Process of Progression of Coronary Artery Lesions From Mild or Moderate Stenosis to Moderate or Severe Stenosis

A Study Based on Four Serial Coronary Arteriograms per Year

Koichi Yokoya, MD; Hisato Takatsu, MD; Takahiko Suzuki, MD; Hiroaki Hosokawa, MD; Shinsuke Ojio, MD; Tetsuo Matsubara, MD; Tsutomu Tanaka, MD; Sachiro Watanabe, MD; Norihiko Morita, MD; Kazuhiko Nishigaki, MD; Genzou Takekura, MD; Toshiyuki Noda, MD; Shinya Minatoguchi, MD; Hisayoshi Fujiwara, MD

Background—The process of progression in coronary artery disease is unknown.

Methods and Results—The subjects were 36 patients with 36 objective vessels with clinically significant progression of coronary artery disease (15% per year) in whom 4 serial coronary arteriograms (CAGs) were performed at intervals of 4 months in a 1-year period. The degree of progression of percent stenosis between each of 2 serial CAGs was classified as marked (M: >15%), slight (S: 5% to 14%), and no progression (N: <5%). From the pattern of progression, the 36 vessels were classified as 14 type 1 vessels with marked progression (N→N→M in 13 vessels and S→S→M in 1 vessel) and 22 type 2 vessels without marked progression (S→S→S in 18 vessels, N→S→S in 4). Percent stenosis at the first, second, third, and final CAGs was 44±14%, 46±13%, 46±13%, and 88±10% (P<0.05 versus first CAG) in type 1 vessels and 44±11%, 50±9%, 59±9%, and 67±9% in type 2 vessels (P<0.05 for second, third, and final CAGs versus first CAG). Type 1 vessels featured the sudden appearance of severe stenosis due to marked progression, angina pectoris, or myocardial infarction (71%) and Ambrose type II eccentric lesions indicating plaque rupture or thrombi (57%). Type 2 vessels featured continuous slight progression of stenosis with smooth vessel walls; angina pectoris (14%) occurred when the percent stenosis reached a severe level. An increase in serum C-reactive protein was observed only in the type 2 vessel group, which suggests a relation between continuous slight progression and inflammatory change.

Conclusions—Two types of stenosis progression provide a new insight into the mechanism of coronary artery disease. (Circulation. 1999;100:903-909.)

Key Words: coronary disease ■ proteins ■ stenosis ■ angiography
with PTCA performed during the 5-year period between 1991 and 1995 in these facilities. Joint meetings were held to retrospectively assess patients who met the following criteria: (1) 4 serial CAGs, performed at 4-month intervals (10 to 14 months before final CAG, 5 to 9 months before final CAG, within 4 months before final CAG, and final CAG), over a period of 1 year; (2) $1 major coronary artery (objective vessel) was present through which a guidewire had not passed, that had not undergone PTCA or CABG before the final CAG, and that had not been an infarct-related artery; (3) serial CAGs were clear for quantitative coronary angiographic analysis and were performed in the same projections; and (4) clinically significant progression was defined as an increase of $15\%$ per year in percent diameter stenosis, which occurred in lesions of $20\%$ diameter stenosis in objective vessels at the initial CAG. This definition of a clinically significant progression was similar to that used in previous studies.²,⁷

A total of 486 patients met criteria 1, 2, and 3. From those patients, 36 objective vessels of 36 patients with annual progression that met the fourth criterion were found (7% incidence of clinically significant progression) (Table). CAGs were performed in these patients at 11 6 1 months before the final CAG (first CAG), 7 6 1 months before the final CAG (second CAG), 3 6 1 months before the final CAG (third CAG), and as a final CAG. The degree of progression in percent diameter stenosis in each of the 3 intervals of the 4 serial CAGs (between each of 2 serial CAGs) was classified as marked progression (M: $\geq 15\%$), slight progression (S: $5\%$ to $14\%$) and no progression (N: $< 5\%$).

The percent diameter stenosis in 36 vessels with annual progression ranged from 20% to 74% at the first CAG. Therefore, as a control without progression, 50 objective vessels (in 50 patients) with a percent diameter stenosis of 20% to 74% at the first CAG that had changes in percent diameter stenosis of $<5\%$ between the first

### Patient and Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Type 1 (n=14)</th>
<th>Type 2 (n=22)</th>
<th>Control Without Progression (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics at first CAG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>67±11</td>
<td>68±10</td>
<td>66±10</td>
</tr>
<tr>
<td>Male</td>
<td>12 (86%)</td>
<td>18 (82%)</td>
<td>39 (78%)</td>
</tr>
<tr>
<td>Myocardial infarction*</td>
<td>12 (86%)</td>
<td>19 (86%)</td>
<td>42 (84%)</td>
</tr>
<tr>
<td>Acute infarction†</td>
<td>8 (57%)</td>
<td>11 (50%)</td>
<td>24 (48%)</td>
</tr>
<tr>
<td>Old infarction</td>
<td>6 (43%)</td>
<td>11 (50%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Q-wave infarction‡</td>
<td>10 (71%)</td>
<td>17 (77%)</td>
<td>36 (72%)</td>
</tr>
<tr>
<td>Non–Q-wave infarction</td>
<td>4 (29%)</td>
<td>5 (23%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>2 (14%)</td>
<td>2 (9%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Characteristics of an objective vessel at first CAG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA (prox/mid/dist)</td>
<td>57% (7/21/29)</td>
<td>59% (14/27/18)</td>
<td>56% (12/28/16)</td>
</tr>
<tr>
<td>LAD (prox/mid/dist)</td>
<td>29% (7/21/0)</td>
<td>27% (5/18/5)</td>
<td>28% (6/18/4)</td>
</tr>
<tr>
<td>LCx (prox/dist)</td>
<td>14% (7/7)</td>
<td>14% (9/5)</td>
<td>16% (6/10)</td>
</tr>
<tr>
<td>Vessel reference, mm</td>
<td>2.97±0.55</td>
<td>3.02±0.56</td>
<td>3.02±0.56</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>8.5±6.4</td>
<td>9.4±7.8</td>
<td>9.1±6.6</td>
</tr>
<tr>
<td>Percent diameter stenosis</td>
<td>44±14%</td>
<td>44±11%</td>
<td>45±11%</td>
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</tbody>
</table>

### Characteristics of 2 nonobjective vessels

<table>
<thead>
<tr>
<th>Vessels with diameter stenosis &gt;75% at first CAG, n</th>
<th>0</th>
<th>0</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-vessel disease</td>
<td>4 (29%)</td>
<td>7 (32%)</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>1-vessel disease</td>
<td>10 (71%)</td>
<td>15 (68%)</td>
<td>34 (68%)</td>
</tr>
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</table>

Vessels that underwent PTCA between first and third CAGs, n

| 1 vessel                                            | 6 (43%) | 10 (45%) | 20 (40%) |
|                                                    | 8 (57%) | 12 (55%) | 30 (60%) |

Restenosis rate

RCA indicates right coronary artery; prox, proximal portion of coronary artery; mid, middle portion of coronary artery; dist, distal portion of coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery. First and third CAGs were performed at 11 and 3 months before final CAG.

*The infarct-related arteries were nonobjective vessels in all patients with infarction.

†Note that 2 patients in type 1, 2 patients in type 2, and 4 patients in the control group had both acute and old myocardial infarction.

‡Note that 2 patients in type 1, 2 patients in type 2, and 4 patients in the control group had both Q-wave and non–Q-wave infarction.
and final CAGs were selected at random from 450 patients without clinically significant progression.

Acute coronary syndrome consists of unstable angina and acute myocardial infarction. Acute myocardial infarction was defined as typical chest pain that continued longer than 30 minutes, newly developed ischemic ST-T changes or Q waves, and elevation of the serum creatine kinase level to 3-fold higher than the upper limit of the normal range. Unstable angina was classified as new-onset angina, which was defined as the new development of ischemic chest pain within the month before the final CAG, and chronic unstable (worsening) angina, which was defined as an increase in the severity of symptoms in patients with chronic stable angina.

**Coronary Arteriography**

To exclude the effect of coronary arterial spasms, all patients were administered an intracoronary injection of nitroglycerin before their CAGs. Arteriograms of the right and left coronary arteries were performed in at least 3 and 6 projections, respectively. The best projection, representing stenosis of the lesion with progression, was selected and examined for changes in percent diameter stenosis by quantitative coronary angiographic analysis by use of a cardiovascular measurement system (Medical Imaging Systems).

Coronary arteriograms were reviewed by 2 independent observers experienced in angiographic interpretation and blinded to the clinical data according to the criteria proposed by Ambrose et al. Briefly, lesions were classified as concentric lesions, type I eccentric lesions, type II eccentric lesions, and multiple irregularities. Interindividual and intraindividual variabilities in the method for assessing progression were measured with coronary arteries with percent diameter stenosis of $<50\%$ and $>50\%$ ($n=20$ in each group). Interindividual variability was $2.5\% \pm 1.7\%$ in the former and $2.1\% \pm 1.8\%$ in the latter group. Intraindividual variability was $1.8\% \pm 1.1\%$ in the former and $2.5\% \pm 1.5\%$ in the latter group.

**Coronary Risk Factors**

Risk factors were investigated at the first CAG, including resting blood pressure, smoking status, presence of diabetes and obesity, and measurement of serum cholesterol. Family history of coronary artery disease was also included. Hyperlipidemia was considered present when the subject was receiving therapy or when the serum total cholesterol was $\geq 240$ mg/dL and/or LDL cholesterol was $\geq 160$ mg/dL. Hypertension was considered present when the subject was receiving therapy, systolic blood pressure was $\geq 140$ mm Hg, and/or diastolic blood pressure was $\geq 90$ mm Hg. Diabetes was considered present when the subject was receiving therapy, the subject had an abnormal glucose tolerance test, or the fasting blood glucose concentration was $\geq 140$ mg/dL. Smoking habit was considered present when the subject smoked a half pack of cigarettes or more per day, and an ex-smoker was defined as a subject who had stopped smoking for $\geq 2$ years. Obesity was judged to be present when the body mass index was $\geq 26$ kg/m$^2$.

**Serum C-Reactive Protein**

Serum C-reactive protein (CRP), an indicator of nonspecific inflammation, was retrospectively examined in all patients at the first, third, and final CAGs and was compared with the data of 200 age- and sex-matched healthy volunteers. Data were excluded if the patient had infectious or collagen disease in which serum CRP was increased. In patients with acute coronary syndrome, serum CRP at the final CAG after onset was used only when blood sampling was performed within 5 hours after onset, because serum CRP may be increased secondary to acute coronary syndrome, especially acute myocardial infarction. In addition, to define precisely whether an increase of serum CRP was the cause or the result of plaque rupture with thrombi, serum CRP was also examined retrospectively in the 72 patients with acute myocardial infarction, a condition indicative of plaque rupture with thrombi, and blood sampling was performed within 3 hours after onset. These patients were selected from the serial patient group with acute myocardial infarction for 5 years from which subjects were selected for the present study.

**Statistical Analyses**

Unpaired Student’s $t$ test was used to compare data between 2 groups. ANOVA was used to compare data among 3 or more groups. $\chi^2$ analysis was used to compare categorical data. A value of $P<0.05$ was considered significant. All data are presented as mean $\pm$ SD.

**Results**

Thirty-six objective lesions in 36 patients showed clinically significant progression of $>15\%$ per year in percent diameter stenosis. Progression was classified as no progression (N; $<5\%$ increase in percent stenosis), slight progression (S; 5\% to 14\% increase), and marked progression (M; $\geq 15\%$ increase). The 36 lesions were classified as 14 type 1 vessels with marked progression ($N\rightarrow N\rightarrow M$ in 13 vessels and $S\rightarrow S\rightarrow M$ in 1 vessel) and 22 type 2 vessels without marked progression ($S\rightarrow S\rightarrow S$ in 18 vessels and $N\rightarrow S\rightarrow S$ in 4 vessels) (Figures 1, 2, and 3).

**Characteristics of Patients**

As shown in the Table, patient characteristics and the characteristics of objective vessels and 2 nonobjective vessels were similar among patients with type 1 and type 2 vessels and the control group at the first CAG.

Between the first and final CAGs, 10 (71\%) of 14 patients with type 1 vessels, 12 (55\%) of 22 patients with type 2 vessels, and 31 (62\%) of 50 patients in the control group were administered aspirin. Among patients with type 1 and 2 vessels and in controls, antiplatelet agents were taken in 56\%, 68\%, and 64\%; coumadin in 50\%, 45\%, and 44\%; nitrate in 100\%, 100\%, and 94\%; and calcium antagonist in 86\%, 73\%, and 78\%, respectively. There were no significant differences in the use of these medications among the above 3 groups.

In patients with type 1 and 2 vessels and control subjects, all patients with hyperlipidemia (43\%, 50\%, and 38\% of subjects, respectively) and hypertension (57\%, 50\%, and 48\%, respectively) were treated with cholesterol-lowering medications.
drugs and antihypertensive drugs. Patients with diabetes mellitus (36%, 32%, and 34%, respectively) were treated with diet therapy, oral hypoglycemic drugs, or insulin. No significant differences in smoking status, obesity, or family history of coronary heart disease were found among the 3 groups.

Changes in Percent Diameter Stenosis in Objective Vessels
The results are shown in Figures 1 through 4. In 14 objective type 1 vessels, the percent diameter stenosis in the first, second, third, and final CAGs was 44±14%, 46±13%, 46±13%, and 88±10%, respectively. The degree of progression per year was 44±15% (range, 22% to 70%). Marked progression was observed between the third and final CAGs, and the increase in percent diameter stenosis ranged from 21% to 66% (mean±SD, 41±15%). In 22 objective type 2 vessels, the percent diameter stenosis in the first, second, third, and final CAGs was 44±11%, 50±9%, 59±9%, and 67±9%, respectively. The degree of progression per year was 23±5% (range, 17% to 33%).

Percent diameter stenosis of the objective vessels was similar between type 1 and type 2 vessels at the first CAG but was significantly greater in type 2 vessels than in type 1 vessels at the third CAG. Percent diameter stenosis at the final CAG was significantly greater in type 1 vessels than in type 2 vessels.

Acute Coronary Syndrome and Lesions of Objective Vessels
All acute coronary syndromes occurred between the third and final CAGs. Acute coronary syndrome was noted in 10 of 14 type 1 vessels and in 3 of 22 type 2 vessels. The difference was significant. In the 10 patients with type 1 vessels, progression between the third and final CAGs was marked in objective vessels (26% to 68%) but not in the nonobjective vessels (−1% to 2%). At the final CAG, percent diameter stenosis of the objective vessels was severe (80% to 100%) but that of the nonobjective vessels was mild or moderate (36% to 71% in maximal percent diameter stenosis of nonobjective vessels). In the 3 patients with type 2 vessels, the progression between the third and final CAGs was slight in the objective vessels (6% to 11%), but no progression was observed in the nonobjective vessels (0% to 1%). Percent diameter stenosis of the objective vessels at the final CAG was severe (80% to 82%) but that of the nonobjective vessels was mild (36% to 48% in maximal percent diameter stenosis of nonobjective vessels). Thus, the culprit lesion in acute coronary syndrome in these patients was not the nonobjective vessels but the objective vessels.

Percent diameter stenosis of the objective vessels in patients with acute coronary syndrome was more severe than in patients without acute coronary syndrome in both type 1 and 2 vessels. Percent diameter stenosis of the objective vessels in CAGs before and after the acute coronary syndrome occurred is shown in Figure 4. In patients with type 1 vessels, percent diameter stenosis was greatest in acute myocardial infarction (97±4%), less in new-onset effort angina (89±5%), and least in those with no clinical events (75±5%) at the final CAG, although it was similar among the above 3 patient groups at the third CAG (50±20%, 49±9%, and 38±10%, respectively) (Figure 4). However, in patients with type 2 vessels, percent diameter stenosis among those with unstable angina and those with no clinical events was 72±3% and 57±7% at the third CAG and 81±1% and 66±7% at the final CAG, respectively. The differences between those with unstable angina and those with no clinical events were significant in each of the third and final CAGs.

Collaterals from nonobjective vessels to objective vessels were observed only at the final CAGs of 5 patients with type
1 vessels, although the degree of collateral was not rich (poor in 2 patients and moderate in 3 patients). All 5 patients had acute myocardial infarction with typical chest pain. The percent diameter stenosis at the final CAG was highest in 5 type 1 vessels with collaterals (97±4%), less in 9 type 1 vessels without collaterals (83±9%), and least in 22 type 2 vessels without collaterals (69±8%). The rate of progression between the third and final CAGs was similar in type 1 vessels with and without collaterals (50±20% and 45±11%, respectively).

Angiographic Morphology in Objective Vessels
Ambrose type II eccentric lesions, indicating plaque rupture and/or thrombus formation,4,8 were seen in 8 of 14 type 1 vessels, 4 of 22 type 2 vessels, and 3 of 50 control vessels. However, in the 3 vessels of control subjects, these lesions were found in each of 4 serial CAGs. Therefore, the number of vessels in which CAG findings before and after the appearance of Ambrose type II eccentric lesions could be observed was 8 in type 1 and 4 in type 2. Ambrose type II eccentric lesions in type 1 vessels were combined with marked progression and those in the type 2 vessels with slight progression. The percent diameter stenosis before the appearance of Ambrose type II eccentric lesions was similar in type 1 (50±17%) and type 2 (62±9%) vessels. However, the percent diameter stenosis after their appearance was significantly greater in type 1 (92±8%) than in type 2 (70±11%) vessels. Except for these vessels, the wall in the vessels was smooth.

Serum CRP
Serum level of CRP in study subjects was within 0.4 mg/dL of that measured in 95% of 200 age- and sex-matched healthy volunteers (0.2±0.1 mg/dL). Serum CRP levels at the first, third, and final CAGs were 0.2±0.3, 0.1±0.1, and 0.1±0.2 mg/dL in the type 1 group (n=11); 0.4±0.4, 0.4±0.4, and 0.3±0.3 mg/dL in the type 2 group (n=18); and 0.2±0.2, 0.2±0.2, and 0.2±0.1 mg/dL in the control group without progression (n=40). Serum CRP was significantly higher in the type 2 group than in the type 1 group or the control group without progression, although the type 1 and control groups showed similar CRP levels. Serum CRP was not increased in the 72 patients with acute myocardial infarction in whom blood sampling was performed within 3 hours after onset of the infarction (0.1±0.2 mg/dL; n=72).

Discussion
The present study revealed 2 different types of processes in the progression of coronary artery disease, type 1 and type 2.

Study Limitations
The mean age and sex differences in patients with type 1 and 2 vessels and control patients were similar to those of usual Japanese patients with coronary heart disease.6 However, the incidences of multivessel disease and myocardial infarction were considerably higher in the progression groups than in usual Japanese patients with coronary heart disease (~50% and 30%, respectively).6 The restenosis rate after PTCA for treatment of lesions in nonobjective vessels in the progression groups was the same as the upper limit of the restenosis rate.
after PTCA in patients with usual coronary heart disease (30% to 50%). However, similarly high incidences were also observed in the control group without progression. In addition, the incidence of objective vessels with progression of stenosis of 7% per year in the present study was similar to that of previous studies. Therefore, these high incidences are independent of the progression of stenotic lesion in the objective vessels, although they are special features of patients with 4 serial CAGs per year.

If the percent diameter stenosis reached a moderate or severe level at the final CAG, PTCA was performed in all vessels in the present study. This study limitation explains why all of the marked progression in type 1 vessels was seen only between the third and final CAGs. There were no fatal cases in the present serial CAG study. It is likely that the absence of fatal cases has underestimated the frequency of patients with severe stenosis, especially in type 1 vessels with rapid and marked progression.

Mechanism of Slight and Marked Progression in Type 1 and Type 2 Vessels

Ambrose type II eccentric lesions were seen in 57% of type 1 vessels and 18% of type 2 vessels. The former was associated with marked progression and the latter with slight progression. CAG is not a precise method to detect plaque rupture or thrombi. Therefore, the presence of Ambrose type II eccentric lesions generally indicates thrombosis or plaque rupture, but its absence does not disprove the presence of small thrombi or plaque rupture. The smooth vessel wall in vessels with continuous slight progression of stenosis suggests a general growth of the plaque volume itself. This is supported by the findings of Flugelman et al that smooth muscle cell proliferation may lead to gradual plaque expansion and thereby to luminal narrowing and unstable angina. However, this angiographic finding of a smooth vessel wall does not disprove the presence of small thrombi due to plaque rupture or endothelial damage. Therefore, the mechanism of sudden marked stenosis progression is probably large thrombi due to plaque rupture and/or endothelial damage and that of continuous slight progression is the growth of plaque volume itself or small thrombi due to plaque rupture and/or endothelial damage.

A relationship between serum CRP and atherosclerosis or acute coronary syndrome has been reported. However, it remains unknown whether an increase in CRP is related to types of progression or the onset of plaque rupture with thrombi and acute coronary syndrome. In the present study, serum CRP was higher in patients with type 2 vessels than those with type 1 vessels or control patients without progression. This suggests that inflammatory change may be involved in one of the mechanisms of gradual progression in coronary stenosis. Meanwhile, there was no evidence of increased serum CRP at the early stage of acute myocardial infarction, a sign of plaque rupture with thrombi. Thus, plaque rupture with thrombi and/or marked progression is independent of the preceding increased level of serum CRP. An increase of serum CRP in acute coronary syndrome may be the result rather than the cause. Recently, Torzewski et al reported tissue CRP in early atherosclerotic lesions of human coronary arteries. Further investigation of the difference in tissue CRP localization among coronary arteries with type 1, type 2, and no stenosis progression is warranted.

Pathophysiological Role of Type 1 and Type 2 Vessels

Generally, acute coronary syndrome depends on the severity of the percent diameter stenosis and the poorness of collateral flow. This was confirmed by the present findings. Acute coronary syndrome occurred with both marked progression of type 1 vessels and slight progression of type 2 vessels when the percent diameter stenosis reached a severe level and the collateral circulation was not rich.

In the present study, the incidence of acute coronary syndrome was higher in type 1 vessels than in type 2 vessels. Acute myocardial infarction and total or subtotal occlusion were not seen in type 2 vessels but only in type 1 vessels. However, percent diameter stenosis was lower in type 2 vessels than in type 1 vessels at the final CAG, and PTCA was performed in most of the type 2 vessels, as well as the type 1 vessels at the final CAG. Therefore, no information on the natural course of type 2 vessels after the final CAG was obtained. In type 2 vessels, slight stenosis progression may continue after the final CAG because the feature is continuous.
slight progression, and acute coronary syndrome may appear when the percent diameter stenosis reaches a more severe level.

In vessels with clinically significant progression for 1 year, most of the marked progression occurred in vessels that previously had no progression rather than in vessels that previously had slight progression. However, this does not mean that the incidence of marked progression occurring in vessels that previously showed no progression is higher than that in vessels that previously had slight progression in all patients with and without significant progression for a year, because the incidence of significant progression for 1 year was only 7% in the present study.

In patients with type 1 vessels, marked stenosis progression with and without acute coronary syndrome appeared suddenly primarily in vessels with smooth vessel walls and without preceding progression. There was no evidence of a preceding increase in serum CRP. Therefore, it is difficult to predict sudden marked stenosis progression and acute coronary syndrome. In patients with type 2 vessels, serum CRP was increased, which suggests that serum CRP may be one of the predictors for type 2 vessels. Percent diameter stenosis at the third and final CAGs was greater in patients with new-onset angina than in patients without it. The degree of progression between the third and final CAGs was similar in both. This suggests that the appearance of new-onset angina depends on the preceding percent diameter stenosis. Because the feature of type 2 vessels was a continuous slight progression, the presence of S→S or S and moderate stenosis (~70% diameter stenosis) would predict that after several months, the percent diameter stenosis reached a severe level as the result of further slight progression, and new-onset angina may occur. This speculation suggests a reason for preventive PTCA in treatment of lesions with moderate stenosis without angina in type 2 vessels. Thus, prediction of acute coronary syndrome is difficult in type 1 vessels but may be possible in type 2 vessels.

In conclusion, the concept of type 1 and type 2 vessels provides important information on the progression of coronary artery disease.

References
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