Coronary Spasm Preferentially Occurs at Branch Points  
An Angiographic Comparison With Atherosclerotic Plaque

Hitoshi Nakagawa, MD; Yoshinobu Morikawa, MD; Yuji Mizuno, MD; Eisaku Harada, MD; Teruhiko Ito, MD; Kunihiko Matsui, MD, MPH; Yoshihiko Saito, MD; Hirofumi Yasue, MD

Background—Coronary spasm plays an important role in the pathogenesis of ischemic heart disease. However, similarities and differences between coronary spasm and atherosclerosis are not known. We examined the angiographic characteristics of coronary spasm in comparison with those of atherosclerosis.

Methods and Results—Thirty-two left anterior descending arteries, 11 left circumflex arteries, and 23 right coronary arteries with spasm and atherosclerotic plaque were analyzed for the localization of spasm in comparison with that of plaque in 47 patients (38 men and 9 women, mean age 66.8±10.3 yrs). Spasm predominantly occurred at the branch point as compared with plaque in each of the 3 arteries (76.7% versus 23.3%, P<0.0001; 72.7% versus 9.1%, P<0.039; and 60.0% versus 10.0%, P=0.002, in the left anterior descending, left circumflex, and right coronary arteries, respectively). Spasm involved the proximal segment less frequently as compared with plaque in each of the 3 arteries (56.7% versus 93.3%, P<0.0001; 18.2% versus 81.8%, P=0.016; and 15.0% versus 75.0%, P<0.0001 in the left anterior descending, left circumflex, and right coronary arteries, respectively). Most spasms occurred at the nonplaque site in each of the 3 arteries (73.3%, P=0.018; 100%, P<0.0001; and 75.0%, P=0.041 in the left anterior descending, left circumflex, and right coronary arteries, respectively).

Conclusion—Coronary spasm preferentially occurred at branch points and nonplaque sites, whereas the atherosclerotic lesion was predominantly localized at the nonbranch points of the curved proximal segments. Coronary spasm may thus be a manifestation of a distinct type of arteriosclerosis different from the lipid-laden coronary atherosclerosis. (Circ Cardiovasc Intervent. 2009;2:97-104.)

Key Words: atherosclerosis ■ coronary spasm ■ endothelium ■ nitric oxide ■ vasoconstriction

Coronary spasm is not only the cause of variant angina but also participates in the pathogenesis of unstable angina, acute myocardial infarction, and sudden death, particularly in Japan. However, precise mechanisms by which coronary spasm occurs are not fully understood. We have shown that endothelial nitric oxide (NO) activity is deficient and endothelial function is impaired in the coronary arteries involved in spasm. Endothelial NO enhances vascular functions, including vessel relaxation, survival of vascular endothelial cells, inhibition of platelet aggregation, and attenuation of leukocyte infiltration. Impaired NO activity has been suggested as the earliest pathophysiological events contributing to atherosclerosis. Although the entire vasculature is exposed to the atherogenic effect of systemic risk factors, atherosclerotic lesions form at specific arterial regions such as curvatures or branch sites where flow is disturbed. Thus, local hemodynamic factors play a major role in the regional localization of atherosclerosis. It is, therefore, possible that coronary spasm also may preferentially occur at the sites of coronary arterial tree where flow is disturbed. However, no previous studies have examined this possibility and the relationship between coronary spasm and atherosclerosis is not clear. This study was designed to examine whether there are predilection sites for spasm in the coronary arteries and, if there are, whether these sites are similar to those of atherosclerosis.

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Flow-generated shear stress is an important physiological stimulus that enhances the production of NO and high shear stress augments the bioavailability of NO, whereas disturbed shear stress reduces it. Although the entire vasculature is exposed to the atherogenic effect of systemic risk factors, atherosclerotic lesions form at specific arterial regions such as curvatures or branch sites where flow is disturbed. Thus, local hemodynamic factors play a major role in the regional localization of atherosclerosis. It is, therefore, possible that coronary spasm also may preferentially occur at the sites of coronary arterial tree where flow is disturbed. However, no previous studies have examined this possibility and the relationship between coronary spasm and atherosclerosis is not clear. This study was designed to examine whether there are predilection sites for spasm in the coronary arteries and, if there are, whether these sites are similar to those of atherosclerosis.

Methods

Patients  Ninety-eight (67 men and 31 women, with a mean age of 65.5±10.1 years ranging from 35 to 86) Japanese patients in whom coronary

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spasm was induced by intracoronary injection of acetylcholine (ACh; Daiichi-Sankyo Co, Tokyo, Japan) and a nitrate (ISDN) into the arteries. After the end of the test, ISDN (0.1 mg) was injected into the coronary artery and angiography was again performed. The specificity of this test for variant or resting angina was 99%.12 The test did not induce coronary spasm in any of the patients with normal coronary angiogram and without ischemic heart disease.12,13 The specificity of this test for spasm arteries was also confirmed in the vitro study.14

Assessment of Coronary Artery Diameter and Length

We quantitatively measured the diameter of the coronary arteries and the distance from the branch point. An end-diastolic frame was digitized and the diameter of the index vessel was measured by CAAS II software (PIE Medical). We defined the branch point as that within 5-mm distal from the apex of the flow divider because the median distance between each adjacent branch was 14.3 mm (interquartile range was 9.1 to 21.1 mm). We divided the left anterior descending (LAD) artery, the left circumflex (LCx) artery, and the RCA into the proximal segments (segments 6, 7, and 9 in the LAD; segments 11 to 13 in the LCx; and segments 1 to 2 in the RCA) and the distal segments (segments 8 and 10 in the LAD; segments 14 and 15 in the LCx; and segments 3 and 4 in the RCA) according to the AHA coronary segment reporting system15 and compared the incidence of spasm between the proximal and distal segments. The coronary diameter was expressed as percent narrowing in luminal diameter after ISDN injection. Total or subtotal obstruction or severe coronary spasm with a lumen diameter <0.4 mm could not be accurately quantified because of technical limitations of the computer-assisted quantitative coronary angiography.16

Laboratory Methods

Fasting blood samples were drawn by venipuncture 1 to 2 days before coronary angiography and the hematologic and biochemical analyses were done using standard laboratory procedures.

Statistical Analysis

Each of the 3 coronary arteries (LAD, LCx, and RCA) was separately analyzed. Discrete variables were expressed as counts and percentages and were compared using McNemar or binomial exact test between the paired data of the same artery. Probability value of <0.05 was considered to be statistically significant. Continuous data were expressed as mean±SD. However, when the variable was significantly skewed, the median (25th to 75th percentile) was reported. Statistical analysis was performed by using commercially available software (SPSS STATISTICS 17.0 BASE WIN, SPSS Japan Inc, Tokyo, Japan). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Table 2 shows the coronary angiographic findings of the 2 groups. In the normal angiogram group, spasm was induced in 106 (45, 28, and 33 in the LAD, LCx, and RCA, respectively) arteries. Of these, 9 (8.5%) were total occlusion, 18 (17.0%) subtotal occlusion, 50 (47.2%) segmental diffuse

### Table 1. Clinical Characteristics of the Study Subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal Angiogram Group (n=51)</th>
<th>Atherosclerosis Group (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>64.2±9.5</td>
<td>66.8±10.3</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>29/22</td>
<td>38/9</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.3±3.8</td>
<td>24.2±3.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19/51 (37%)</td>
<td>25/47 (53%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8/51 (16%)</td>
<td>17/47 (36%)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>32/51 (63%)</td>
<td>28/47 (60%)</td>
</tr>
<tr>
<td>Leukocyte, per μL</td>
<td>6,160</td>
<td>6,330</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.6±1.7</td>
<td>14.0±2.1</td>
</tr>
<tr>
<td>Platelet, ×10¹²/μL</td>
<td>24.1±8.0</td>
<td>24.8±7.5</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>0.99 (0.32–2.81)</td>
<td>2.00 (0.48–3.52)</td>
</tr>
<tr>
<td>Total protein, g/dL</td>
<td>6.6±0.4</td>
<td>6.8±0.6</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.9±0.3</td>
<td>3.9±0.4</td>
</tr>
<tr>
<td>Triglyceride, mmol/L</td>
<td>1.52±0.70</td>
<td>1.71±0.65</td>
</tr>
</tbody>
</table>

*Median (25th and 75th percentile). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

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Induction of Coronary Spasm

Ca-channel blockers and other vasodilators, if they had been administered, were stopped for at least 5 days. Coronary spasm was induced by intracoronary injection of ACh (Daiichi-Sankyo Co) after diagnostic catheterization in the morning. The details of the method were previously reported.11 Briefly, ACh was injected in incremental doses of 20, 50, and 100 μg into the left coronary artery and then 20 and 50 μg into the right coronary artery (RCA) in 20 seconds under continuous monitoring of ECG and blood pressure. Coronary spasm induced by this method usually disappeared spontaneously within 1 to 2 minutes and both the left coronary artery and RCA could be examined separately unless severe spasm occurred in the left coronary artery and necessitated the prompt injection of isosorbide dinitrate (ISDN) into the arteries. After the end of the test, ISDN (0.1 mg) was injected into the coronary artery and angiography was again performed. The specificity of this test for variant or resting angina was 99%.12 The test did not induce coronary spasm in any of the patients with normal coronary angiogram and without ischemic heart disease.12,13 The specificity of this test for spasm arteries was also confirmed in the vitro study.14
spasm involving the branch site and 29 (27.4%) diffuse and extensive spasm involving the entire arterial tree affecting the proximal and distal epicardial vessels and their branches. Five shifted from entire artery spasm into total occlusion. Accordingly, 34 (32.1%) of the 106 spasms involved the entire arterial tree in this group. Spasm of 1 vessel, 2 vessels, and 3 vessels was demonstrated in 16, 15, and 20 patients, respectively. Of the 44 patients in whom ACh was injected into both the left coronary artery and RCA, 15 had 1-vessel, 9 had 2-vessel, and 20 had 3-vessel spasm, and thus most (65.9%) patients had multivessel coronary spasm demonstrated. For the analysis of the localization of spasm at branch or nonbranch point, 34 (12 LAD, 10 LCx, and 12 RCA) entire artery diffuse spasms were excluded and the remaining 72 arteries (33 LAD, 18 LCx, and 21 RCA) were analyzed. Spasm occurred at the branch point in 27 (81.8%) of 33 LAD, 17 (94.4%) of 18 LCx, and 17 (81.0%) of 21 RCA. Coronary spasm thus preferentially occurred at the branch point in all of the 3 arteries (Figure 1). Spasm involved the proximal segment in 23 (69.7%) of the 33 LAD, 12 (66.7%) of the 18 LCx, and 4 (19.0%) of the 21 RCA. Thus, spasm occurred more frequently at the proximal than the distal segments in the LAD, whereas it occurred more frequently at the distal than the proximal segments in the RCA (Figure 2). This is probably related to the fact that branch site is more numerous at the proximal segment in the LAD, whereas it is more numerous at the distal segment in the RCA\textsuperscript{15} and confirms the close relation of the branch point to spasm. In the atherosclerosis group, the organic stenosis was identified in the 66 (32 LAD, 11 LCx, and 23 RCA) arteries as shown in Table 2. Of these, 52 (22 LAD, 8 LCx, and 22 RCA) arteries had 25% to 75% and 14 (10 LAD, 3 LCx, and 1 RCA) arteries had 75% to 90% luminal diameter narrowing. Thus, most (78.8%) patients had mild to moderate organic stenosis in the atherosclerosis group. Spasm was induced in 66 (32 LAD, 11 LCx, and 23 RCA) arteries. Of these, 6 (9.1%) were total occlusion, 9 (13.6%) were subtotal occlusion, 48 (77.2%) were segmental diffuse spasm, and 3 (4.5%) were entire artery diffuse spasm. Two shifted from entire artery diffuse spasm into total occlusion. Accordingly, the entire artery diffuse spasm occurred in 5 (7.6%) of the 66 spasms in the atherosclerosis group. Spasm was induced in 66 (32 LAD, 11 LCx, and 23 RCA) arteries. Of these, 6 (9.1%) were total occlusion, 9 (13.6%) were subtotal occlusion, 48 (77.2%) were segmental diffuse spasm, and 3 (4.5%) were entire artery diffuse spasm. Two shifted from entire artery diffuse spasm into total occlusion. Accordingly, the entire artery diffuse spasm occurred in 5 (7.6%) of the 66 spasms in the atherosclerosis group (Table 2). For the analysis of the localization of spasm at the branch or nonbranch points, 5 entire artery diffuse spasms were excluded and the remaining 61 (30 LAD, 11

<table>
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<th>Table 2. Coronary Angiographic Findings</th>
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<tr>
<td>Normal Angiogram Group</td>
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<tr>
<td>Entire artery spasm</td>
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<tr>
<td>LAD, n</td>
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<tr>
<td>LCX, n</td>
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<tr>
<td>RCA, n</td>
</tr>
<tr>
<td>Total, n</td>
</tr>
<tr>
<td>LAD, n</td>
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<tr>
<td>Proximal segment, n (%)</td>
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<tr>
<td>LCX, n</td>
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<tr>
<td>Proximal segment, n (%)</td>
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<tr>
<td>RCA, n</td>
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<tr>
<td>Proximal segment, n (%)</td>
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<tr>
<td>Total, n</td>
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</tbody>
</table>

LAD indicates left anterior descending artery; LCA, left coronary artery; LCX, left circumflex artery; RCA, right coronary artery.

Figure 1. Comparison of the involvement of coronary spasm between the branch and nonbranch points in the normal angiogram group. LAD, left anterior descending coronary artery; LCX; left circumflex artery; RCA, right coronary artery.
LCx, and 20 RCA) were analyzed for comparison of localization between spasm and plaque in the atherosclerosis group. Spasm occurred at the branch site in 23 (76.7%) of the 30 LAD, 8 (72.7%) of the 11 LCx, and 12 (60.0%) of the 20 RCA. These results are in agreement with those in the normal angiogram group. On the other hand, plaque was localized at the branch point in only 7 (23.3%) of the 30 LAD, 1 (9.1%) of the 11 LCx, and 2 (10.0%) of the 20 RCA. Thus, there was a significant difference in the involvement of the branch point between spasm and plaque in each of the 3 arteries (P = 0.039 in LCx, and P = 0.002 in RCA, respectively) (Figure 3). Spasm involved the proximal segment in 17 (56.7%) of the 30 LAD, 2 (18.2%) of the 11 LCx, and 3 (15.0%) of the 20 RCA, whereas plaque was localized at the proximal segment in 28 (93.3%) of the 30 LAD, 9 (81.8%) of the 11 LCx, and 15 (75.0%) of the 20 RCA. Thus, there was a significant difference in the involvement of the proximal segment between spasm and plaque in each of the 3 arteries (P < 0.0001 in LAD, P = 0.016 in LCx, and P = 0.0001 in RCA, respectively) (Figure 4). In accordance with these results, most spasms occurred at the nonplaque site in each of the 3 arteries (P = 0.018 in LAD, P < 0.0001 in LCx, and P = 0.041 in RCA, respectively) (Figure 5). Spasm thus preferentially occurred at branch points and nonplaque sites, whereas the plaque preferentially occurred at nonbranch point sites of the proximal segment in each of the 3 coronary arteries. Paired data using 2×2 tables for Figures 1 to 5 are shown in Online Data supplements.

Nineteen (17.9%) of the 106 spasms in the normal angiogram group and 11 (16.7%) of the 66 in the atherosclerosis group were associated with ST-segment elevation and the 87 (82.1%) and 55 (83.3%) with ST-segment depression on the ECG, respectively, indicating that coronary spasm with ST-segment depression is more numerous than that with ST-segment elevation in both groups (P < 0.0001, respectively). Of the 11 spasms with ST-segment elevation, 8 (72.7%) involved the organic stenosis and 8 were total or subtotal occlusion in the atherosclerosis group.

Figures 6 and 7 show the representative angiograms of spasm in the normal angiogram group and those of atherosclerosis group, respectively.

Discussion

This study showed that most spasms were diffused and extensive, and the substantial number of these involved the entire arterial tree affecting the proximal and distal epicardial vessels and their intramural branches in the normal angiogram group. These findings are in agreement with the results of our previous angiographic study and also with our intravascular ultrasound study, which revealed the presence of these findings in the normal angiogram group.

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**Figure 2.** Comparison of the involvement of coronary spasm between the proximal and distal segments in the normal angiogram group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

**Figure 3.** Comparison of the involvement of the branch point between spasm and plaque in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

**Figure 4.** Comparison of the involvement of spasm (%)

<table>
<thead>
<tr>
<th></th>
<th>Proximal Segment</th>
<th>Distal Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>23/33</td>
<td>10/33</td>
</tr>
<tr>
<td>LCx</td>
<td>12/18</td>
<td>6/18</td>
</tr>
<tr>
<td>RCA</td>
<td>4/21</td>
<td>17/21</td>
</tr>
</tbody>
</table>

**Figure 5.** Comparison of the involvement of branch point (%)

<table>
<thead>
<tr>
<th></th>
<th>Spasm</th>
<th>Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>23/30</td>
<td>7/30</td>
</tr>
<tr>
<td>LCx</td>
<td>8/11</td>
<td>1/11</td>
</tr>
<tr>
<td>RCA</td>
<td>12/20</td>
<td>2/20</td>
</tr>
</tbody>
</table>

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of diffuse intimal thickening in an entire coronary artery in patients with coronary spasm and normal angiograms. Accordingly, the results strongly suggest that systemic factors play an important role in the pathogenesis of coronary spasm. On the other hand, the atherosclerotic plaque lesion was focal and largely localized to the proximal segments in agreement with previous studies. This suggests that local factors are more important in the pathogenesis of atherosclerosis as compared with those of coronary spasm.

We have shown that endothelial NO activity is deficient and endothelial function impaired in the spasm arteries. NO not only modulates vasomotor tone, but also inhibits inflammation, production of reactive oxygen species, vascular smooth muscle proliferation, and platelet aggregation, and reduced endothelial NO activity represents the early steps in the development of atherosclerosis. The endothelium is exposed to shear stress and unidirectional laminar shear stress in straight parts of the arterial tree potently stimulates NO production, whereas disturbed flows at curvatures or branches have the opposite effect.

Studies of human coronary arteries provide evidence that regions prone to the development of atherosclerosis occur at sites of intimal thickening, which is mainly composed of smooth muscle cells (SMCs), suggesting that SMCs in intimal thickening play a pathogenic role in the initiation and development of atherosclerosis. Low shear stress occurs at the curvature or upstream of stenosis, whereas oscillatory shear stress occurs downstream of stenosis or branch points. Recent studies revealed that low–shear stress lesions contained fewer SMCs and more lipids and were larger and more progressive and vulnerable, whereas oscillatory–shear stress lesions contained more SMCs and fewer lipids and are more stable.

This study further showed that spasm preferentially occurred at the branch point or downstream of the flow divider where shear stress is presumed to be oscillatory both in the normal angiogram and atherosclerosis groups. This is in agreement with the result of Selwyn’s group, which showed that branch point constricted more intensely than nonbranch sites in response to ACh infusion. On the other hand, the atherosclerotic stenosis was localized predominantly at the nonbranch point of the curved proximal segment where shear stress is presumed to be low. Thus, there was a difference in the predilection site between the spasm and atherosclerotic plaque and most spasms occurred at different sites from those of the plaque. These results thus suggest that atherosclerosis does not contribute to the occurrence of spasm or rather tends...
to suppress it and are in agreement with those of Maseri’s
group. However, MacAlpin reported on the basis of the
literature that most spasms were localized at the site of an
organic lesion. The discrepancy between his results and ours
may probably be explained by the difference of the study
subjects. He reported on the patients with “variant angina,” ie,
angina associated with ST elevation on ECG. On the other
hand, most spasms were associated with ST depression and
mild to moderate organic stenosis in the atherosclerosis group
of this study.

Coronary spasm has risk factors, such as smoking and
aging, and is associated with endothelial dysfunction, inflammation, and intimal thickening. It thus shares the
common risk and pathogenetic factors with atherosclerosis. However, atherosclerosis is characterized by subendothelial
retention of atherogenic lipoproteins and develops early from infants, and is usually associated with hyperlipidemia,
whereas coronary spasm does not occur in the young but in the old patients (mean age of 65.5 ± 10.1 in this
study), and hyperlipidemia is not a risk factor for coronary
spasm. Indeed, Morikawa et al have recently reported by
using intravascular optical coherence tomography that the
spasm arteries with normal angiogram had a diffuse intimal
thickening and contained almost no lipid deposits, whereas
the no-spasm arteries with normal angiogram had either
intimal thickening containing lipid deposits or had no intimal
thickening.

Coronary spasm is caused by abnormal contraction of
vascular SMCs and therefore contractile and not synthetic
phenotype SMCs are likely to play a crucial role in the

Figure 6. Coronary angiograms during spasm induced by ACh
injection and after ISDN in the normal angiogram group. A,
Severe diffuse spasm involving the entire RCA appeared after
ACh (left) and converted into a total occlusion at the origin of
the artery 2 minutes later (center, arrow). After ISDN, the artery
was marked dilated and normal (right). B, Severe diffuse spasm
involving the entire left coronary artery including intramural
branches appeared after ACh (left, arrow heads) and disap-
ppeared after ISDN (right). C, Severe diffuse spasm involving
the entire arterial tree of both the LAD and LCx appeared after ACh
injection (left, arrow heads) and disappeared after ISDN (right).
ACh indicates acetylcholine; ISDN, isosorbide dinitrate; LAD, left
anterior descending artery; LCx, left circumflex artery; RCA,
right coronary artery; *, a pacing catheter.

Figure 7. Coronary angiograms during spasm induced by ACh
injection and after ISDN in the atherosclerosis group. A, A sub-
total occlusion spasm with diffuse vasoconstriction involving
the curved proximal segment of the LAD and a focal spasm at the
branch site of the LCx appeared after ACh (left, arrows and
arrow heads) and disappeared after ISDN (right). A significant
organic stenotic lesion was revealed at the curved proximal seg-
ment (right, arrow). Spasm was superimposed on the lesion (left,
arrow). B, Subtotal occlusion at the proximal segment and dif-
fuse spasm at its distal branch site of the LAD appeared after
ACh (left, arrow and arrow heads) and disappeared after ISDN,
revealing a severe organic stenosis at the nonbranch site of the
curved proximal segment (right, arrow). Despite severe stenosis,
total occlusion did not occur at this site during spasm. C, Diff-
fuse spasm occurred at the distal branches, not at the site of
severe organic stenosis at the curved proximal segment of the
LAD after ACh (left, arrow heads and arrow). A severe organic
stenosis lesion was revealed at the nonbranch site of the curved
proximal segment after ISDN (right). ACh indicates acetylcho-
line; ISDN, isosorbide dinitrate; LAD, left anterior descending
artery; LCx, left circumflex artery; RCA, right coronary artery;
*, a pacing catheter.
pathogenesis of coronary spasm. We, therefore, propose that coronary spasm may be a manifestation of coronary arteriosclerosis distinctly different from coronary atherosclerosis, which is characterized by lipid accumulation and SMCs of synthetic phenotype. Intriguingly, the incidence of coronary spasm, particularly variant angina, has decreased recently, whereas that of hyperlipidemia has risen in Japan. This study further demonstrates that most coronary spasms were associated with ST-segment depression rather than ST segment elevation on ECG and thereby confirms the concept that variant angina is only one aspect of the spectrum of coronary spasmodic myocardial ischemia.

**Study Limitations**

In this study, we defined the site of spasm as that of total or subtotal obstruction or as that of the most severe and proximal constriction in the case of multifocal or segmental diffuse spasm and the site of atherosclerotic lesion as that of the most narrowed in each artery for the purpose of analysis. However, spasm is often, diffuse and or multifocal, or even migrates from site to site and thus the actual images of spasm may be more complex and dynamic than described in this study. Atherosclerotic lesions also are often multifocal. In this study, however, most atherosclerotic lesions were mild and mostly monofocal, because we excluded the patients with multivessel or severe organic stenosis disease from the study. Thus, the results of this study may not necessarily be applicable to advanced atherosclerotic lesions with multiple plaques. Moreover, angiogram is not sensitive enough to detect atherosclerosis because it is highly likely that vascular remodeling may have occurred, and thus, the patients in the normal angiogram group in this study might not have been free from atherosclerosis. In this study, we did not perform the intravascular ultrasound examination concurrently with angiography and thus could not present the data on shear stress and constituents of vessels walls. However, we have previously shown that the intimal thickening involved the entire arterial tree in the patients with coronary spasm and normal angiogram using intravascular ultrasound.

**Conclusions**

Diffuse spasm involving the entire arterial tree occurred in a substantial number of angiographically normal or almost normal coronary arteries in the patients with chest pain. Spasm preferentially occurred involving branch points, whereas atherosclerosis was predominantly focal and localized at the nonbranch points of the curved proximal segments. Most spasms occurred at the sites different from those of the atherosclerotic plaque. These results strongly suggest that coronary spasm may be a manifestation of a distinct type of arteriosclerosis different from the lipid-laden coronary atherosclerosis.

**Sources of Funding**

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**Disclosures**

None.

**References**

Coronary spasm plays an important role in the pathogenesis of ischemic heart disease. However, similarities and differences between coronary spasm and atherosclerosis are not known. This study examined the angiographic characteristics of coronary spasm in comparison with those of atherosclerotic plaque, first in the angiographically normal or almost normal coronary arteries and then in those with atherosclerotic plaque. The results showed that diffuse spasm involving the entire artery appeared in the substantial number of the angiographically normal arteries and that spasm preferentially occurred at branch points in both the angiographically normal arteries and those with plaque. On the other hand, plaque was predominantly localized at nonbranch point sites of the curved proximal segments. Most spasms did not occur at the sites of plaque. These results suggest that coronary spasm may be a manifestation of a distinct type of arteriosclerosis different from the lipid-laden coronary atherosclerosis. This study, thus, may provide a new insight into the pathogenesis not only of coronary spasm but also of atherosclerosis and may explain at least partially the decline of the number of coronary spasm with the increase of hyperlipidemia among Japanese in recent years.
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SUPPLEMENTAL MATERIAL

Coronary Spasm Preferentially Occurs at Branch Points
 -an angiographic comparison with atherosclerotic plaque -

Hitoshi Nakagawa, MD, Yoshinobu Morikawa, Yuji Mizuno, MD, Eisaku Harada, MD, MD, Teruhiko Ito, MD, Kunihiko Matsui, MD, MPH*, Yoshihiko Saito, MD#, Hirofumi Yasue, MD.
### Table 1:

<table>
<thead>
<tr>
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<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
</tr>
</thead>
<tbody>
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<td>Branch</td>
<td>Non-branch</td>
<td>Branch</td>
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<td>Non-species</td>
<td>0</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Total</td>
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<td>10</td>
<td>17</td>
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<tr>
<td><em>P</em></td>
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<td>0.9007</td>
<td>0.0001</td>
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### Table 2: (similar table structure as Table 1 for different categories and *P* values)

<table>
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</thead>
<tbody>
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<td>Non-branch</td>
<td>Branch</td>
</tr>
<tr>
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<td>17</td>
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<td>Total</td>
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<td>20</td>
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<tr>
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</tbody>
</table>

### Table 3: (similar table structure as Table 1 for different categories and *P* values)

<table>
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</thead>
<tbody>
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<td><em>P</em></td>
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### Table 4: (similar table structure as Table 1 for different categories and *P* values)

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<th>LCx</th>
<th>RCA</th>
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<td>Non-branch</td>
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<td>Non-species</td>
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<tr>
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<td><em>P</em></td>
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**Figure legends**

Figure 1. Comparison of the involvement of coronary spasm between the branch and non-branch points in the normal angiogram group. Branch indicates the branch point; Non-branch, the non-branch point; LAD, left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Figure 2. Comparison of the involvement of coronary spasm between the proximal and distal segments in the normal angiogram group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Figure 3. Comparison of the involvement of the branch point between spasm and plaque in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Figure 4. Comparison of the involvement of the proximal segment between spasm and plaque in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.

Figure 5. Comparison of the involvement of spasm between the plaque and non-plaque sites in the atherosclerosis group. LAD indicates left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery.