Unstable Angina and Coronary Arteriographic Findings with Special Reference to Coronary Vasospasm

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The organic stenosis of the coronary artery and vasospasm induced by ergonovine maleate (EM) were examined by cine angiography in 106 cases with unstable angina. They were divided into 5 groups: new angina at rest (27 cases), new angina of effort (15 cases), changing pattern from effort to rest (41 cases), crescendo-type angina at rest (20 cases) and changing pattern from rest to effort (3 cases).

The following results were obtained: The incidence of a 75% or more organic stenosis was significantly lower in new angina at rest (52%) and crescendo-type angina at rest (55%) than in changing pattern from rest to effort (95%) (p < 0.005). The incidence of a 90% or more organic stenosis was significantly lower in new angina of effort than in changing pattern from effort to rest (46% vs 88%, p < 0.01). On the other hand, the incidence of a 50% or more spastic narrowing provoked by EM was 94% in new angina at rest, 90% in crescendo-type angina at rest, 56% in new angina of effort and 64% in changing pattern from effort to rest. In all 3 cases of changing pattern from rest to effort, total obstructions due to coronary spasm were found. However, there were no significant differences among these groups.

Unstable angina is a quite complicated disease from the point of view of pathophysiology. Its definition differs from report to report. This study deals with our clinical investigations in order to clarify the possible participation of coronary spasm in unstable angina on the basis of coronary arteriography and the ergonovine provocation test.

MATERIALS AND METHODS

The subjects were selected from the patients who underwent coronary arteriography at Kokura Memorial Hospital. Table I shows their clinical diagnosis. They were divided into 2 groups: 1) 83 patients who met the American Heart Association (AHA) criteria for unstable angina and 2) 23 patients who did not meet this criteria. The former group consisted of 27 patients with new rest angina (ranging in age from 43 to 73 with an average of 60.4), 15 patients with new effort angina (35–74 years old, average 55.9), and 41 patients with changing pattern (from effort to rest) (21–81 years old, average 57.6). The latter group consisted of 20 patients with crescendo-type angina at rest (ranging in age from 46 to 75 with an average of 64.7) and 3 patients (53–59 years old, average 56.0) with changing pattern (from rest to effort). In addition, 20 patients with variant angina and 10 patients with effort angina were studied for comparison.

Patients in the unstable stage were treated with nitrates and Ca²⁺-antagonists, and coronary

Key Words:
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Coronary arteriography
Ergonovine
Provocation test

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TABLE I PATIENTS PROFILES

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Female : Male</th>
<th>Age (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>27</td>
<td>1 : 4.4</td>
<td>43 ~ 73 (60.4)</td>
</tr>
<tr>
<td>of effort</td>
<td>15</td>
<td>1 : 4.0</td>
<td>35 ~ 74 (55.9)</td>
</tr>
<tr>
<td>Changing pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E → R</td>
<td>41</td>
<td>1 : 3.1</td>
<td>21 ~ 81 (57.6)</td>
</tr>
<tr>
<td>R → R</td>
<td>20</td>
<td>1 : 5.7</td>
<td>46 ~ 75 (64.7)</td>
</tr>
<tr>
<td>R → E</td>
<td>3</td>
<td>0 : 3.0</td>
<td>53 ~ 59 (56.0)</td>
</tr>
<tr>
<td>Total</td>
<td>106</td>
<td>21 : 85</td>
<td>21 ~ 81 (59.2)</td>
</tr>
</tbody>
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E = effort, R = rest, R → R = crescendo type

New Rest Angina

organic stenosis (n=27)

EM test (n=18)

Fig.1. Coronary arteriographic findings in new angina at rest. See text for details. EM = ergonovine maleate; 0 = no vessel involvement; 1 = one-vessel involvement; 2 = two-vessel involvement; 3 = three-vessel involvement

The coronary arteriograms were evaluated using a Tagarno viewer by at least 3 physicians. An organic coronary stenosis of 75% or more was considered significant and they were divided into 3 groups: greater than or equal to 75% and less than 90% (75% stenosis); greater than or equal to 90% and less than 99% (90% stenosis); 99% or greater (99% stenosis).

The EM provocation tests were considered positive when the diameter of a coronary artery was reduced by 50% or more after the administration of EM as compared with that measured after the administration of ISDN. The spastic...
### TABLE II  SUMMARY OF CORONARY ARTERIOGRAPHIC FINDINGS IN NEW ANGINA AT REST, NEW ANGINA OF EFFORT AND ANGINA WITH CHANGING PATTERN (FROM EFFORT TO REST)

<table>
<thead>
<tr>
<th>Organic stenosis</th>
<th>( &gt; 99% )</th>
<th>( &gt; 90% )</th>
<th>( &gt; 75% )</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>3/27</td>
<td>13/27</td>
<td>14/27</td>
<td>3/27</td>
</tr>
<tr>
<td>( \text{p} &lt; 0.005 )</td>
<td>( \text{p} &lt; 0.005 )</td>
<td>( \text{p} &lt; 0.005 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of effort</td>
<td>5/15</td>
<td>7/15</td>
<td>11/15</td>
<td>2/15</td>
</tr>
<tr>
<td>( \text{p} &lt; 0.025 )</td>
<td>( \text{p} &lt; 0.01 )</td>
<td>( \text{ns} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{E} \rightarrow \text{R} )</td>
<td>30/41</td>
<td>35/41</td>
<td>38/41</td>
<td>0/41</td>
</tr>
</tbody>
</table>

% narrowing due to spasm (EM test) | \( > 90\% \) | \( > 75\% \) | \( > 50\% \) | \( < 50\% \) |
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</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>14/18</td>
<td>15/18</td>
<td>17/18</td>
<td>1/18</td>
</tr>
<tr>
<td>( \text{ns} )</td>
<td>( \text{ns} )</td>
<td>( \text{ns} )</td>
<td>( \text{ns} )</td>
<td></td>
</tr>
<tr>
<td>( \text{E} \rightarrow \text{R} )</td>
<td>9/17</td>
<td>11/17</td>
<td>5/9</td>
<td>6/17</td>
</tr>
</tbody>
</table>

\( \text{E} \rightarrow \text{R} = \text{changing pattern from effort to rest}; \) \( \text{EM} = \text{ergonovine maleate} \)

**New Effort Angina**

**Changing Pattern Angina (E→R)**

**Fig. 2.** Coronary arteriographic findings in new angina of effort. See text for details. Abbreviations are the same as in Fig. 1.

**Fig. 3.** Coronary arteriographic findings in angina with changing pattern (from effort to rest). See text for details. LMT = left main trunk. Other abbreviations are the same as in Fig. 1.

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narrowing of the coronary arteries after this test was divided into 3 groups: greater than or equal to 50% and less than 75% (50% spasm); greater than or equal to 75% and less than 99% (75% spasm); 99% or greater (99% spasm).

RESULTS

The left panels in Fig. 1 show the frequency and the degree of organic coronary stenosis in new rest angina. The frequency of organic coronary stenosis in each degree of stenosis is on the vertical axis, and the number of the stenotic branches are shown on the horizontal axis. The right panels in this figure show the response to the EM provocation test (EM test). The degree of coronary spasm after the EM test is given on the ordinates. In the left bottom panel a 75% coronary stenosis is plotted against the number of stenotic arteries. As shown in this graph, a 75% narrowing was found in 52% of the patients, that is, narrowing of less than 75% was found in 48% of the patients. As shown in the left middle and top panels, a 90% narrowing was found in 48% of the patients, and a 99% narrowing in 11%. After the EM test, on the other hand, a 50% spasm was found in 94% of the patients, a 75% spasm in 79%, and a 99% spasm in 78%. Cases with single coronary artery disease often showed a severe spastic narrowing.

In new rest angina, organic coronary stenosis was mild, and most cases had single- or two-vessel disease. No three-vessel disease was found in our cases with a 90% stenosis, and cases with a 99% stenosis were few in number. After the EM test a 50% spasm occurred in 17 of 18 patients. A large number of our patients showed a positive reaction to the EM test.

Figure 2 indicates a similar study performed on patients with new effort angina. In this study, 75% stenosis was present in 73% of the patients. Most patients had single-vessel disease.
Fig. 6. Comparison of coronary arteriographic findings between new angina at rest and variant form of angina. Abbreviations are the same as in Fig. 1.

Fig. 7. Comparison of coronary arteriographic findings between new angina of effort and stable effort angina. Abbreviations are the same as in Fig. 1.
| TABLE III PROGNOSIS AND CLINICAL COURSE OF UNSTABLE ANGINA ACCORDING TO EACH TYPE |
|---------------------------------|-----------------|-----------------|-----------------|
| **At rest**  
(n = 27) | **stable** | **26** | **CABG** | **2** | **death** | **1** |
| | **unstable** | **1** | **AMI** | **1** | **CABG** | **1** |
| | **of effort**  
(n = 15) | **stable** | **15** | **CABG** | **1** | **AMI** | **1** |
| | **unstable** | **0** | | | | |
| **Changing pattern** | **E → R**  
(n = 41) | **stable** | **35** | **CABG** | **9** | **sudden death** | **1** |
| | | **unstable** | **6** | **CABG** | **5** | | **death** | **2** |
| | | **stable** | **6 (15%)** | | | | **death** | **1** |
| | | **unstable** | **2 (10%)** | | | | |
| | **R → R**  
(n = 20) | **stable** | **18** | **CABG** | **1** | | | |
| | | **unstable** | **2** | | | | |
| | **R → E**  
(n = 3) | **stable** | **3** | **CABG** | **1** | **sudden death** | **1** |
| | | **unstable** | **0** | | | | |

_CABG = coronary-aortic bypass graft; AMI = acute myocardial infarction; E = effort; R = rest; R → R = crescendo type_

(Left bottom). Further, a 90% stenosis was present in 46% of the patients with single- or two-vessel disease (left middle), and a 99% stenosis was observed in 33% of the patients with single-vessel disease (left top).

After the EM test, on the other hand, a 50% spasm was found in 56% of the patients (right bottom), a 75% spasm in 56% (right middle) and a 99% spasm in 33% (right top). In new effort angina, therefore, a 75% stenosis was predominant, and none of the patients with a 90% stenosis had three-vessel disease.

Figure 3 shows the findings of a similar study performed on cases with changing pattern angina. In this study, a 75% stenosis was found in 95% of the patients, and many of these had two- or three-vessel disease (left bottom).

Eighty-eight percent of patients were found to have a 90% stenosis (left middle), and a 99% stenosis was also found in 76%, and some of these had not only two- or three-vessel disease but also left main trunk disease (LMT) (left top). After the EM test, both 50% and 75% spasms occurred in 65% of the patients (right bottom and middle). Moreover, a 99% spasm was observed in 53% (right upper). In short, many patients with changing pattern angina had multi-vessel disease, including left main trunk disease.

Findings obtained from the patients with organic coronary stenosis are summarized in Table II. The occurrence rate of a 75% stenosis was significantly higher in new rest angina than in both changing pattern angina (p < 0.005) and new effort angina (p < 0.01). Between new effort angina and new rest angina, however, there was no significant difference in the degree of coronary stenosis. On the other hand, spastic narrowing was induced by EM at a higher rate in new rest angina. Coronary spasm, however, also occurred at a high rate in the other 2 types of angina, and there were no statistically significant differences among these 3 types.

Figure 4 shows the results in patients with the crescendo-type of rest angina, which is a subtype of changing pattern angina. A 75% stenosis was found in 55% of patients (left bottom), a 90% stenosis in 35% (left middle) and a 99% stenosis in 10% (left top). After the EM test, a 50% spasm was found in 90% of the patients (right bottom) and 75% spasm in 64% (right middle). These results suggest that coronary spasm may be involved in the development of the crescendo-

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type of rest angina. Figure 5 shows the results in changing pattern angina (from rest to effort). The cases of this group were too small in number to obtain any conclusion, but EM induced coronary spasm in all 3 cases. Coronary spasm may also play some role in the development of changing pattern angina (from rest to effort).

In Figure 6 findings from variant angina (not unstable) and those from new rest angina (unstable angina) are compared. Organic stenosis was slightly milder in variant angina than in new rest angina. A 75% stenosis was found in 40% of the patients with variant angina and in 52% of new rest angina; a 90% stenosis was found in 30% and 48%, and a 99% stenosis in 5% and 11%, respectively. There were similar results after the EM test.

In Fig. 7 findings from new effort angina and stable effort angina are shown. Organic stenosis was slightly more marked in stable effort angina than in both unstable effort angina and new effort angina. A 75% stenosis was found in 90% of the patients with stable effort angina and in 73% of new effort angina; a 90% stenosis was observed in 70% and 46%, and 99% stenosis in 40% and 33%, respectively. After the EM test, a 90% or less spasm was found at a somewhat higher rate in new effort angina than in stable effort angina, but its difference was statistically not significant.

The prognosis and clinical course of the patients with unstable angina are shown in Table III. Twenty-six out of 27 patients with rest angina became stable, and the one who remained unstable underwent aorto-coronary (AC) bypass surgery. Two of the 26 patients underwent AC bypass surgery and one of these died of acute myocardial infarction (AMI). All 15 patients with new effort angina eventually became stable, and one of these underwent AC bypass surgery and one developed AMI. Thirty-five out of 41 patients with changing pattern became stable. Nine out of the 35 patients underwent AC bypass surgery, one of whom became stable and then unstable again, and sudden death occurred in one case of this group. Five out of 6 patients with unstable angina underwent AC bypass surgery and 2 of these died, and the remaining one died in the stage of unstable angina. The crescendo-type of rest angina became stable in 18 of 20 patients, and one of these underwent AC bypass surgery. The other 2 remained unstable until their death. In patients with changing pattern from rest to effort angina, all 3 patients became stable, and one underwent AC bypass surgery and one died suddenly.

**DISCUSSION**

Whenever unstable angina is discussed, controversy begins concerning its definition. As its definition differs from one investigator to the other2–4 coronary arteriographic findings in this disorder also vary with each investigator. In this paper we studied coronary arteriographic findings in unstable angina and the participation of coronary spasm in unstable angina according to the AHA report. A number of reports have been published on unstable angina, and the incidence of organic coronary stenosis is extremely variable.5–12 No more than 6% of 1,286 cases with unstable angina investigated between 1972 and 1978 had normal coronary arteries.13 However, these reports have become unreliable in accordance with the development of methodology. There has been a report that 5 to 40% (22% on the average) had a single stenosis of more than 70%.13 It has also been reported that the greater part of the patients with unstable angina had triple-vessel disease.5,6,8,10 Victor et al.14 have reported that in 15 of 75 patients unstable angina of a less than 90-day duration was characterized by significant coronary heart disease. Single-, double- and triple-vessel diseases were observed in 52%, 18% and 15%, respectively. They concluded that new unstable angina was most commonly associated with single-vessel disease of the left anterior descending artery.

In the present investigation coronary stenosis was found in 52% of the patients with new angina at rest, 73% of new angina of effort and 95% of changing pattern angina. The former 2 groups usually had single- or double-vessel diseases, while the greater part of the latter one had triple-vessel disease. Furthermore, coronary stenosis was milder in the patients with new angina at rest or new angina of effort in the present study. In the patients with changing pattern, on the other hand, the coronary arteriographic findings were nearly comparable with those reported by other investigators. Between variant angina and new angina at rest there was no significant difference in coronary arteriographic findings (coronary stenosis), and 94% of the patients had a positive ergonovine provocation test. These findings suggest that the cause of unstable state in new angina at rest is attribut-

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able not to coronary stenosis, but mainly to coronary spasm, as reported by Maseri et al.\textsuperscript{15} When the coronary arteriographic findings were compared between effort angina (which was not unstable angina) and new angina of effort (which was unstable angina), the former generally had more marked coronary stenosis. This also suggests that some factors other than coronary stenosis may be responsible for the unstable state of angina. Collaterals have been proposed as one of such factors.\textsuperscript{16} In the present investigation, however, the collaterals were not taken into consideration. It should also be noted that 56\% of our patients had a positive reaction to the ergonovine provocation test. This finding suggests the participation of coronary spasm. Patients with changing pattern usually had advanced coronary stenosis, especially left main trunk disease and double- or triple-vessel disease, and 65\% of patients had a positive reaction to the ergonovine provocation test. From these findings 2 conditions for inducing unstable angina are 1) coronary blood flow does not increase commensurately with an increase in myocardial oxygen demand which results from an elevation in blood pressure and heart rate and 2) coronary blood flow itself decreases due to the occurrence of coronary spasm. From the standpoint of prognosis and therapy, the present findings strongly suggest that changing pattern angina is true unstable angina, that is, refractory angina with a poor prognosis. It was also revealed that the crescendo-type of rest angina, a subtype of changing pattern angina, may be of iatrogenic origin which is caused by the use of $\beta$-blockers and so on. Careful management should be emphasized in the treatment of angina.

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