Pathogenesis and Natural Course of Unstable Angina
— A Prospective and Retrospective Study —

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In order to evaluate the natural history of unstable angina and to clarify the relationship between unstable angina and myocardial infarction, we studied the natural course of 128 patients with unstable angina prospectively and analyzed the characteristics of preinfarctional angina in 250 patients with acute myocardial infarction in a retrospective study.

Prospective Study: During a 3-month follow-up period, 23 of 128 patients (18.0%) developed myocardial infarction, 40 (31.3%) remained with angina pectoris and 65 (50.8%) became free from anginal attacks. No significant difference was found in the occurrence rate of myocardial infarction between the patients without a history of myocardial infarction (Group I) and those with a history (Group II). The persistence rate of angina pectoris was higher in patients with a history of angina pectoris than in those without a history. Newly developed effort angina (EA) remained or developed into myocardial infarction more frequently than newly developed, rest angina (RA) (p < 0.05). Disappearance rate of angina in RA of the crescendo type was higher than EA of the crescendo type. Similarly, new RA disappeared more frequently than new EA. In Group I no significant differences in the occurrence rate of myocardial infarction and in the persistence and the disappearance rate of angina pectoris was observed between the prolonged type and the frequent type of angina. In Group II, however, the occurrence rate of myocardial infarction in the prolonged type of angina was higher than in the frequent type, but the disappearance rate of angina in the former type was significantly higher than that in the latter type (p < 0.05). The coronary artery lesion was more severe in Group II than in Group I. Patients with persisting angina pectoris complicated more commonly with severe coronary artery lesion than those with disappearing angina pectoris.

Retrospective Study: One hundred and thirty-nine out of 250 patients (55.6%) with acute myocardial infarction had a history of angina pectoris before the onset of infarct. Sixty patients (24.0%) had unstable angina (new onset 13.6%; crescendo type 10.4%), 28 (11.2%) stable EA, 21 (8.4%) RA and 30 (12.0%) a prodrome. The incidence of preinfarctional angina in patients with previous myocardial infarction was 70.5% and this value was higher than that in those without previous myocardial infarction (48.8%). At the end of the follow-up period (mean: 7 months), 126 out of 186 patients (67.7%) had no postmyocardial infarctional angina, 43 (23.1%) had EA, 12 (6.4%) had RA and 5 (2.7%) developed myocardial infarction. While the new onset type of preinfarctional unstable angina disappeared in 70.4% after the onset of infarction, the disappearance rate of the crescendo type was only 30.0% (p < 0.05). The coronary artery lesion in patients with crescendo angina was more severe than that in those with new onset angina.

Key Words:
Unstable angina
Pathogenesis
Natural course

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In spite of the advent of the coronary care unit the immediate mortality rate of acute myocardial infarction has still been high and the approach to prevent acute myocardial infarction was one of the most important problems in acute coronary care. Many investigators have reported that unstable angina presages acute myocardial infarction or sudden death. However, the pathogenesis of unstable angina does not only depend on one factor but probably on multiple factors, i.e., progression of coronary atherosclerosis, insufficiency of collateral circulation and intermittent coronary obstruction resulting from reversible platelet aggregation or spasm of the coronary artery. Therefore, in order to analyze the pathogenesis of unstable angina, we attempted to study the natural course of unstable angina, and evaluate the contribution of a history of angina pectoris and/or myocardial infarction, and types of angina to the development of myocardial infarction in a prospective study. Furthermore, we also attempted to determine the incidence of preinfarctional angina by a retrospective analysis of the records of patients who had experienced acute myocardial infarction.

MATERIALS AND METHODS

Prospective Study

One hundred and twenty-eight consecutive patients with unstable angina admitted to our hospital from January, 1981 to March, 1982, were studied. Eighty-six were men and 42 women, and their mean age was 62.0, ranging from 44 to 84. We defined unstable angina as follows: 1) angina of recent onset (within the past 4 weeks), either rest angina (RA) or angina on effort (EA) and 2) crescendo angina: increased duration (prolonged type, > 30 min) or increased in frequency of attacks (frequency type, > 3 times/day) with a decreased responsiveness to nitrates. In same cases the serum CPK level was normal or rose only minimally (under 200 IU/L), but their electrocardiograms did not show new Q waves. We followed up these patients for 3 months either at an outpatient clinic or in-hospital, and studied their natural course. Coronary angiography was performed using Judkins' technique on 83 patients. Each coronary arteriogram was evaluated by 2 observers without knowledge of their clinical findings. A stenosis of 75% or more was defined as significant narrowing of the coronary artery.

Retrospective Study

Two hundred and fifty patients with acute myocardial infarction admitted to our hospital from January, 1980 to December, 1981 were studied retrospectively. One hundred and ninety patients were men and 60 women, and their mean age was 61.1, ranging from 36 to 83. We investigated the presence or absence of a history of angina pectoris before admission in all patients and followed up these patients. Preinfarctional angina were divided into 5 categories: unstable angina (new onset type), unstable angina (crescendo type), angina on effort (EA), rest angina (RA) and a prodrome. The prodrome was defined as newly developed chest pain within 3 days before the onset of myocardial infarction. Coronary angiography was performed on 140 patients in a similar fashion as in the prospective study.

RESULTS

Prospective Study

In order to evaluate the natural course of 128 patients with unstable angina, we subdivided these patients into 4 groups according to the presence of a history of angina pectoris and/or myocardial infarction (Table I). Eighty-three patients in Group I had no previous myocardial infarction: 36 of these had no history of angina pectoris (Group I-a) and the remaining 47 had a history of angina pectoris (Group I-b). Forty-five patients in Group II had a previous myocardial infarction: 16 patients had no history of angina pectoris (Group II-a) and the remaining 29 had a history of angina pectoris (Group II-b).

Natural Course of Unstable Angina

During a 3-month follow-up period, 23 of 128 patients (18.0%) developed myocardial infarction, 65 (50.8%) remained with angina pectoris and 40 became free from angina pectoris (31.3%) (Fig. 1).

Factors Influencing Natural Course of Unstable Angina

History of Angina Pectoris and/or Myocardial Infarction

Myocardial Infarction Rate: Three months after the diagnosis of unstable angina, 16 of 83 patients (19.3%) who had no history of previous myocardial infarction (Group I) developed myocardial infarction (25.0% of Group I-a and 14.9% of Group I-b) (Fig. 1). On the other hand,
TABLE I THE FOUR SUBGROUPS OF 128 PATIENTS WITH UNSTABLE ANGINA

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Past history</th>
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<tr>
<td></td>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>I - a</td>
<td>36</td>
<td>-</td>
</tr>
<tr>
<td>I - b</td>
<td>47</td>
<td>-</td>
</tr>
<tr>
<td>II - a</td>
<td>16</td>
<td>+</td>
</tr>
<tr>
<td>II - b</td>
<td>29</td>
<td>+</td>
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</table>

![Graph showing the natural course of unstable angina during a 3-month follow-up period. MI = myocardial infarction.]

7 of 45 patients (15.6%) in Group II developed myocardial infarction (18.8% of Group II-a and 13.8% of Group II-b). Thus, no significant relation was found between the incidence of myocardial infarction and a history of previous myocardial infarction and/or angina pectoris.

Persistence of Angina Pectoris: Angina pectoris disappeared in 26 of 83 patients (31.3%) in Group I and remained in 41 patients (49.4%) (Fig. 1). The persistence rate of angina pectoris in Group I-a was 30.6% and that in Group I-b was 63.8%. Thus, angina pectoris was more frequently remained in Group I-b than in Group I-a (p < 0.05). On the other hand, in Group II 24 patients (53.3%) had angina pectoris during a 3-month follow-up period and the persistence rate of angina pectoris was higher in Group II-b (58.0%) than in Group II-a (43.8%). Thus, angina pectoris in patients with unstable angina who had a history of angina pectoris remained in more cases.

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Characteristics of Unstable Angina and Its Natural Course

Figure 2 shows the relationship between the types of unstable angina pectoris and its natural course.

Patients without a History of Myocardial Infarction (Group I): The occurrence rate of myocardial infarction (myocardial infarction rate) was significantly higher in newly developed effort angina (EA) than in newly developed rest angina (RA) (p < 0.001). Similarly, crescendo EA more commonly developed into myocardial infarction than crescendo RA (p < 0.05). While 15 of 26 patients (58.0%) with newly developed RA (new RA) had no angina pectoris during a 3-month follow-up period, angina pectoris disappeared in only one of 10 patients with newly developed EA (new EA) (p < 0.05) (Fig. 2). Thus, new EA more frequently remained or developed into myocardial infarction than new RA. The disappearance rate of angina
TABLE II  CORONARY ARTERIOGRAPHIC FINDINGS IN 83 PATIENTS WITH UNSTABLE ANGINA

<table>
<thead>
<tr>
<th>Group</th>
<th>Prognosis</th>
<th>Coronary arteriographic findings</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td>0VD</td>
</tr>
<tr>
<td>I - a</td>
<td>AP (-)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>AP (+)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>1</td>
</tr>
<tr>
<td>I - b</td>
<td>AP (-)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>AP (+)</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>0</td>
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<tr>
<td>II - a</td>
<td>AP (-)</td>
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<td></td>
<td>AP (+)</td>
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<td></td>
<td>MI</td>
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<tr>
<td>II - b</td>
<td>AP (-)</td>
<td>1</td>
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<tr>
<td></td>
<td>AP (+)</td>
<td>0</td>
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<td></td>
<td>MI</td>
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Abbreviations: 0VD = no significant coronary artery lesion; SVD = single vessel disease; DVD = double vessel disease; TVD = triple vessel disease; LMCAD = left main coronary artery disease; AP (-) = angina pectoris disappeared; AP (+) = angina pectoris remained; MI = myocardial infarction developed

Fig.2. The natural course of unstable angina. Relation of the types of unstable angina to the occurrence rate of myocardial infarction and the persistence rate of angina pectoris.

pectoris was 33.3% in crescedo RA and 12.5% in crescedo EA, but this difference was statistically not significant. The disappearance rate of angina pectoris was higher in new RA than in crescedo RA, but this difference was not significant. No significant differences in the myocardial infarction rate, the persistence and the disappearance rate of angina pectoris were also observed between new EA and crescedo EA.

Patients with a History of Myocardial Infarction (Group II): No significant difference in the myocardial infarction rate was found between EA and RA. The myocardial infarction rate also
Fig. 3. The natural course of unstable angina. Relation of the types of crescendo angina to the occurrence rate of myocardial infarction and the persistence rate of angina pectoris.

Fig. 4. Incidence of preinfarctional angina in 250 patients with acute myocardial infarction (MI).

did not relate to the types of unstable angina. While angina pectoris disappeared in 38.5% of new RA, no angina pectoris disappeared in new EA. Similarly, the disappearance rate in crescendo RA (50.0%) was significantly higher than that in crescendo EA (11.1%) (p < 0.05). No significant differences in the myocardial infarction rate, the persistence and the disappearance rate of angina pectoris were observed between new onset angina and crescendo angina.

Types of Crescendo Angina and Its Natural Course

We divided crescendo angina into the prolonged and the frequent type of angina for further examination.

Patients without a History of Previous Myocardial Infarction (Group I): As shown in Fig. 3, no significant differences in the myocardial infarction rate, the persistence and the disappearance rate of angina pectoris were found between the patients with the prolonged type of unstable angina and those with the frequent type.

Patients with a History of Previous Myocardial Infarction: Myocardial infarction rate in patients with prolonged angina was higher than that in those with frequent angina. The incidence of angina which disappeared in the former group was significantly higher than that in the latter group (p < 0.05).

Unstable Angina and Coronary Artery Lesion

Among 83 patients who underwent coronary angiography, 19 (22.9%) had no significant coronary artery lesion (0VD), 30 (36.1%) single vessel disease (SVD), 13 (15.7%) double vessel disease (DVD), 19 (22.9%) triple vessel disease (TVD) and 2 (2.4%) left main coronary artery disease (LMCAD) (Table II). The coronary artery lesion was more severe in Group II than in Group I. In Group I, 16 of 18 patients (88.9%), in whom angina had disappeared during the 3-month follow-up period, had 0VD or SVD, and TVD was observed in only 2 patients. On the other hand, the incidences of 0VD, SVD, DVD, TVD and LMCAD in 29 patients with persisting angina
Fig. 5. Natural course of preinfastrional angina following acute myocardial infarction in the surviving 186 patients. EA = effort angina; RA = rest angina; MI = myocardial infarction.

Fig. 6. Relation of preinfastrional angina to coronary arteriographic findings. OVD = no significant coronary artery lesion; SVD = single vessel disease; DVD = double vessel disease; TVD = triple vessel disease; RA = rest angina.
pectoris were 31.0%, 24.1%, 13.8%, 27.6% and 3.4%, respectively. Thus, the coronary artery lesion was more severe in patients with persisting angina pectoris than in those in whom angina pectoris had disappeared.

**Retrospective Study**

*Incidence of Preinfarctional Angina*

One hundred and thirty-nine out of 250 patients (55.6%) with acute myocardial infarction had a history of angina pectoris before the onset of infarct (Fig. 4). Sixty patients (24.0%) had unstable angina (new onset 13.6%, crescendo 10.4%), 28 (11.2%) stable EA, 21 (8.4%) RA, 30 (12.0%) a prodrome, and 111 (44.4%) had no preinfarctional angina. Of 172 patients without a history of previous myocardial infarction, 84 patients (48.8%) had angina pectoris, 36 (20.9%) unstable angina (new onset 14.0%, crescendo 7.0%), 14 (8.1%) stable EA, 12 (7.0%) RA and 22 (12.8%) prodrome. On the other hand, the incidence of a history of angina pectoris in 78 patients with previous myocardial infarction was 70.5%: unstable angina 30.8% (new onset 12.8%, crescendo 17.9%), stable EA 17.9%, RA 11.5% and a prodrome 10.3%). Thus, preinfarctional angina especially unstable angina and stable EA occurred more commonly in patients with previous myocardial infarction than in those without previous myocardial infarction.

*Natural Course of Preinfarctional Angina*

One hundred and eighty-six patients with acute myocardial infarction who survived and could be followed up, were studied retrospectively. Their mean follow-up period was 7 months, ranging from 3 months to one year and 2 months. At the end of the follow-up period, 126 of 186 patients (67.7%) had no postmyocardial infarctional angina, 43 (23.1%) had EA, 12 (6.4%) had RA and 5 (2.7%) developed myocardial infarction (Fig. 5). After myocardial infarction, angina pectoris in the patients with the new onset type of preinfarctional angina disappeared in 70.4% and remained in the other 29.6%. On the other hand, the disappearance rate of the crescendo type of preinfarctional angina was 30.0%. Thus, the crescendo type of angina pectoris remained more frequently following myocardial infarction than the new onset type of angina (p < 0.05). The persistence rates of angina pectoris in patients with EA and in those with RA were 53.0 and 54.0%, respectively.

Seventy-two percent of patients with prodrome had no postmyocardial angina. Fourteen out of 89 patients without preinfarctional angina also had angina following myocardial infarction.

**Preinfarctional Angina and Coronary Artery Lesion**

The relation of preinfarctional angina to coronary artery lesion were studied in 140 patients who underwent coronary arteriography within 3 months after myocardial infarction. Fifty-nine of 140 patients (42.1%) had SVD, 44 (31.4%) DVD, 20 (14.3%) TVD and 17 (12.1%) OVD (Fig. 6). In patients with new onset of angina 9.1% had OVD, 68.2% SVD, 9.1% DVD and 13.6% TVD. The incidences of OVD, SVD, DVD and TVD in patients with crescendo angina were 0%, 33.3%, 46.7% and 20.0%, respectively. Thus, the coronary artery lesion was more severe in patients with crescendo angina than in those with new onset of angina. In patients with RA 33.3% had OVD, 44.4% SVD, 11.1% DVD and 11.1% TVD. The incidences of OVD, SVD, DVD and TVD in patients with stable EA were 6.7%, 26.7%, 33.3% and 33.3%, respectively. Thus, patients with EA had more severe coronary artery lesion than those with RA.

**DISCUSSION**

Unstable angina is considered a pre-state to developing into myocardial infarction and many investigators have reported the high incidence of myocardial infarction in patients with unstable angina pectoris. However, unstable angina includes many types of angina pectoris and its pathogenesis may not be determinable only by a single mechanism. In the prospective and the retrospective study we analyzed the incidence of myocardial infarction in patients with unstable angina, and the incidence of preinfarctional angina and its natural course in patients with acute myocardial infarction were also investigated.

**Prospective Study**

*Incidence of Myocardial Infarction*

In our present series, 18.0% of patients with unstable angina developed myocardial infarction during a 3-month follow-up period and no significant relation was found between a history of myocardial infarction or angina pectoris and the incidence of myocardial infarction. Since 1956,
when Levy\textsuperscript{2} published the first prospective study of the natural history of patients with unstable angina, many investigators have reported the development of myocardial infarction from unstable angina\textsuperscript{3–12}. The studies in the 1960s indicated the occurrence rate of myocardial infarction as 20 to 80\%\textsuperscript{3–6}. After 1970s rate declined sharply and the improvement of the clinical course of unstable angina were considered resulting from the development of medical therapy, i.e., $\beta$-blockers, long-acting nitrates, Ca antagonists and so on.\textsuperscript{11–13}

In patients without previous myocardial infarction, EA, especially new EA, developed more commonly into myocardial infarction than did RA. One reason for this is that the coronary artery lesion was more severe in patients with EA than in those with RA. Another reason is that one of the mechanisms of unstable angina is transient or intermittent myocardial ischemia due to coronary artery vasospasm, being commonly observed in RA.\textsuperscript{14} In patients without previous myocardial infarction, no significant difference in the myocardial infarction rate was observed between the patients with the prolonged type of angina and those with the frequent type of angina. On the other hand, in patients with previous myocardial infarction, the myocardial infarction rate was higher in the prolonged type than in the frequent type. Thus, some caution is need in the treatment of patients with the prolonged type of angina pectoris.

Persistence of Angina Pectoris

In 31.3\% of the patients with unstable angina, the symptoms of angina disappeared within 3 months. Fulton et al.\textsuperscript{7} have followed up 167 patients with unstable angina and reported that 16\% of patients developed myocardial infarction or died and in one half of the remaining patients symptoms of unstable angina disappeared within 3 months. This disappearance was in agreement with our findings. During our follow-up period, the disappearance rate of angina pectoris was higher in patients with RA than in those with EA. This finding suggests that one of the mechanisms of RA may be transient myocardial ischemia. No significant difference in the disappearance rate of angina pectoris was found between the prolonged type of angina and the frequent type of angina in patients without myocardial infarction. On the other hand, anginal symptoms in the prolonged type disappeared more commonly than that in the frequent type in patients with previous myocardial infarction. We cannot explain this difference, and further examination is needed.

Unstable Angina and Coronary Artery Lesion

In our 83 patients who underwent coronary angiography, 22.9\% had normal or minimally involved vessels, 36.1\% single vessel disease, 18.1\% double vessel disease, 22.9\% triple vessel disease and 2.4\% left main coronary artery disease. Plotnick\textsuperscript{15} had studied the extent of the coronary artery lesions in 200 patients with unstable angina and reported that 92\% had a greater than 70\% narrowing of at least one major coronary artery, i.e., 8\% had 0VD, 22\% SVD, 24\% DVD and 46\% TVD (17\% LMCAD). Other investigators have also reported that 6 to 14\% of patients with unstable angina had normal coronaries and 4 to 20\% LMCAD.\textsuperscript{16–20} Such a wide spectrum of the coronary artery lesions in unstable angina may cause a wide variability in the patients' prognosis.

Retrospective Study

Incidence of Preinfarctional Angina

In our study the incidence of preinfarctional angina was 43.4\%, prodrome 12.0\% and no symptom 44.6\%. Sixty of 109 patients (55.0\%) with preinfarctional angina had unstable angina. Many investigators have reported that the incidence of prodromal symptoms and prodromes of unstable angina was 40–80\% and 25–70\%, respectively.\textsuperscript{15–22} In our series, preinfarctional angina was observed more commonly in patients with a history of previous myocardial infarction than in those without previous myocardial infarction. One possible explanation for this difference may be that the coronary artery lesion in patients with previous myocardial infarction was more severe than in those without previous myocardial infarction. Another possibility may be that preinfarctional angina in patients with reinfarction included postmyocardial infarction angina complicated following first myocardial infarct.

Natural Course of Preinfarctional Angina after Myocardial Infarction

Preinfarctional angina following myocardial infarction disappeared in 50.6\%, remained in 48.1\% and developed into myocardial infarction in 1.3\%. New angina disappeared in 70.4\%, rest angina in 46.1\%, crescendo angina in 30.0\% and

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the prodrome in 72.2%. These results indicate that new onset angina and prodrome easily disappeared following myocardial infarction. On the other hand, crescendo angina, RA and EA commonly persisted. Although further examination on the persistence of preinfarctional angina after myocardial infarction must be done, the types of preinfarctional angina are considered one of the factors which determine the prognosis of preinfarctional angina.

Preinfarctional Angina and Coronary Artery Lesion

In our study, the coronary artery lesion was more severe in patients with the crescendo type of unstable angina, stable EA and a prodrome than in those with unstable angina of the new onset type, rest angina and in those free from angina. This difference in the extent of coronary artery lesion among these types of preinfarctional angina may influence the natural course of preinfarctional angina.

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