenosis, and Functional Stenosis

There was no correlation between FFRmyo and %DS (Figure 1). Likewise, neither PeakVO2 nor AT correlated with %DS (Figure 2). There was no correlation between the double products and FFRmyo or %DS (Figure 3). On the other hand, there was a positive correlation between oxygen uptake and the double products: r=0.761 (P<0.01) at peak and r=0.775 (P<0.01) at the AT. In addition, a significant positive correlation was observed between FFRmyo and PeakVO2 (r=0.534, P<0.05) and between FFRmyo and the AT (r=0.542, P<0.05) (Figure 4).

Discussion

The results of this study showed (1) a positive correlation between FFRmyo and PeakVO2: [r=0.534 (P<0.05)] and between FFRmyo and the AT [r=0.452 (P<0.05)], (2) no significant correlation between %DS and FFRmyo, and (3) no correlation at all between %DS and PeakVO2 or between %DS and the AT.

The diagnostic accuracy of FFRmyo for assessing functional stenosis is more than 90%, which is higher than for any other invasive or noninvasive test.8-9 When FFRmyo was used to divide patients into a group in which stenosis was most likely to be physiologically significant (FFRmyo <0.75) and a group in which it was not, the overlap between the 2 groups for angiographic severity was so large that it suggested angiography could not be used to predict the absence or presence of inducible ischemia in individual patients.6,7 Our finding that there was no correlation between

### Table 2. Angiographic Data and FFRmyo

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Affected artery</th>
<th>RD (mm)</th>
<th>MLD (mm)</th>
<th>Stenosis (%)</th>
<th>Lesion length (mm)</th>
<th>FFRmyo</th>
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<tbody>
<tr>
<td>1</td>
<td>LCX</td>
<td>4.29</td>
<td>1.66</td>
<td>61.4</td>
<td>16.2</td>
<td>0.88</td>
</tr>
<tr>
<td>2</td>
<td>LCX</td>
<td>2.91</td>
<td>1.27</td>
<td>56.3</td>
<td>10.8</td>
<td>0.83</td>
</tr>
<tr>
<td>3</td>
<td>LAD</td>
<td>2.06</td>
<td>0.73</td>
<td>64.4</td>
<td>17.2</td>
<td>0.78</td>
</tr>
<tr>
<td>4</td>
<td>LCX</td>
<td>3.59</td>
<td>2.06</td>
<td>42.7</td>
<td>6.7</td>
<td>0.85</td>
</tr>
<tr>
<td>5</td>
<td>LAD</td>
<td>2.39</td>
<td>0.76</td>
<td>68.4</td>
<td>7.9</td>
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<tr>
<td>6</td>
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<td>1.08</td>
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<tr>
<td>7</td>
<td>LAD</td>
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<td>0.91</td>
<td>68.4</td>
<td>7.8</td>
<td>0.86</td>
</tr>
<tr>
<td>8</td>
<td>LCX</td>
<td>2.56</td>
<td>0.61</td>
<td>76.4</td>
<td>22.9</td>
<td>0.88</td>
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<tr>
<td>9</td>
<td>LAD</td>
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<tr>
<td>10</td>
<td>LAD</td>
<td>3.58</td>
<td>1.43</td>
<td>60.18</td>
<td>8.76</td>
<td>0.86</td>
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<tr>
<td>11</td>
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<td>0.74</td>
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<tr>
<td>12</td>
<td>LCX</td>
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<td>13</td>
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<td>14</td>
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<tr>
<td>15</td>
<td>RCA</td>
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<tr>
<td>Mean</td>
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<td>1.12</td>
<td>61.7</td>
<td>13.6</td>
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<tr>
<td>SD</td>
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<td>0.89</td>
<td>0.45</td>
<td>9.1</td>
<td>6.3</td>
<td>0.66</td>
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FFRmyo, myocardial fractional flow reserve; QCA, quantitative coronary angiography; RD, reference diameter; MLD, minimum luminal diameter; LCX, left circumflex coronary artery; LAD, left anterior descending coronary artery; RCA, right coronary artery.
Table 3. Anaerobic Threshold, OSubscript2 Uptake, and Hemodynamic Data at Rest and During Exercise

<table>
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<tr>
<th>Endpoint of CPX test</th>
<th>SBP (mmHg) (max/min)</th>
<th>HR (beats/min)</th>
<th>DBP (mmHg) (max/min)</th>
<th>Double product</th>
<th>Target HR</th>
<th>Shortness of breath</th>
<th>Leg fatigue</th>
<th>Shortness of breath</th>
<th>Target HR</th>
<th>90% of maximum HR.</th>
</tr>
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<td>Rest</td>
<td>AT</td>
<td>17.1</td>
<td>11.1</td>
<td>136.3</td>
<td>77.6</td>
<td>71</td>
<td>97.8</td>
<td>14.3</td>
<td>90</td>
<td>53.1</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>3.2</td>
<td>2.0</td>
<td>19.8</td>
<td>11.9</td>
<td>8.6</td>
<td>11.9</td>
<td>25.1</td>
<td>16.3</td>
<td>6.6</td>
</tr>
</tbody>
</table>

- Peak \( \text{V}O_2 \), oxygen uptake at peak exercise; AT, anaerobic threshold at the corresponding oxygen uptake; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Target HR, 90% of maximum HR.

%DS calculated from quantitative coronary angiography and the 3 functional parameters, namely, FFR\text{myo}, peak\( \text{V}O_2 \), and AT, is consistent with earlier studies.

FFR\text{myo} reflects the maximum achievable blood flow to the myocardium supplied by a stenotic artery as a fraction of normal maximum flow, and is an accurate and specific index of the severity of epicardial stenosis.\(^8,9\) Generally, one of the most important determinants of myocardial ischemia is endothelial function.\(^1,2,14\) In patients with a higher maximal exercise tolerance, sufficient myocardial perfusion is achieved because of improved endothelium-dependent vasodilation and collateralization.\(^1,15\) In addition, it has been reported that an increase in functional capacity is associated with an increase in coronary flow reserve (coronary flow velocity response to adenosine) and that impaired overall functional capacity is independently associated with coronary microvascular dysfunction.\(^1\) Thus, a reduction in coronary flow reserve apparently reflects both epicardial and microvascular disease.\(^1,16,17\) Other studies have shown that exercise training improves endothelium-dependent vasodilation in both epicardial coronary vessels and resistance vessels in patients with coronary artery disease.\(^2\) Exercise brings about a change in the relationship between myocardial blood flow and coronary pressure in patients with moderate stenosis; the linear relationship between perfusion pressure and blood flow at exercise in cases of a moderate stenosis of the epicardial artery shifted upward and were closer to those found with hyperemia than those for the subendocardial artery.\(^1,18\) Such results are consistent with those of our study, indicating that there is a positive correlation between FFR\text{myo} and functional capacity and little, if any, relationship between %DS and functional capacity. The reason why FFR\text{myo} does not correlate with the maximum double product appears to be associated with the endpoint of the CPX test. In the present study, none of the patients experienced anginal pain or significant ST depression during the CPX test. Because the maximal double product is important as an angina threshold, it should correlate with FFR\text{myo} when exercise is terminated because of myocardial ischemia. In the absence of myocardial ischemia, which was the case in the present study, peak\( \text{V}O_2 \) may be a more appropriate index for measuring exercise capacity. In addition, exercise increases the levels of catecholamines, which may be responsible for the improvement in blood flow and
oxygen delivery to the skeletal muscles.\textsuperscript{19} This may be one of reasons why FFR_{myo}, which was measured during hyperemia induced by adenosine, showed a significant correlation with oxygen uptake but not with the double product.

When treating patients with coronary artery disease and stable angina, the goal of treatment is complete, or nearly complete, elimination of anginal chest pain and a return to normal activity with good functional capacity.\textsuperscript{20,21} Although PCI has become a common initial management strategy for patients with stable coronary artery disease, studies have
shown that it does not reduce the long-term rates of death risk, myocardial infarction or other major cardiovascular events when combined with optimal medical therapy. Nonetheless, for approximately 24 months, PCI accompanied by optimal medical therapy does relieve angina and improve the self-assessed health status to a greater degree than that achieved by optimal medical therapy alone. In addition, a greater benefit of PCI is observed in patients with more severe and more frequent angina. Therefore, the importance of PCI in terms of rapid relief of symptoms must be critically weighed against the inherent risks and the higher cost of the procedure. From that viewpoint, FFRmyo can be used for immediate decision-making in the catheterization laboratories. However, under other circumstances, a noninvasive procedure would be preferable. Assessment of exercise capacity using a CPX test is not invasive and can be used together with metabolic equivalent values to serve as an index of daily activity. CPX testing is useful over self-assessed health status, which is subjective and can vary among patients depending upon their symptom complexity and their unique perceptions, expectations, and preferences. For instance, patients with more severe angina and several coexisting medical problems may be satisfied with some reduction in the symptoms that enables them to perform only limited daily life activities. Another investigation has indicated that 6,500–8,500 steps/day should be considered as the minimal goal and optimal level of physical activity for secondary prevention of cardiovascular disease. For assessment of daily activity or for secondary prevention, CPX testing is a noninvasive guide to functional capacity and treatment efficacy.

PCI significantly increased AT and peakVO₂ in patients with peakVO₂ <15 ml·kg⁻¹·min⁻¹, whereas it yielded no significant improvement in those with peakVO₂ >15 ml·kg⁻¹·min⁻¹. It is noteworthy that an FFRmyo value of 0.75 reflects stenoses associated with inducible ischemia and hence appears to be similar to a peakVO₂ value of 15.0.

A previous study showed that routine FFRmyo measurement with angiographic guidance resulted in a significant reduction in major adverse cardiac effects, even when patients underwent PCI with drug-eluting stents. Cardiac rehabilitation is an important strategy for secondary prevention, provided there is no risk of inducible ischemia. Exercise training can improve myocardial perfusion, as revealed by myocardial scintigraphy, as well as maximal exercise capacity. Therefore, it may be possible to improve FFRmyo by increasing exercise capacity through training.

Study Limitations
This study has several important limitations. Our study evaluated a small group of Japanese men with stable angina warranting referral for coronary angiography, which limits generalization of the results. We measured FFRmyo at only one point in time, so unknown or unmeasured factors that could potentially alter the responses at other time points were not studied. In addition, it was a nonrandomized study in which the study population was small, and the results reflected the experience of a single center only. Therefore, the study lacks the obvious advantages of a larger, multicenter, multinational randomized study. Inclusion criteria for this study were restrictive and hence limited the number of study patients, even though intermediate coronary heart disease and the resultant myocardial ischemia are known to be important factors that affect the daily activity of numerous individuals. This study included a very high proportion of diabetic patients (67%). Although glucose levels were efficiently controlled by administration of only α-glucosidase inhibitors or diet therapy alone, our study did not reflect the vascular functional changes that are induced by hyperglycemia. A larger, multicenter, multinational randomized study is warranted to clarify these issues.

Conclusions
Japanese men with reduced FFRmyo are likely to have reduced functional capacity as assessed by a CPX test. CPX testing may offer a noninvasive measure of myocardial ischemia that is associated with the fractional flow reserve.

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Disclosure

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References


