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

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Nakagawa: Coronary spasm at branch points

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Total word count: 5906
Abstract

**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 (LAD), 11 left circumflex (LCx) and 23 right coronary arteries (RCA) 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). Spasm predominately occurred at the branch point as compared with plaque in each of the 3 arteries (76.7 vs. 23.3%, \(P<0.0001\), 72.7 vs. 9.1%, \(P<0.039\), and 60.0 vs. 10.0%, \(P=0.002\) %, in the LAD, LCx and RCA, respectively). Spasm involved the proximal segment less frequently as compared with plaque in each of the 3 arteries (56.7 vs. 93.3%, \(P<0.0001\), 18.2 vs. 81.8%, \(P=0.016\), and 15.0 vs.75.0%, \(P<0.0001\) in the LAD, LCx and RCA, respectively). The majority of spasm occurred at the non-plaque site in each of the 3 arteries (73.3 %, \(P=0.018\), 100%, \(P<0.0001\), and 75.0 %, \(P=0.041\), in the LAD, LCx and RCA, respectively).

**Conclusion** Coronary spasm preferentially occurred at branch points and non-plaque
sites, whereas the atherosclerotic lesion was predominantly localized at the non-branch 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.

**Key Words:** atherosclerosis, coronary spasm, endothelium, nitric oxide, shear stress.
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.\textsuperscript{1-3} 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.\textsuperscript{4} Endothelial NO enhances vascular functions, including vessel relaxation, survival of vascular endothelial cells, inhibition of platelet aggregation, and attenuation of leukocyte infiltration.\textsuperscript{5,6} Impaired NO activity has been suggested as the earliest pathophysiological events contributing to atherosclerosis.\textsuperscript{7,8}

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.\textsuperscript{5,9,10} 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.\textsuperscript{9,10} 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. The present 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 males and 31 females, with a mean age of 65.5 ± 10.1 years ranging from 35 to 86) Japanese patients in whom coronary spasm was induced by intracoronary injection of acetylcholine (ACh; Daiichi Sankyo Co, Tokyo, Japan) were the subjects of this study. They had been admitted to our hospital because of chest pain or ECG abnormalities suspected of ischemic heart disease between January 2003 and January 2009. The study consisted of the 2 parts: the first part of the 51 patients with normal or almost normal coronary angiogram (<25 % stenosis of luminal diameter) in whom the confounding effect of organic stenosis on coronary flow could be excluded (normal angiogram group) and the second part of the 47 patients with organic stenosis (25 - 90 % stenosis of luminal diameter) (atherosclerosis group) based on the consensus of 3 - 4 investigators. We defined coronary spasm as a total or subtotal occlusion or severe diffuse constriction of an angiographically demonstrable coronary artery associated with transient ischemic ST segment changes on ECG. In each spasm artery, we defined the site of spasm as that of total or subtotal occlusion or as that of the most severe and proximal constriction in the case of segmental diffuse or multi-focal spasm and the site of atherosclerotic lesion (plaque) as the most narrowed based on the consensus of 3 - 4 investigators.
sensus of 3 - 4 investigators. Patients with recent myocardial infarction, acute coronary syndrome, left main trunk disease, severe organic stenosis of >90 %, multi-vessel coronary disease with >75 % organic stenosis, heart failure, liver disease, creatinine level >1.5 mg/dl, acute inflammation, malignant diseases, and cholesterol lowering medication within a month were excluded from the study. None of the study patients were on statins or other lipid-lowering drugs. The clinical characteristics of the study patients are presented in Table 1. Hypertension was defined as >140/90 mmHg and diabetes mellitus as fasting plasma glucose >7mmol/L (126 mg/dL) or 2 hour post load glucose >11.1mmol/L (200 mg/dL).

The protocol of this study was approved by the institutional review board and each patient provided written informed consent.

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 acetylcholine (ACh) (Daiichi-Sankyo Co., Tokyo, Japan) after diagnostic catheterization in the morning. The details of the method were previously reported. Briefly, ACh was injected in incremental doses of 20, 50 and 100 µg into the left coronary artery (LCA) and then 20, 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 1-2 minutes and both the LCA 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 (0.1mg) was injected into the coronary artery and angiography was again performed. The specificity of this test for variant or resting angina was 99%. The test did not induce coronary spasm in any of the patients with normal coronary angiogram and without ischemic heart disease. The specificity of this test for spasm arteries was also confirmed in the vitro study.

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 segment 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 9.1-21.1mm). We divided the left anterior descending artery (LAD), the left circumflex artery (LCx) and RCA into the proximal segments (segment 6,7,9 in the LAD; segment 11,12,13 in the LCx; and segment 1-2 in the RCA) and the distal seg-
ments (segment 8,10 in the LAD, segment 14,15 in the LCx; and segment 3-4 in the RCA) according to the AHA coronary segment reporting system\textsuperscript{15} 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.\textsuperscript{16}

**Laboratory methods**

Fasting blood samples were drawn by venipuncture 1-2 days before coronary angiography and the hematological 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. \( P \) value of <0.05 was considered to be statistically significant. Continuous data were expressed as mean \( \pm \) SD. However, when the variable was significantly skewed, the median (25th to 75th percentile) was reported. Statistical analysis was performed by using commer-
cially 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 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 as well as 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 one 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 LCA and RCA, 15 had one-vessel, 9 two-vessel, and 20 three-vessel spasm and thus the majority (65.9%) of the patients had multi-vessel coronary spasm demonstrated.

For the analysis of the localization of spasm at branch or non-branch 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 in 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 in 4 (19.0%) of the 21 RCA. Thus, spasm occurred more frequently at the proximal than the distal segments in the LAD, while 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 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) as shown in Table 2. Of these, 52 (22 LAD, 8 LCx and 22 RCA) had 25 - 75% and 14 (10 LAD, 3 LCx and 1 RCA) 75 - 90% luminal diameter narrowing. Thus, the majority (78.8%) 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, 9 (13.6%) subtotal occlusion, 48 (77.2%) segmental diffuse spasm, and 3 (4.5%) 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 atheroscle-
rosis group (Table 2). For the analysis of the localization of spasm at the branch or non-branch points, 5 entire artery diffuse spasms were excluded and the remaining 61 (30 LAD, 11 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 in 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 ($P<0.0001$ in LAD, $P=0.039$ 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, while 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, the majority of spasm occurred at the non-plaque site in each of the 3 arteries ($P=0.018$ in LAD, $P<0.0001$ in LCx, and $P=0.041$ in RCA, respectively) (Fig-
Spasm thus preferentially occurred at branch points and non-plaque sites, while the plaque preferentially occurred at non-branch point sites of the proximal segment in each of the 3 coronary arteries. Paired data using 2×2 tables for Figure 1-5 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

The present study showed that the majority of spasm was diffuse and extensive and the substantial number of these involved the entire arterial tree affecting the proximal and distal epicardial vessels as well as 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 (IVUS) study which revealed the existence 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 to those of coronary spasm.

We have shown that endothelial nitric oxide (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.\textsuperscript{5,9,10}

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.\textsuperscript{22-24} Low shear stress occurs at the curvature or upstream of stenosis, whereas oscillatory shear stress occurs downstream of stenosis or branch points.\textsuperscript{9,10} Recent studies revealed that low shear stress lesions contained fewer SMCs and more lipids, and were larger and more progressive and vulnerable,\textsuperscript{10,25,26} whereas oscillatory shear stress lesions contained more SMCs and fewer lipids and are more stable.\textsuperscript{25}

The present 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\textsuperscript{9,10} 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 non-branch sites in response to ACh infusion.\textsuperscript{27} On the other hand, the atherosclerotic stenosis was localized predominantly at the non-branch point of the

CIRCULATIONAHA/2008/803767 R12
curved proximal segment where shear stress is presumed to be low.\textsuperscript{9,10} Thus, there was a difference in the predilection site between the spasm and atherosclerotic plaque and the majority of spasm 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 those of Maseri’s group.\textsuperscript{1,28} However, MacAlpin reported on the basis of the literature that the majority of spasm was localized at the site of an organic lesion.\textsuperscript{29} 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”, i.e. angina associated with ST-elevation on ECG. On the other hand, the majority of spasm was associated with ST depression and mild to moderate organic stenosis in the atherosclerosis group in the present study.

Coronary spasm has risk factors such as smoking and aging,\textsuperscript{18-21} and is associated with endothelial dysfunction,\textsuperscript{2,4} inflammation\textsuperscript{20,30} and intimal thickening.\textsuperscript{18} It thus shares the common risk and pathogenetic factors with atherosclerosis.\textsuperscript{7,8} However, atherosclerosis is characterized by subendothelial retention of atherogenic lipoproteins,\textsuperscript{7,8,22-26} develops early from infants,\textsuperscript{31} and is usually associated with hyperlipidemia,\textsuperscript{7,8,32} while coronary spasm does not occur in the young but in the old (mean age of 65.5 ± 10.1 in this study) and hyperlipidemia is not a risk factor for coronary spasm.\textsuperscript{18-21} Indeed, Mo-
rikawa and his coworkers have recently reported by using intravascular optical coherence tomography (OCT) 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 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. Recent studies showed that oxidized lipids suppress SMCs marker genes and that lipid lowering promotes accumulation of mature SMCs. To be noted in this connection is the fact that the patients with coronary spasm with angiographically normal or almost normal coronary arteries are less prone to develop acute myocardial infarction as compared with those with other types of unstable angina. Intriguingly, the incidence of coronary spasm, particularly variant angina, has decreased recently, whereas that of hyperlipidemia has risen in Japan.
The present study further demonstrates that the majority of coronary spasm was associated with ST segment depression rather than ST segment elevation on ECG and thereby confirms the concept that variant angina or resting angina is only one aspect of the spectrum of coronary spastic myocardial ischemia. 42

**Study Limitations**

In the present 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 multi-focal 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 2. Atherosclerotic lesions also are often multi-focal. In the present study, however, the majority of atherosclerotic lesion was mild and the lesion mostly mono-focal, because we excluded the patients with multivessel or sever 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 since 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 athe-
rosclerosis. In the present study, we did not perform the IVUS 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 IVUS.

**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 non-branch points of the curved proximal segments. The majority of spasm 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

This study was supported in part from Japan Heart Foundation, Tokyo, and Japan Vascular Disease Research Foundation, Kyoto, Japan

Disclosures

None.
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mated incidence and clinical and coronary arteriographic findings in 138 patients.
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.

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 ap-
peared 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 spasms involving the entire left coronary artery including intramural branches appeared after ACh (left, arrow heads) and disappeared 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. * indicates a pacing catheter.

Figure 7. Coronary angiograms during spasm induced by ACh injection and after ISDN in the atherosclerosis group. (A) A subtotal 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 segment (right, arrow). Spasm was superimposed on the lesion (left, arrow). (B) Subtotal occlusion at the proximal segment and diffuse 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 non-branch site of the curved proximal segment (right, arrow). Despite severe stenosis, total occlusion did not occur at this site during spasm. (C) Diffuse 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 non-branch site of the curved proximal segment after ISDN (right). Abbreviations are as
in Figure 6.
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* median (25th and 75th percentile) ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphate kinase; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
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<tr>
<td>Total, n</td>
<td>34</td>
<td></td>
<td>5</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>LAD, n</td>
<td>33</td>
<td></td>
<td>30</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Proximal segment, n (%)</td>
<td>23 (69.7)</td>
<td></td>
<td>17 (56.7)</td>
<td>&lt;0.0001</td>
<td>28 (93.3)</td>
</tr>
<tr>
<td>LCX, n</td>
<td>18</td>
<td></td>
<td>11</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Proximal segment, n (%)</td>
<td>12 (66.7)</td>
<td></td>
<td>2 (18.2)</td>
<td>0.016</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td>RCA, n</td>
<td>21</td>
<td></td>
<td>20</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Proximal segment, n (%)</td>
<td>4 (19.0)</td>
<td></td>
<td>3 (15.0)</td>
<td>&lt;0.0001</td>
<td>15 (75.0)</td>
</tr>
<tr>
<td>Total, n</td>
<td>72</td>
<td></td>
<td>61</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
<table>
<thead>
<tr>
<th>Branch Point</th>
<th>Non-Branch Point</th>
<th>Involvement of Spasm (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td></td>
<td>81.8%</td>
</tr>
<tr>
<td></td>
<td>27/33</td>
<td>18.2%</td>
</tr>
<tr>
<td></td>
<td>6/33</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>LCx</td>
<td></td>
<td>94.4%</td>
</tr>
<tr>
<td></td>
<td>17/18</td>
<td>5.6%</td>
</tr>
<tr>
<td></td>
<td>1/18</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>RCA</td>
<td></td>
<td>81.0%</td>
</tr>
<tr>
<td></td>
<td>17/21</td>
<td>19.0%</td>
</tr>
<tr>
<td></td>
<td>4/21</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>
Involvement of Spasm (%)

**LAD**
- Proximal Segment: 30.3% (23/73)
- Distal Segment: 10.0% (10/73)
- Overall: 69.7%

**LCx**
- Proximal Segment: 33.3% (12/36)
- Distal Segment: 6.9% (6/36)
- Overall: 66.7%

**RCA**
- Proximal Segment: 81.0% (4/5)
- Distal Segment: 19.0% (17/5)
- Overall: 81.0%

P-values:
- LAD: P = 0.037
- LCx: P = 0.238
- RCA: P = 0.007
<table>
<thead>
<tr>
<th>Artery</th>
<th>Spasm Plaque</th>
<th>Involvement of Branch Point (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>23/30</td>
<td>76.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LCx</td>
<td>8/11</td>
<td>72.7%</td>
<td>0.039</td>
</tr>
<tr>
<td>RCA</td>
<td>12/20</td>
<td>60.0%</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Spasm: 7/30, 23.3%
Plaque: 1/11, 9.1%

Spasm: 2/20, 10.0%
Proximal Involvement (%)

LAD

$P < 0.0001$

Spasm

17/30

93.3%

Plaque

28/30

56.7%

LCx

$P = 0.016$

Spasm

2/11

18.2%

Plaque

9/11

81.8%

RCA

$P < 0.0001$

Spasm

3/20

15.0%

Plaque

15/20

75.0%
Involvement of Spasm (%)

<table>
<thead>
<tr>
<th>Site</th>
<th>LAD</th>
<th>LCx</th>
<th>RCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque</td>
<td>26.7% (8/30)</td>
<td>0% (0/11)</td>
<td>25.0% (5/20)</td>
</tr>
<tr>
<td>Non-Plaque</td>
<td>78.3% (22/30)</td>
<td>100% (11/11)</td>
<td>75.0% (15/20)</td>
</tr>
</tbody>
</table>

P-values:
- LAD: P = 0.018
- LCx: P < 0.0001
- RCA: P = 0.041
Coronary Spasm Preferentially Occurs at Branch Points: an angiographic comparison with atherosclerotic plaque
Hitoshi Nakagawa, Yoshinobu Morikawa, Yuji Mizuno, Eisaku Harada, Teruhiko Ito, Kunihiko Matsui, Yoshihiko Saito and Hirofumi Yasue

*Circ Cardiovasc Interv.* published online February 20, 2009;
*Circulation: Cardiovascular Interventions* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

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SUPPLEMENTAL MATERIAL

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-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.
**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.