Enhanced Secretion of Insulin Plays a Role in the Development of Atherosclerosis and Restenosis of Coronary Arteries: Elective Percutaneous Transluminal Coronary Angioplasty in Patients With Effort Angina

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Objectives. We investigated the relation between insulin and coronary atherosclerosis and restenosis of the coronary arteries, by performing elective percutaneous transluminal coronary angioplasty (PTCA).

Background. Insulin is known to promote atherosclerosis of the arteries and has been implicated in the development of restenosis after PTCA.

Methods. Of 210 angina patients who underwent PTCA, newly detected lesions in 35 consecutive nondiabetic subjects without previous intervention on the same main coronary arteries were analyzed after a 75-g oral glucose tolerance test (OGTT) and follow-up coronary angiography. Atherosclerotic lesions were evaluated by pattern, severity and extent. Restenosis was defined as loss of gain, the percentage of loss of the initial gain in the coronary diameter achieved by PTCA > 50%.

Results. Patients with restenosis had a significantly higher extent index (a marker of atherosclerosis), insulin area, ratio of insulin area to glucose area, insulinogenic index and minimal lumen diameter after PTCA than those without restenosis (p = 0.001, 0.011, 0.002, 0.016 and 0.041, respectively). Simple regression analysis revealed that only the ratio of insulin area to glucose area (a relative marker of enhanced insulin secretion) significantly correlated with the extent index (p = 0.035). Extent index, insulin area, the ratio of insulin area to glucose area and insulinogenic index significantly correlated with loss of gain (p = 0.001, 0.010, 0.002 and 0.032, respectively). Stepwise multiple regression analyses revealed that extent index and the ratio of insulin area to glucose area significantly correlated with loss of gain.

Conclusions. Enhanced secretion of insulin during the OGTT might be useful as a predictor of coronary atherosclerosis and of restenosis after elective PTCA in nondiabetic patients with effort angina.

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Insulin is known to have a variety of in vivo actions, mainly in the regulation of glucose metabolism in organs such as the liver, and in muscle and adipose tissue mediated through insulin receptors. Insulin has been reported to be involved in the development of atherosclerosis, coronary heart disease, or both through several mechanisms such as stimulation of cholesterol synthesis, proliferation and migration of arterial smooth muscle cells (1), increasing triglycerides and decreasing high density lipoprotein (HDL) concentrations in plasma (2) and binding of low density lipoprotein to both arterial smooth muscle cells and monocyte macrophages (1). It has also been reported that atherosclerosis was present at the site of coronary vasospasm (3) and that hyperinsulinemia contributes to the pathogenesis of severe coronary vasospasm (4,5).

On the other hand, insulin has been reported to have vasodilative effects mediated via an unidentified beta-adrenergic mechanism (6), an inhibitory effect on norepinephrine and angiotensin-II–induced vasoconstriction (7) and anti-thrombogenic actions through the augmentation of prostacyclin synthesis (8). A definite outlook, however, of the effect of insulin on the development of atherosclerosis and restenosis after percutaneous transluminal coronary angioplasty (PTCA) is not clear to date. It is not only interesting but also important to understand which is more important for the development of atherosclerosis and restenosis, reduction of insulin action or compensatory hyperinsulinemia. It has been reported that enhanced sensitivity of the tissue to insulin by thiazolidinedione reduces plasma levels of insulin, leading to a favorable impact on several known cardiovascular risk factors with non–insulin-dependent diabetes mellitus (9). This study implicated the importance of restoration of the tissue sensitiv-
ity to the actions of insulin; however, the question still remains to be solved as to which is primarily important, higher concentration of insulin per se or reduction of sensitivity to insulin, in the development of atherosclerosis or restenosis, or both, after PTCA.

On the basis of the information available today, it is very important to investigate whether insulin really contributes to the development of atherosclerosis, restenosis, or both, after PTCA. We therefore designed this study to investigate the effect of insulin on the development of coronary atherosclerosis and restenosis of the coronary arteries by performing elective PTCA on nondiabetic, nonobese patients with effort angina.

Methods

Study patients. From September 1993 through June 1997, 210 patients underwent elective PTCA for effort angina at Kamo Hospital. The patients who underwent direct PTCA for acute myocardial infarction or impending myocardial infarction or unstable angina were not included in this number. Of the 210 patients, 35 consecutive nonobese, nondiabetic patients who had elective PTCA on 35 lesions in previously nonintervened arteries were enrolled for the final analysis in the present study. Exclusion criteria were 1) previous coronary angioplasty at the same major artery (n = 76), 2) history and diagnosis of diabetes mellitus including the patients diagnosed by the oral glucose tolerance test (OGTT) in this study after the putative entry (n = 68), 3) stent implantation or directional coronary atherectomy (n = 34), 4) failure of PTCA (n = 14), 5) body mass index (BMI = body weight/height$^2$) >28 kg/m$^2$ (n = 2), 6) complications of cardiogenic shock (n = 1), 7) patients without OGTT (n = 22) and 8) patients without follow-up coronary angiography because of transfer to other institutions (n = 11). According to these criteria, 175 patients were excluded because they met more than one of these criteria. All of the patients gave their informed consent to this study.

Elective PTCA. Elective PTCA was performed within a few days after the angiographic diagnosis of angina was made with coronary arterial stenosis over 75% of reference diameter (RD). Success of the PTCA was defined as a more than 20% improvement in the percent diameter stenosis with less than 50% residual stenosis at the target lesion without a major in-hospital complication within 1 month (death, Q-wave myocardial infarction or need for bypass surgery or repeat angio-

### Abbreviations and Acronyms

- BMI = body mass index
- HDL = high density lipoprotein
- MLD = minimal lumen diameter
- OGTT = oral glucose tolerance test
- PTCA = percutaneous transluminal coronary angioplasty
- RD = reference diameter

### Research Background

The present study. Exclusion criteria were 1) previous coronary artery disease (n = 34), 2) failure of PTCA (n = 14), 3) number of occlusions of the 3 major coronary arteries (max = 3), 4) total number of stenoses (≥50% narrowing) in 15 segments of the arteries (max = 15[max] × 3[max] stenotic lesions in each segment = 45) and 3) number of occlusions of the 3 major coronary arteries (max = 3). Extent, or the length of atherosclerotic injury, was quantified by assigning a score of 0 (normal), 1 (abnormal: any narrowing or irregularity or both ≤10% of the length), 2 (10 < abnormal ≤50%) or 3 (50% < abnormal) to each of the 15 segments of the arterial tree. Extent index was calculated by dividing the extent score by the number of segments that could be properly visualized by antegrade flow. Thus the extent index could range from 0 (score of 0) to a maximum of 3 (score of 45 divided by 15 segments).

Measurement of cardiac angiogram. Follow-up coronary angiography was performed about 3½ months after PTCA. Coronary arterial diameters were measured by quantitative coronary arteriography with the use of a CAMAC-300 (GOODMAN Co., Nagoya, Japan) independently by two cardiologists without any knowledge of the patient profiles, and the mean value of the two measurements was used. The percentage of the remaining stenosis in terms of the ratio of the dilated arterial diameter to the corresponding RD (% residual stenosis) was defined as (1-minimal lumen diameter [MLD]/RD) × 100, in which RD was determined by measuring the lumen diameter proximal to the lesion. Loss of gain was defined as a percentage of the loss of the initial gain in the coronary diameter achieved by PTCA; therefore loss of gain = (1-MLD at follow-up coronary angiography/MLD after PTCA) × 100. Restenosis was defined as loss of gain ≥50%.

Oral glucose tolerance test. A fasting blood sample from each patient was obtained in the morning after overnight fasting, and then a 75-g glucose solution was given orally. Blood samples were obtained before (0) and 0.5, 1, 2 and 3 h after the glucose load. Plasma levels of glucose were measured by a glucose-dehydrogenase method with the use of a New Glucorder analyzer (Analytical Instrument Co., Tokyo, Japan). Plasma levels of insulin were measured by radioimmunoassay with the use of an Insulin Ria bead II (Dainabot Co., Tokyo, Japan), Concentrations of glucose and insulin in plasma were determined at all five time points, and the following indexes were calculated: insulinogetic index (ratio of Δ plasma insulin
to Δ plasma glucose, an index of insulin response to glucose during the first 0.5 h of OGTT, insulin area (integration of insulin concentrations over the 3-h period of OGTT), ratio of insulin area to glucose area (insulin area divided by glucose area; glucose area is the integration of glucose concentrations over the 3-h period of OGTT). According to the recommendation by the Japan Diabetes Society on the diagnosis of diabetes mellitus, patients were diagnosed as having diabetes mellitus when fasting plasma glucose was equal to or greater than 140 mg/dL, plasma glucose 2 h after the load was equal to or greater than 200 mg/dL, or both. When fasting plasma glucose was less than 110 mg/dL, and glucose 1 and 2 h after load was less than 160 mg/dL and less than 120 mg/dL, respectively, the subjects were classified as normal. The patients having glucose levels other than described were diagnosed as having borderline diabetes mellitus. Factors of lipid metabolism, total cholesterol, HDL cholesterol and triglycerides, were analyzed in all subjects.

Statistical analysis. Results were expressed as mean ± SD in text, tables and figures. All of the statistical analyses were performed using StatView Version 4.5 (Abacus Concepts, Inc., Berkeley, California). The unpaired t test was used for parametric data when normal distribution and equal dispersion were recognized. Otherwise the Welch test or the Mann–Whitney U test was used when appropriate. Differences in the categorical data (gender, existence of borderline diabetes, hypertension, etc.) between the two groups were analyzed by the chi square test, and the Fisher exact test was used when appropriate. Two-way repeated measures analyses of variance followed by Scheffe’s multiple comparisons test were performed for the evaluation of differences in the OGTT data between the two groups or patients with and without restenosis. Simple regression analyses were performed to analyze the correlation between an index of atherosclerosis or extent index and the patients’ basic characteristics (age, BMI, serum levels of total cholesterol, HDL cholesterol, triglycerides) and OGTT results. Also, simple regression analyses were performed to investigate the correlation between an index of restenosis or loss of gain and the basic characteristics, the atherosclerotic indexes, OGTT results and PTCA data (RD, size of balloon, % residual stenosis, MLD after PTCA, days to follow-up coronary angiography). Stepwise multiple regression analyses were performed to investigate the contributions of age, BMI, serum levels of total cholesterol and triglycerides, fasting plasma levels of glucose and insulin, the ratio of insulin area to glucose area and insulinogenic index to extent index. Stepwise analyses were also performed to investigate the contributions of age, serum levels of total cholesterol, triglycerides, MLD after PTCA, extent index, ratio of insulin area to glucose area and days to follow-up coronary angiography to the loss of gain. p Values <0.05 were considered statistically significant.

Results

Patient characteristics. Table 1 shows clinical and PTCA characteristics of patients with and without restenosis after PTCA. The mean age of the 35 patients was 64.4 ± 8.4 years (mean ± SD) and 28 patients (80%) were men. Twenty-two patients (63%) were defined as having hypertension and 22 (63%) as being smokers. Mean BMI was 22.9 ± 2.0 kg/m². Mean serum levels of total cholesterol, HDL cholesterol and triglycerides were 202 ± 38 mg/dL, 47.1 ± 11 mg/dL and 131 ± 85 mg/dL, respectively. Coronary angiography revealed that newly developed responsible lesions for angina were in the left anterior descending coronary artery in 17 (49%), in the right coronary artery in 11 (31%) and in the left circumflex coronary artery in 7 (20%). Before PTCA, mean MLD was 0.51 ± 0.31 mm, mean RD was 2.8 ± 0.6 mm and the size of balloon used for PTCA was 2.7 ± 0.5 mm. After PTCA, % residual stenosis was 29.3 ± 11% and mean MLD was 1.98 ± 0.5 mm. Restudy was performed 107 ± 23 days (range: 70 to 161) after PTCA.

Table 1. Clinical and Percutaneous Transluminal Coronary Angioplasty Characteristics in Patients With and Without Restenosis After Percutaneous Transluminal Coronary Angioplasty

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Restenosis (+)</th>
<th>Restenosis (-)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borderline diabetes, n (%)</td>
<td>9 (64)</td>
<td>12 (57)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>67.4 ± 4.2</td>
<td>62.3 ± 9.9</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (86)</td>
<td>16 (76)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>11 (79)</td>
<td>11 (52)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>5 (37)</td>
<td>14 (67)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.4 ± 1.9</td>
<td>22.6 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>201 ± 36</td>
<td>203 ± 40</td>
<td>NS</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48.1 ± 13.8</td>
<td>46.5 ± 9.8</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>144 ± 113</td>
<td>122 ± 67</td>
<td>NS</td>
</tr>
<tr>
<td>PTCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of balloon (mm)</td>
<td>2.61 ± 0.49</td>
<td>2.68 ± 0.48</td>
<td>NS</td>
</tr>
<tr>
<td>RD (mm)</td>
<td>2.57 ± 0.54</td>
<td>2.93 ± 0.60</td>
<td>NS</td>
</tr>
<tr>
<td>% residual stenosis</td>
<td>31.8 ± 6.5</td>
<td>27.6 ± 11.8</td>
<td>NS</td>
</tr>
<tr>
<td>MLD after PTCA (mm)</td>
<td>1.75 ± 0.39</td>
<td>2.13 ± 0.58</td>
<td>0.041</td>
</tr>
<tr>
<td>Lesion, n (LAD/LCX/RCA)</td>
<td>7/25</td>
<td>10/56</td>
<td>NS</td>
</tr>
<tr>
<td>Days to restudy</td>
<td>109 ± 24</td>
<td>107 ± 23</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. BMI = body mass index; HDL = high density lipoprotein; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; MLD = minimal lumen diameter; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; RD = reference diameter.
Atherosclerotic Indexes in Patients With and Without Restenosis After Percutaneous Transluminal Coronary Angioplasty

<table>
<thead>
<tr>
<th>Restenosis (+)</th>
<th>Restenosis (-)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 14</td>
<td>n = 21</td>
<td></td>
</tr>
<tr>
<td>Pattern, n(typeA/B/C)</td>
<td>0/14/0</td>
<td>4/16/1</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessels diseased</td>
<td>1.43 ± 0.65</td>
<td>1.14 ± 0.36</td>
</tr>
<tr>
<td>Stenoses</td>
<td>2.93 ± 1.90</td>
<td>2.24 ± 1.41</td>
</tr>
<tr>
<td>Occlusions</td>
<td>0.50 ± 0.65</td>
<td>0.19 ± 0.40</td>
</tr>
<tr>
<td>Extent index</td>
<td>1.34 ± 0.15</td>
<td>0.93 ± 0.38</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; pattern = classification of the changes in the pattern of atherosclerotic lesion according to American College of Cardiology/American Heart Association standards (ref. 11); severity = atherosclerotic severity of the lesion scored by vessels diseased (>70% narrowing) and the total number of stenoses (≥50% narrowing) in 15 segments (15 × [0–3] = 0–45), and occlusions of the three major coronary arteries (0–3); extent index is calculated by dividing extent score 0 (normal), 1 (abnormal: any narrowing or irregularity ≤10% of the length, or both), 2 (10% < abnormal ≤50%), 3 (50% < abnormal) to each of the 15 segments of the arterial tree ([0–3] × 15 = 0–45) by the number of segments properly visualized by antegrade flow (0–15), accordingly ranging from 0 to 3. Extent score was not calculated when antegrade flow was not detected at the particular segment.

Parameter that correlated with the extent index or the existence of coronary atherosclerosis (R² = 0.13, p = 0.035).

Evaluation of the patients with and without restenosis.
Restenosis was observed in 14 of 35 patients (40%). Neither clinical nor PTCA (Table 1) characteristics of these patients, except for MLD after PTCA, showed significant correlation with the development of restenosis. The MLD after PTCA was significantly (p < 0.05) smaller in patients with restenosis than in those without restenosis. Scorings of atherosclerotic indexes and results of the OGTT in patients with and without restenosis are shown in Tables 2 and 3, respectively. Among the atherosclerotic indexes, extent index, or the length of the atherosclerotic lesion, was the only variable which was shown to be significantly associated with restenosis (p = 0.001). Among the OGTT results, insulin area, the ratio of insulin area to glucose area and the insulogenic index were shown to be significantly associated with restenosis (p = 0.011, 0.002 and 0.016, respectively). No other variables were significantly associated with restenosis. Changes in plasma levels of glucose and insulin during the 3 h of OGTT in these patients are depicted in Figure 1. Although the plasma levels of glucose did not differ significantly between patients with and without restenosis, the plasma levels of insulin were significantly higher (p = 0.007) in patients with restenosis during the early phase of the OGTT or at 30 min (p = 0.005) and 1 h (p = 0.037) after the glucose load.

Assessment for restenosis after PTCA. To study associations between the development of restenosis or loss of gain and the patients’ characteristics, the atherosclerotic indexes, OGTT results and PTCA variables, simple regression analyses were performed between loss of gain and these variables. Loss of gain was significantly correlated with extent index (R² = 0.31, p = 0.001), insulin area (R² = 0.19, p = 0.009), the ratio of insulin area to glucose area (R² = 0.25, p = 0.002) and insulogenic index (R² = 0.13, p = 0.032). Other variables did not significantly correlate to loss of gain. Stepwise multiple regression analyses were also performed to determine whether clinical results, PTCA characteristics, the atherosclerotic indexes and OGTT results were to be independent contributors of loss of gain. These analyses revealed that extent index and the ratio of insulin area to glucose area were the only two independent variables that significantly correlated with loss

| Glucose area (mg/dL × h) | 376 ± 65 | 395 ± 100 | NS |
|--------------------------|----------|-----------|    |
| Fasting plasma insulin (µU/mL) | 6.14 ± 2.98 | 5.52 ± 4.24 | NS |
| Insulin area (µU/mL × h) | 214 ± 112 | 130 ± 73 | 0.011 |
| Insulin area/glucose area | 0.56 ± 0.24 | 0.33 ± 0.17 | 0.002 |
| Insulogenic index | 1.21 ± 0.65 | 0.60 ± 0.72 | 0.016 |

Table 3. Oral Glucose Tolerance Test Results in Patients With and Without Restenosis After Percutaneous Transluminal Coronary Angioplasty

Data are presented as mean ± SD. NS = not significant.
of gain or the development of restenosis after PTCA ($R^2 = 0.41, p < 0.001$).

**Discussion**

**Patient characteristics.** In this study we excluded the patients who had a history of previous PTCA on the same major coronary artery in which the responsible lesion for effort angina was newly diagnosed. This exclusion criterion was applied to eliminate the influences of factors of the injury induced by previous PTCA and of the healing process that may cause complex and diverse effects on the development of atherosclerosis or restenosis or both. We also excluded the patients with diabetes mellitus because their metabolic responses to glucose load, including the release of insulin and the uptake of glucose, are considered to be abnormal, thus affecting the results of the OGTT. To elucidate a specific mechanism or a predictor of restenosis after PTCA, patients who had undergone directional atherectomy ($n = 4$) were excluded in this study because directional atherectomy is considered to cause more profound injuries to coronary vasculature than balloon angioplasty. These exclusion criteria were applied to make the interpretation of the OGTT results as straightforward as possible with regard to the effect of insulin on atherosclerosis or restenosis after PTCA. These two exclusion criteria substantially decreased the number of patients for final analysis; however, these exclusion criteria were critically important for the analyses and interpretation of our results to avoid presumably huge and strong effects of the preceding injury on coronary arteries by PTCA and of diabetes mellitus on the metabolism of coronary vasculature.

**Coronary atherosclerosis.** It has been known that diabetes mellitus is a risk factor of coronary atherosclerosis (12,13). In more recent studies it has been shown that elevated fasting insulin (14,15), or postload insulin (1,14,16), is associated with coronary artery disease. In the present study, we found that the extent index, an index of the degree of coronary atherosclerosis, significantly and positively correlated with the ratio of insulin area to glucose area. This result may indicate that the ratio of insulin area to glucose area, reflecting the enhanced secretion of insulin relative to plasma glucose level, can serve as a predictor or an indicator of the existence of coronary atherosclerosis, if checked when patients develop effort angina. Several mechanisms by which insulin is involved in the development of coronary atherosclerosis have been reported: through stimulating arterial smooth muscle cell proliferation (1), aggravating dyslipidemia (16,17), modulating metabolisms of several biochemical substances such as procoagulant or anti-coagulant factors and several growth factors (15). It is noteworthy here that insulin area did not, but the ratio of insulin area to glucose area did, significantly correlate with the extent index in our population of nondiabetic patients with angina. This result suggests that not insulin per se, but the ratio of insulin to glucose or a relative surplus of insulin is a very important factor in the development of coronary atherosclerosis. This result may also suggest that the effect of insulin on vessel walls is attenuated, or that a condition like “insulin resistance,” as in the organs and tissues of hyperinsulinemic patients (18), is developed in the coronary arteries of these patients. In other words, attenuated responses of coronary arteries to the enhanced secretion of insulin in these patients would account for the failure of the insulin area but the success of the ratio of insulin area to glucose area as a significant predictor of the existence of atherosclerosis.

**Restenosis after PTCA.** Diabetes mellitus (19), length of stenotic lesions (20), residual percent diameter (20) and MLD after PTCA (21) have been reported as risk factors of restenosis after PTCA. The present study is the first to report that enhanced secretion of insulin observed until 1 h after the glucose load is an independent predictor of restenosis after elective PTCA in nondiabetic, nonobese patients with effort angina. Mechanisms underlying the development of restenosis after PTCA are currently considered to be derived from elastic recoil (22), thrombus formation (23–25), proliferation and migration of smooth muscle cells (26) or mixtures of secondary effects, such as the secretion of stimulatory factors for smooth muscle cell proliferation (27). Insulin is considered at least in part to be directly or indirectly involved in all of these mechanisms of restenosis. Insulin is known to potentiate proliferation and migration of smooth muscle cells directly, or indirectly through the secretion of stimulatory factors for the proliferation (1,28,29). Long-term recoil of the overstretched arteries by PTCA is proposed to be derived from the replacement of the injured medial smooth muscle cells by the proliferated cells (22). This replacement process will be theoretically stimulated by the action of insulin. Insulin has also been reported to be involved in thrombus formation through attenuating endogenous fibrinolytic activities by modulating the plasminogen activator and inhibitor systems (30). In more recent studies of restenosis, exaggerated intimal hyperplasia has been observed in restenotic lesions of the arteries after various types of coronary intervention (31), and smooth muscle cell proliferation has been implicated to the increased rate of restenosis through the action of insulin (19). Because insulin has a wide variety of actions with regard to the development of atherosclerosis or of coronary restenosis or both, it is difficult to pinpoint the definitive mechanism as to how the enhanced secretion of insulin after glucose load leads to the development of restenosis after PTCA in patients with effort angina.

**Restenosis after PTCA and coronary atherosclerosis.** This study confirmed a strong correlation between the extent of preceding coronary atherosclerosis or extent index and the development of restenosis or loss of gain in our study patients. Although possibly different mechanisms are functioning between the progression of coronary atherosclerosis and the development of restenosis after PTCA, arterial endothelial injury as the first step of atherosclerosis (32) is inevitable in the coronary arteries on which PTCA was performed. Proliferation of coronary arterial smooth muscle cells lying just beneath the endothelial cells damaged by PTCA will be stimulated repeatedly by the enhanced insulin secretion following the ingestion of foods or glucose load, resulting in the acceleration of
restenosis. Enhanced secretion of insulin after glucose load significantly correlated with both extent index and loss of gain, but the correlation coefficients were larger with the marker of restenosis (loss of gain) than that of atherosclerosis (extent index). This result may suggest that the enhanced insulin secretion exerts more rapid and profound effects on proliferation of smooth muscle cells in the coronary arteries mechanically damaged by PTCA than in those chronically damaged by atherosclerosis.

**Study limitations.** Our study group was small because of the strict inclusion criteria adopted for final analysis of the patients. We evaluated the development of restenosis by relatively early restudies at an angiographic follow-up of 107 ± 23 days after PTCA. The present study would therefore have been underpowered to detect the difference in specific variables, to include all of the restenosis for the analysis and to exclude possible artifacts from the analysis.

**Conclusions.** In this study we found that nondiabetic patients with effort angina who showed enhanced secretion of insulin during the OGGT have a high risk not only for coronary atherosclerosis but also for restenosis after elective PTCA.

**References**