The Response to Drug Therapy in Unstable Angina on the Basis of Coronary Angiography Findings

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Among 366 unstable angina pectoris patients at our hospital, myocardial infarction was common (15.7%) in those with attacks of chest pain lasting for at least 20 min. There was also a high incidence (30.3%) when chest pain continued after the start of inpatient treatment. To investigate the etiology of unstable angina, coronary arteriography was performed in both the unstable and stable stages in these patients and the results were compared. The role of coronary spasm and coronary thrombosis in unstable angina was investigated, and the efficacy of continuous infusion of either diltiazem or isosorbide dinitrate as treatment for these patients was compared. Coronary arteriography in the unstable stage showed, no clear differences in the morphology of the stenotic site and the degree of stenosis between the patients with and without infarcts when urokinase or isosorbide dinitrate were injected into the coronary arteries. When drug treatment was effective, the angina was stabilized without any improvement in the degree of stenosis or the morphology of the involved coronary vessel. Thus, it was difficult to predict the response to treatment from coronary arteriography performed in the unstable stage. Diltiazem was more effective than isosorbide dinitrate, and it appears that some action other than coronary dilatation was involved in achieving the remission of unstable angina.

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The relationship of thrombosis and coronary artery morphology to the pathogenesis of myocardial infarction (MI) in unstable angina (UA) is currently being debated, and invasive methods of treatment like percutaneous transluminal coronary angioplasty have also become a topic of discussion. In an attempt to prevent myocardial infarction by early treatment, angina pectoris in which an infarct is likely to occur is classified as unstable angina, but the diagnostic criteria vary widely, so that the prognosis (especially with respect to the occurrence of infarction) naturally varies from series to series. Granting the difficulty of predicting the occurrence of myocardial infarction, after diagnosing unstable angina, we conducted a retrospective study to determine the patients in whom myocardial infarction was likely to occur, based on the history and the morphology of the stenotic segment on coronary angiography. We then conducted a prospective study to elucidate patient outcome, as well as assessing coronary thrombosis and vasospasm during the unstable period by coronary angiography.

Key words:
Unstable angina
Intracoronary thrombolysis
Isosorbide dinitrate
Diltiazem
Coronary angiography findings

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and comparing the results with angiographic findings during the stable period. We also compared the efficacy of calcium antagonists and nitrates for the prevention of infarction in unstable angina patients.

[1] Investigation of the relationship between the incidence of MI and the type of UA

Methods
We evaluated the incidence of MI in 366 successive UA patients from 1982 to 1989. The patients were classified according to the AHA criteria as new-onset exertional angina (NE), new-onset rest angina (NR), or changing pattern angina (CP), as well as on the basis of whether or not the episodes of chest pain persisted for 20 min or more (long angina, LA).

Results (Table I)
Out of the 366 patients, there were 290 (79.2%) whose episodes of angina were controlled by drug therapy during the unstable period of their hospital stay and 76 patients (20.8%) in whom the angina continued. MI occurred in 40 patients (10.9%). The NE, NR, and CP groups consisted of 58, 85, and 223 patients, respectively, and the corresponding incidences of MI were 13.8, 5.9, and 12.1%. The differences among these groups were not significant. With respect to the relationship between LA and MI, there were 32 patients (15.7%) who developed MI among the 204 UA patients with LA versus 8/162 (4.9%) without LA. Moreover, after instituting inpatient therapy a total of 25/76 LA patients developed MI, a high rate of 30.3%, making it obvious that it was necessary to treat drug-resistant UA with

Table I

<table>
<thead>
<tr>
<th>Description</th>
<th>n</th>
<th>AMI</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>new onset at effort</td>
<td>58</td>
<td>8</td>
<td>13.8</td>
</tr>
<tr>
<td>new onset at rest</td>
<td>85</td>
<td>5</td>
<td>5.9</td>
</tr>
<tr>
<td>changing pattern</td>
<td>223</td>
<td>27</td>
<td>12.1</td>
</tr>
<tr>
<td>total</td>
<td>366</td>
<td>40</td>
<td>10.9</td>
</tr>
<tr>
<td>prolonged rest angina (+)</td>
<td>204</td>
<td>32</td>
<td>15.7</td>
</tr>
<tr>
<td>prolonged rest angina (-)</td>
<td>162</td>
<td>8</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Description</th>
<th>EFFECT (+)</th>
<th>EFFECT (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISDN (n=34)</td>
<td>1 (3%)</td>
<td>33 (97%)</td>
</tr>
<tr>
<td>UK (n=24)</td>
<td>1 (4%)</td>
<td>23 (96%)</td>
</tr>
</tbody>
</table>

extreme caution.

[2] Investigation of the response to drug therapy on the basis of coronary angiography (CAG) findings

Methods
CAG was performed in all UA patients who had an episode of chest pain lasting 20 min or more within 24 h of their previous episode, and the CAG findings were evaluated for the 51 patients in whom an angina-related vessel was identified.

Results
When we examined the morphology of the stenotic segment using the Ambrose classification, concentric type stenosis was present in 16%, type I eccentric stenosis in 25%, type II eccentric stenosis in 29%, multiple irregularities in 20%, and complete occlusion in 10%. Evidence of thrombosis was found in 25%. We then divided the patients into a group in whom drug therapy was effective (24 patients) and a group in whom it was ineffective (27 patients). The second group developed LA even after inpatient therapy was instituted. We then compared the degree of stenosis, the extent of development of collateral pathways, the morphology of the stenotic segment, and the presence or absence of thrombus at the site of stenosis. However, there were no significant differences with respect to any of these parameters, so it appears to be difficult to predict the response to drug therapy from the CAG findings.

[3] Comparison of coronary angiography findings at the time of admission and after drug therapy

Methods
The subjects consisted of 34 patients with UA, classified according to the AHA or
TABLE III EFFECT OF CONTINUOUS INFUSION OF ISDN OR DTZ FOR UNSTABLE ANGINA

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>angina (-)</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>DTZ monotherapy</td>
<td>13</td>
<td>11</td>
<td>85</td>
</tr>
<tr>
<td>ISDN monotherapy</td>
<td>21</td>
<td>10</td>
<td>48</td>
</tr>
<tr>
<td>total</td>
<td>34</td>
<td>27</td>
<td>79</td>
</tr>
</tbody>
</table>

AHA-based diagnostic criteria, in whom chest pain persisting 20 min or more had occurred within the 24 h preceding admission. CAG was performed in all of these patients during the unstable period at the time of admission. Intracoronary (IC) injection of isosorbide dinitrate (ISDN) was performed in all of the patients and an IC urokinase (UK) infusion was given to 24 patients, so that the involvement of coronary vasospasm and thrombus could be evaluated. CAG was performed again during the stable period 2–3 weeks later and the findings were compared with those obtained on admission.

Results (Table II)
There was only 1 patient each with clear changes in the degree of stenosis and coronary morphology in response to IC ISDN and UK when CAG was performed on admission. The drug-responsive group consisted of 28/34 patients (82%) and the remaining 6 made up the drug-resistant group. CAG performed during the stable period in the effective group showed an improvement in the degree of stenosis in 5 patients (19%), but there were 3 (11%) who showed progression, despite that fact that angina attacks had stopped, and 20 (70%) who showed no changes.

[4] Evaluation of the continuous infusion of isosorbide dinitrate (ISDN) and diltiazem (DTZ) in patients with UA

Methods
We evaluated the protective effect of high-dose continuous infusion of ISDN and diltiazem for preventing angina and MI in a randomized comparison trial.

Results (Fig. 1 and Table III)
Attacks stopped in 10/21 patients (48%) in the ISDN group and in 6 patients after combined treatment with DTZ. Attacks stopped in 11/13 patients (85%) in the DTZ group, but it was impossible to control the other 2 despite concomitant treatment with ISDN. There were no differences between the ISDN and DTZ with respect to number of branches of the coronary arteries affected or the severity of stenosis of the culprit.
vessel. When the CAG findings obtained on admission and during the stable period 2 weeks after admission were compared, no clearcut changes could be identified in the degree of stenosis or the morphology of the culprit vessel in the drug-responsive group. DTZ had a higher efficacy than ISDN and it seems that an action other than vasodilation was involved in resolving the UA.

**DISCUSSION**

Since it is generally difficult to predict whether or not myocardial infarction will occur in angina patients, a great deal of attention has been paid to angina patients in whom myocardial infarction is most likely to occur, i.e., those with unstable angina. In this hospital, the incidence of myocardial infarction in unstable angina is 11%, and similar rates were recently reported by other institutions. Although no differences in the incidence of myocardial infarction have been found based on an analysis of pathologic type according to the AHA classification, myocardial infarction does occur more often in patients with prolonged angina attacks persisting for 20 min or more and in patients who still have attacks despite receiving impatient therapy. For this reason, patients with unstable angina who had episodes of chest pain persisting for 20 min or more were selected as our subjects for a retrospective study of the CAG findings within 24 h of such an attack. Although the stenosis of the involved vessel(s) has been reported to be eccentric type II in a high 60-75% of cases by Ambrose, the proportion in the present study was only 29%. However, stenosis of the smooth concentric type accounted for only 16% of the lesions, while 84% were so-called complex lesions.

Thrombi were detected in 25% of the lesions. In recent reports, the incidence of thrombosis has been reported to be a high 41-57%. There is also a report stating that the shorter the interval is between the last episode and contrast imaging, the higher becomes the percentage of thrombi detected. However, in this study the interval between the last episode and imaging was less than 24 h and previous studies included findings obtained up to 5 days later, making the time factor difficult to assess. Whether or not thrombi can be accurately diagnosed on the basis of coronary angiography remains questionable, and no clear definition exists. When lesions where the morphology was clearly altered by fibrinolytic agents, lesions in which a defect image could be observed from several directions, and lesions showing complete occlusion with protruding and irregular or indistinct edge were defined as thrombotic lesions, the incidence was 25%. Thus, the frequency of thrombus involvement in the unstable period is quite low, and it is difficult to draw any conclusion concerning the response to drug therapy or the prognosis based on whether or not thrombi are present.

Intracoronary thrombolysis (ICT) was performed to treat the culprit vessels within 24 h after an attack in the unstable angina patients with chest pain persisting for 20 min or more, and although we are still continuing a prospective study on thrombus involvement, the morphology of the stenosis has so far showed a definite change in response to ICT in only one case. While the possibility that some thrombi were not dissolved by ICT cannot be ruled out, the frequency with which images suggesting thrombus were identified was very low. CAG performed again during the stable period when angina attacks had stopped and the results were compared with the acute findings; the 8 cases in which there was a change in the degree of stenosis (5 cases of improvement and 3 cases of progression) and thrombi were presumed to have been involved accounted for more than 30%. The improvement in the degree of stenosis may have been due to a decrease in vascular tone following the unstable period and there is also the possibility that the progression of stenosis was due to progression of atherosclerosis, so it cannot be concluded that thrombi were definitely involved in all of these 8 patients. Consequently, it seems difficult to postulate that thrombi have a major role in the unstable period of unstable angina. The fact that the number of subjects was small and that few angiograms were obtained during the attacks may partly account for our results differing from those reported elsewhere. However, few authors have found fibrinolytic agents to be efficacious in the treatment of unstable angina, which appears to be consis-
tent with the results of the present study. The degree of stenosis and the morphology at the stenotic site did not change in 70% of the patients in whom attacks stopped in response to drug therapy. On the other hand, there is a report stating that when unstable angina developed in patients who had previously undergone CAG, the degree of stenosis in the responsible vessel had progressed by 76%. It was unclear, however, exactly when the progression occurred. Consequently, it is difficult to demonstrate that angina becomes stable or unstable solely as a result of changes in the degree of stenosis of the involved coronary artery.

The incidence of myocardial infarction in patients with unstable angina at our institution was 11% from 1982 to 1989, with no great improvement being seen over the past 10 years. Moreover, since patients with early infarcts occurring within 3 days of admission accounted for 60%, the initial therapy at the time of admission is obviously important. In this study, we compared ISDN with DTZ and found that DTZ was more effective. Since, as mentioned earlier, no changes in the degree of stenosis of the culprit vessel were detected, it appears possible that a calcium antagonist effect of DTZ other than vasodilatation exerted a direct protective action on the myocardium. Thus, it seems that abnormal myocardial calcium flux may be involved in the onset of unstable angina, additional studies on a larger series of patients are needed to further investigate this point.

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