Angiographic Evaluation of Culprit Lesions in Acute Coronary Syndrome

Relation to the Original Site on Previous Coronary Angiography

Taro Saito, MD; Haruhiko Date, MD; Izumi Taniguchi, MD; Shouta Nakamura, MD; Hideki Oka, MD; Yuji Mizuno, MD; Katsu Noda, MD; Seishi Yamashita, MD; Shuechi Oshima, MD; Hirofumi Yasue, MD*

Culprit lesions in acute coronary syndrome [acute myocardial infarction (AMI) and unstable angina pectoris (UAP)] were examined angiographically in 222 patients who had previously undergone coronary angiography (CAG). The observation period lasted 5 years after primary CAG in medically treated patients (group M, 127 cases) and after final follow-up CAG in patients treated by percutaneous transluminal coronary angioplasty (PTCA) (group B, 95 cases). There were 33 AMIs, including 5 deaths (22/127, 17.3%, in group M vs 11/95, 11.6%, in group B; p < 0.01) and 189 UAPs (105/127, 82.7%, in group M vs 84/95, 88.4%, in group B, NS). High-grade stenoses (>75%) were found in 76 (39.8%) patients in group M, of which 41 lesions (54%) resulted in acute coronary syndromes (ACSs). In group M, ACSs resulted from insignificant stenosis (<50%) in 67 (53%) patients and from significant stenosis (>50%) in 60 (47%) patients. In group B, ACSs resulted from insignificant stenosis in 78 (82%) patients and from significant stenosis in 17 (18%) patients. Out of 95 PTCA sites, high-grade restenosis occurred in 5 lesions and ACSs (2 AMI, 14 UAP) in 16 (16.8%). We conclude that ACSs are more likely to develop from insignificant lesions than from significant lesions. High-grade stenoses are prone to become occlusive lesions and PTCA reduces this potential risk. Most target sites of PTCA that escaped restenosis were stable in the long term. (Jpn Circ J 1998; 62: 359–363)

Key Words: Coronary artery disease; Progression; Repeat angiography

It is commonly accepted that the process of atherosclerotic progression in coronary artery disease is not uniform. Repeat coronary angiography (CAG) for the observation of culprit lesions in acute myocardial infarctions (AMIs) provides detailed insight into the progressive nature of coronary artery disease and the mechanism of acute coronary syndromes (ACSs). Although we have a basic understanding of ACSs, we do not know enough about the relationship between the severity of narrowing at primary CAG and future coronary events. Percutaneous transluminal coronary angioplasty (PTCA) is an effective means of reducing narrowing and modifying lesion characteristics. Comparison of the culprit lesion of ACSs with the results of previous CAG in medically treated patients with high-grade stenosis treated by PTCA may aid understanding of the relationship between the severity of stenosis and coronary events. Another point of interest is whether or not PTCA sites that escape high-grade restenosis develop into stable plaques and how this is related to the frequency of the future coronary events. In this study, we report the angiographic findings in 222 patients with ACS.

(Received June 13, 1997; revised manuscript received November 4, 1997; accepted November 10, 1997)
Cardiovascular Division, Kumamoto Central Hospital, and *Division of Cardiology, Kumamoto University, Kumamoto, Japan

Patient Population

From January 1984 to April 1996, 222 patients underwent repeat CAG because of AMI or unstable angina (UAP). To ensure an equal observation period in each group, we included in the study medically treated patients who underwent repeat CAG within 5 years after primary CAG and PTCA-treated patients in whom the target lesion escaped high-grade stenosis and who underwent repeat CAG within 5 years after final follow-up CAG. Informed consent was received from all patients and/or their families. Patients who had previously been treated with coronary bypass surgery and repeat CAG for angiographic follow-up after coronary intervention were excluded. Patients who received repeat CAG because of atypical symptoms or a false-positive stress test and did not have culprit lesions were also excluded from this study.

The patients' clinical characteristics are shown in Table 1. Their mean age was 66 years and 73.8% were men. The mean interval between the 2 procedures was 1187 ± 489 days. Coronary artery disease extent was classified as follows: old myocardial infarction (OMI) was present in 76 patients (34.2%), left main trunk disease in 10 patients (4.5%), 1-vessel disease in 103 patients (46.4%), 2-vessel disease in 70 patients (31.5%), and 3-vessel disease in 18 patients (8.1%). After primary CAG, 127 patients were treated medically and 95 patients received PTCA. Men (78.7% vs 67.4%, NS) and patients with OMI (40.2% vs 26.3%, NS) were included more
Table 1  Patient Clinical Characteristics

<table>
<thead>
<tr>
<th>Number</th>
<th>Male (%)</th>
<th>Age (mean)</th>
<th>Interval (day)</th>
<th>DM (%)</th>
<th>HL (%)</th>
<th>HT (%)</th>
<th>Smoking (%)</th>
<th>OMI (%)</th>
<th>LMTD (%)</th>
<th>0VD (%)</th>
<th>1VD (%)</th>
<th>2VD (%)</th>
<th>3VD (%)</th>
<th>High-grade stenosis (&gt;75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>222</td>
<td>164 (74)</td>
<td>65.8 ± 1187.4</td>
<td>13</td>
<td>6.2</td>
<td>22.8</td>
<td>22.6</td>
<td>76 (34.2)</td>
<td>10 (4.5)</td>
<td>31 (13.9)</td>
<td>103 (46.4)</td>
<td>70 (31.5)</td>
<td>18 (8.1)</td>
<td>170 (76.6)%</td>
</tr>
<tr>
<td>Medical</td>
<td>127</td>
<td>100 (79)</td>
<td>66.4 ± 1169.5</td>
<td>13.1</td>
<td>5.8</td>
<td>23.5</td>
<td>23.6</td>
<td>51 (40.2)</td>
<td>6 (4.7)</td>
<td>31 (24)</td>
<td>51 (40.2)</td>
<td>35 (27.6)</td>
<td>10 (7.8)</td>
<td>76 (59.8)%</td>
</tr>
<tr>
<td>PTCA</td>
<td>95</td>
<td>54 (67)</td>
<td>65.0 ± 1211.4</td>
<td>12.6</td>
<td>5.6</td>
<td>22.5</td>
<td>20.8</td>
<td>25 (26.3)</td>
<td>4 (4.2)</td>
<td>15 (25)</td>
<td>52 (54.7)</td>
<td>35 (36.8)</td>
<td>8 (8.4)</td>
<td>94 (98.9)%</td>
</tr>
</tbody>
</table>

OMI, old myocardial infarction; DM, diabetes mellitus; HL, hyperlipidemia; HT, hypertension; LMTD, left main trunk disease; 0VD, 1-vessel disease; 1VD, 2-vessel disease; 2VD, 3-vessel disease.

High-grade stenosis was observed more frequently in the PTCA group than the Medical group *p<0.01.

Stenotic distribution at follow-up CAG after successful primary PTCA and first TLR

![Graph showing stenotic distribution at follow-up CAG after successful primary PTCA and first TLR.](image)

Fig1. Left, stenotic status of 95 target sites at follow-up CAG. Among the restenotic sites (2695, 27%), 17 lesions were revascularized. Among the 17 target lesion revascularization (TLR) sites, 3 sites were revascularized and all lesions escaped high-grade restenosis. Finally, 2 lesions remained as high-grade stenosis with good collateral flow and 1 lesion remained as 75–90% stenosis. CAG, coronary angiography; PTCA, percutaneous transluminal coronary angioplasty.

Stenotic distribution of 17 TLR-sites at follow-up CAG and second TLR

![Graph showing stenotic distribution of 17 TLR-sites at follow-up CAG and second TLR.](image)

Fig2. Right, target lesion revascularization (TLR) sites. Second TLRs: 3 lesions: final follow-up CAG findings: 0%=1, 25%=1, 50%=1.

Table 2  Cardiac Events and Repeat Coronary Angiography

<table>
<thead>
<tr>
<th>Number</th>
<th>AMI (%)</th>
<th>Cardiac death</th>
<th>UAP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>222</td>
<td>33 (14.9)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Medical</td>
<td>127</td>
<td>*22 (17.3)</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>PTCA</td>
<td>95</td>
<td>*11 (11.6)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

AMI, non-fatal acute myocardial infarction; UAP, unstable angina.

AMI occurred more frequently in the PTCA group than the Medical group (*p<0.01).

The frequency of UAP was similar in both groups.

frequently in the medical group than the PTCA group. The frequency of risk factors was the same in both groups. The extent of coronary artery disease was generally greater in the PTCA group than in the medical group.

High-grade stenosis (>75% according to the American Heart Association's (AHA) criteria) meeting our hospital's criteria for intervention was found in 76/127 (59.8%) of patients in the medical group and in 94/95 (99%) patients in the PTCA group.

Definitions and Data Analysis

All eligible data were derived from the database of Kumamoto Central Hospital and reconstructed for analysis. Statistical analysis was performed using the unpaired Student's t test or χ² analysis for comparison. A p value of less than 0.05 was considered significant.

A diagnosis of AMI was made when ST elevation or depression with chest pain lasted more than 30 min and the patient’s serum creatinine phosphate level increased to more than twice the normal range. A diagnosis of UAP was made when full-dose treatment with antianginal drugs was necessary to control worsening angina or newly developed angina in asymptomatic patients or patients who were well controlled after initiation of optimized medication. AMI, UAP, and death as a result of a coronary event were grouped into ACSs.

Stenosis evaluation was performed visually according to the AHA criteria. The culprit lesion was compared precisely with the previous CAG findings in order to define exactly the site responsible for the event. In the PTCA group, the target site itself and the area around the target site dilated with the balloon were considered to be the original site.

Treatment of the Medical Group and the PTCA Group

Patients in the medical group received long-acting nitrate and diltiazem or β-blocker. Anticoagulant therapy with aspirin, ticlopidine, or warfarin was added depending on the severity of coronary artery disease.

Balloon angioplasty was repeated a maximum of 3 times with the aim of avoiding restenosis or having only mild-grade stenosis (≤75%). The process of multiple PTCA procedures is demonstrated in Fig1. Out of 95 patients, 78 patients underwent 1 procedure, 17 patients underwent 2 procedures, and 3 patients underwent 3 procedures. The bottom line of multiple procedures is shown in Fig4 (left); in 3 cases high-grade restenosis could not be avoided.

Diabetes mellitus and hyperlipidemia were treated aggressively, and both groups of patients were instructed regarding change of lifestyle and dietary and smoking habits.
Results

Reasons for Repeat CAG

A total of 222 patients underwent repeat CAG for ACSs. Table 2 itemizes the events that resulted in repeat CAG. There were 5 cardiac deaths; of these, 2 patients received CAG as part of extensive cardiac resuscitation under death on arrival conditions and the other 3 patients were treated by primary PTCA when in shock and did not survive. The lesions responsible were complete obstruction of the feeding artery to other occlusive arteries in 2 cases, very proximal occlusion of the left anterior descending artery in 1 case and occlusion of the right coronary artery in 2 cases. Three lesions were jump-up lesions from insignificant stenosis and the other 2 lesions developed from 90% stenosis. All these patients were within the AMI section in the medical group. Of 33 patients who survived AMI, 22 patients (17.3%) were from the medical group and 16 patients (11.6%) from the PTCA group. Of 189 patients with UAP, 105 were from the medical group (58.7%) and 84 patients (41.3%) from the PTCA group.

Time Interval Between Primary and Repeat CAG

In Fig 2 cardiac events are shown according to the time interval. Almost half the events occurred in the first 2 years. The PTCA group exhibited no clear time trend.

Comparative Angiographic Findings of Culprit Lesions for ACSs

Medical Group. Fig 3 shows the distribution of the most severe stenosis at primary CAG (Fig 3, left) and culprit lesions for ACSs (Fig 3, right) in the medically treated group. More than 76 lesions with greater than 90% stenosis were included in this group. Actual cardiac events occurred in 41 patients (47/71, 53.9%) with the most severely stenosed lesions. The lesions most frequently leading to ACSs were those that were least severely stenosed (46/127, 36.2%).

PTCA Group. Fig 4. shows the distribution of the most severe stenosis at final follow-up CAG (Fig 4, left) and the culprit lesions for ACSs (Fig 4, right) in the PTCA group. As a result of multiple PTCA procedures, 3 lesions remained as high grade with more than 90% stenosis.

In contrast to the medical group, most culprit lesions (65/95, 68.4%) developed from the least severe stenosis (0–25% group).

Sixteen PTCA target sites into culprit lesions for ACSs (1695, 16.8%), with the remaining 84 culprit lesions (84/95, 83.2%) being newly developed sites. Two culprit lesion resulted in AMI: one progressed from a site with 0% stenosis and one from a site with 50% stenosis. The other 14 culprit lesions resulted in newly developed...
Fig 4. Left: distribution of the most severe stenosis in the PTCA group at final follow-up CAG. Right: the culprit lesions are reviewed in comparison with the final follow-up CAG. In the UAP group, 10 patients had two culprit lesions that developed from sites with <25% stenosis, which were counted as 1 site. Sixteen target sites (16.095, 16.8%) were responsible for events: 2 for AMI and 14 for newly developed angina. The bold number in the right column indicates events triggered by the PTCA sites with acceptable stenotic status at final follow-up.

Binary mode comparison

Fig 5. The sites of culprit lesions for events were categorized into 2 groups; less than 50% or more than 50% stenosis. In the medically treated group, events occurred with the same frequency in both these groups. In the PTCA group, events developed more frequently from sites of less than 50% stenosis.

angina: 8 developed from sites with <25% stenosis, 4 from sites with 25–50% stenosis, 1 from a site with 50–75% stenosis and 1 from a site with >90% stenosis.

Binary Mode Comparison of the Sites for ACS Culprit Lesions

In Fig 5 the sites of culprit lesions are divided into 2 categories, i.e., sites with insignificant (<50%) and significant stenosis (>50%), and the frequency of coronary events in the 2 groups is compared. In medically treated patients, 67 events resulted from insignificant stenoses and 60 events resulted from significant stenoses (67/127, 53% vs 60/127, 47%, NS). In PTCA patients, 78 events resulted from insignificant stenoses and 17 events resulted from significant stenoses (78/95, 82% vs 17/95, 18%, p<0.001). AMI did not develop from the significant stenosis in any patient in the PTCA group.

Discussion

Recently, much evidence has accumulated that coronary events develop not necessarily from the most severely stenosed lesions, but predominantly from mildly or moderately stenosed lesions. The mechanism of progression of atherosclerosis was well documented in a new classification of the AHA Medical/Scientific Statement, in which plaque rupture and subsequent thrombosis were shown to play a major part in ACSs. Rapid progression from insignificant stenosis ("new lesion") is undoubtedly an important mechanism in coronary event evolution.

However, the reported incidence of "new lesions" in ACSs varies between 20% and 80%, apparently in accordance with the extent of coronary artery disease among the study population. In a report in which AMI in 80 out of 92 patients was attributed to "new lesions," patients with greater than 90% stenosis were not included. In another report, in which AMI in 18 out of 23 patients developed from less than 70% initial stenosis, it is unclear how many patients in the study population had high-grade stenosis. Nobuyoshi reported that in 23 out of 39 (59%) new AMI patients, the culprit lesions progressed from <50% stenosis. However, the number of patients with lesions with 90% stenosis was not stated.

In addition, all the above reports excluded patients who were treated with PTCA, and thus there is a possibility that high-grade stenosis of more than 90%, which is another focus of our study, was not included in consideration.

On the other hand, in a recent angiographic study, it was found that most high-grade stenotic lesions consisted of lipid-rich yellow plaque, and thrombi were frequently observed not only in patients with unstable but also in patients with stable angina. Thus, the relation between coronary events and stenotic lesions with varying degrees...
of narrowing is not fully understood.

The binary mode comparison of our study revealed that the events developed more frequently from insignificant lesions, which is concordant with previous reports.

More detailed analysis of the medical group, among which 59.8% (76 lesions) of patients had high-grade stenosis (>75%), demonstrated that the incidence of ACSs was almost equal among those with insignificant and significant stenosis. Among 76 patients with high-grade stenosis, 41 experienced ACSs. Among the PTCA group, most ACSs developed from low-grade lesions. This apparent difference from the medical group could suggest that, although high-grade stenoses do not necessarily develop to ACSs, the risk of ACSs could be reduced significantly by PTCA.

Kaski et al. recently reported that, out of 214 patients awaiting PTCA, 1 patient died, 15 patients suffered AMI, 35 developed UAP, and in 23 patients lesions became occluded at a median interval of 8 months. They concluded that adverse events are not uncommon in target lesions for PTCA. Their results indicate directly, and our results indirectly, that a large portion of high-grade stenoses contain high-risk complex lesions that may trigger coronary events.

It is believed that the atherosclerotic lesions that cause escape restenosis become stable plaque because the neointima securely covers the plaque.13 There were 16 target sites (16.9%, 16.8%) that were associated with cardiac events. However, if we include 171 patients from the PTCA group who received repeat CAG and were excluded because there were no actual events, the incidence was 16 out of 212 (7.5%). We conclude that if PTCA sites that escape restenosis rarely trigger coronary events and remain stable in the long term.

Weintraub et al.14 reported that the determinant of long-term outcome after PTCA is the atherosclerotic status of the remaining coronary arteries. It is well known that coronary arteries that appear normal on angiography are not normal when examined by ultrasound.15

Thus, the clinical implication is that, because "new lesions" developing from stenosis that is insignificant on primary CAG are an important determinant of long-term outcome, it is essential to find predictors of disease progression and to introduce appropriate medical treatment to eliminate them.18,19 In the PTCA group, most coronary events developed from low- to mid-grade stenosis, which indicates that successful PTCA does not necessarily guarantee a favorable prognosis. Consequently, the importance of medical treatment must be borne in mind even after successful PTCA.

Limitations

Our results are based on data derived only from symptomatic patients who returned for repeat CAG. It is well known that some oclusions are silent and that not all symptomatic patients return for repeat CAG. It is necessary to conduct further prospective studies to determine the likelihood of progression to ACS.

Conclusion

We conducted repeat CAG for ACSs in 222 patients.

We draw the following conclusions. (1) ACSs develop more frequently from insignificant stenosis than from significant stenosis. (2) High-grade stenosis (>90%) is prone to develop into ACSs and PTCA could reduce the risk of this kind of coronary event. (3) PTCA target sites might become stable plaque and rarely trigger coronary events. (4) Successful PTCA treatment without high-grade restenosis does not necessarily indicate a favorable long-term outcome because of potential new lesion development.

References