Coronary Angiographic Findings in Various Types of Unstable Angina
— Study on the Pathophysiology of Unstable Angina —

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Coronary angiographic findings were studied in 129 patients with various types of unstable angina in order to clarify the pathophysiology of unstable angina. The subjects were divided into 3 types: effort angina (E), rest angina (R), and effort and rest angina (E+R), and each of these 3 types was subdivided into group I (new onset), II (recurrent) and III (changing pattern). 1) R had less severe coronary lesions than E or E+R. 2) Severity and distribution of coronary atherosclerotic lesions in unstable angina were similar to those in stable angina. 3) Incidence of coronary spasm is higher in unstable R and E+R than in stable R and E+R, respectively. 4) Unstable R and E+R with frequent attacks were associated with a higher frequency of coronary spasm and severe proximal coronary stenosis than those without frequent attacks, respectively. 5) Among unstable E+R-III (changing pattern), the patients who developed E+R from E showed significantly higher incidence of multiple vessel disease than those who developed E+R from R and significantly lower incidence of spontaneous spasm than those with E+R, who remained with the same pattern but in whom the frequency and/or the intensity of the attack increased, without any significant difference in the severity of coronary stenosis from other 2 subgroups.

It is concluded that coronary spasm as well as severe coronary atherosclerotic lesions may be responsible for the unstable state of angina. Especially in R and E+R, coronary spasm is the most important factor responsible for the unstabilization of angina.

Unstable angina is defined as a spectrum of acute symptomatic manifestations of ischemic heart disease interposed between stable angina and acute myocardial infarction. A variety of other terms have also been employed, including impending infarction intermediate coronary syndrome and so on. Although there is widespread use of the term "unstable angina", the pathophysiology of unstable angina is not completely understood. The purpose of this study is to clarify the pathophysiology of unstable angina by analyzing coronary angiographic findings according to its types and clinical course.

Key Words:
Coronary spasm
Effort angina
Rest angina
Effort and rest angina

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MATERIALS AND METHODS

The subjects included 129 patients with
TABLE 1  CLASSIFICATION OF SUBJECTS WITH UNSTABLE ANGINA

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<tbody>
<tr>
<td>Unstable angina</td>
<td></td>
</tr>
<tr>
<td>Effort angina (E)</td>
<td>48 cases</td>
</tr>
<tr>
<td>E—I</td>
<td>16</td>
</tr>
<tr>
<td>E—II</td>
<td>7</td>
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<tr>
<td>E—III</td>
<td>25</td>
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<tr>
<td>Rest angina (R)</td>
<td></td>
</tr>
<tr>
<td>R—I</td>
<td>12</td>
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<tr>
<td>R—II</td>
<td>3</td>
</tr>
<tr>
<td>R—III</td>
<td>16</td>
</tr>
<tr>
<td>Effort and rest angina (E + R)</td>
<td>50</td>
</tr>
<tr>
<td>E + R—I</td>
<td>9</td>
</tr>
<tr>
<td>E + R—II</td>
<td>4</td>
</tr>
<tr>
<td>E + R—III</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
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|                |        |
| Stable angina  |        |
| E              | 32     |
| R              | 4      |
| E + R          | 8      |
| Total          | 44     |

Unstable angina was defined basically according to the American Heart Association (AHA) Committee Report, which includes the following 3 groups: 1) new angina of effort, 2) changing pattern and 3) new angina at rest. In the present patients the symptom, chest pain, began within 3 weeks before hospitalization and its last episode occurred within one week before admission. All patients had neither ECG changes reflecting recent myocardial infarction nor elevation of the serum myocardial enzyme levels.

We classified the 129 patients with unstable angina into the following 3 types: effort angina (E), rest angina (R) and effort and rest angina (E+R). Each of these 3 types was then subdivided into 3 groups, i.e., group I (new onset), group II (recurrent: recurrence of angina at least after a 6-month interval of freedom from attacks) and group III (changing pattern: more than a 3 times increase of the frequency of anginal attack, often associated with changing types of angina, especially in E+R). The 129 patients with unstable angina were finally subdivided into the following 9 subgroups: 16 patients with E—I, 7 with E—II, 25 with E—III, 12 with R—I, 3 with R—II, 16 with R—III, 9 with E+R—I, 4 with E+R—II and 37 with E+R—III (Table 1). Twenty-four of these 129 patients were associated with old myocardial infarction. In order to clarify the pathophysiology of unstable angina, CAG

Fig.1. Coronary angiographic findings in various types of unstable angina. I = Group I (new onset), II = Group II (recurrent), III = Group III (changing pattern). A p value less than 0.05 shows statistically significant difference in the incidence of organic lesions of the coronary artery.

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Fig. 2. Incidence and site of a 90–99% stenosis of the coronary artery in various types of unstable angina. Abbreviations are the same as in Fig. 1.

Fig. 3. Incidence of spontaneous spasm and spasm induced by ergonovine or by ergometer exercise in various types of unstable angina. *Five patients with effort angina who showed no significant coronary lesions underwent a spasm provocation test. Abbreviations are the same as in Fig. 1.
findings obtained from 44 patients with stable angina were also compared with those of unstable angina.

Selective CAG using the Sones technique was undertaken in all patients and occlusive disease with a narrowing of more than 75% of the luminal diameter was defined as significant. Spasm provocation test by ergonovine maleate or by ergometer exercise was performed in patients with R and E+R who had no severe proximal coronary stenosis. Ergonovine maleate (0.2 mg~0.4 mg) was given intravenously and CAG was repeated 3 min after ergonovine injection or during attack. A multistage bicycle exercise test in the supine position with an initial work load of 50 watts and subsequent increments of 25 watts every 3 min was performed and CAG was repeated immediately after exercise. Coronary spasm was considered to be documented when the coronary segment was reduced more than 50% (ergonovine) or 20% (ergometer exercise) in diameter or obstructed completely as compared with the initial angiographic appearance. The interval from the onset of unstable angina to the performance of CAG was 2~8 weeks (average 4 weeks).

Twelve-lead ECG and treadmill test were performed in all subjects.

Statistical analysis was performed according to the chi-square test and Fisher's exact probability test.

RESULTS

CAG Findings in Various Types of Unstable Angina

Among 48 patients with E, 19 patients (40%) had triple vessel disease (TVD), 17 (35%) double vessel disease (DVD), 5 (10%) single vessel disease (SVD) and 7 (35%) no significant lesions (N) as shown in Fig. 1. E-I showed a tendency towards less severe coronary lesions than E-II and E-III (p < 0.001). On the other hand, among 31 patients with R, 1 (3%) had TVD, 7 (23%) DVI, 7 (23%) SVD and 16 (51%) N. There were no significant differences in the severity and the distribution of coronary atherosclerotic lesions among groups R-I, II and III. The CAG of 50 patients with E+R revealed TVD in 7 (14%), DVI in 12 (24%), SVD in 18 (36%) and N in 13 (26%). There were also no significant differences among groups E+R-I, II and III. The incidence of multi-vessel disease in R was significantly lower than that in E (p < 0.001) and in E+R (p < 0.01) as shown in Fig. 1. Incidence of subtotal occlusion of the proximal coronary artery was significantly higher in E (p < 0.001) and E+R (p < 0.001) than in R as shown in Fig. 2.

Unstable Angina and Coronary Spasm

Coronary spasm was observed in 53 patients with R or E+R as shown in Fig. 3. Spontaneous
Fig. 5. Coronary angiographic findings in unstable and stable angina. TVD = three vessel disease, DVD = double vessel disease, SVD = single vessel disease, NSL = no significant lesions.

Fig. 6. Incidence and site of a 90–99% stenosis in various types of unstable and stable angina.
attack and/or increased initial tonus were demonstrated in 32 patients with R and E+R. Coronary spasm was induced by an administration of ergonovine maleate or ergometer exercise in 38 of 41 patients (93%) with R and E+R who underwent a provocation test. Five patients with E also showed spasm during the ergometer exercise.

Among 40 patients with frequent anginal attacks of more than 3 times a day (the so-called impending infarction), 23 (58%) showed a subtotal occlusion of the proximal coronary artery and 15 (38%) demonstrated a spontaneous coronary artery spasm. Incidences of spontaneous spasm in R and the severity of coronary lesions in E+R were significantly higher than those without frequent attacks (p < 0.005 and p < 0.001, respectively) (Fig. 4).

CAG Findings in Patients with Unstable and Stable Angina

There were no significant differences in the severity of coronary atherosclerotic lesions between unstable and stable angina, except in rest angina (Figs. 5 and 6). In patients with R and E+R, incidence of spontaneous spasm or increased initial tonus was significantly higher in unstable angina than in stable angina (p < 0.01 and p < 0.001, respectively) (Fig. 7).

Fig. 7. Incidence of spontaneous spasm and the rate of positive spasm provocation tests in various types of unstable and stable angina.

Fig. 8. Coronary angiographic findings in 3 subgroups of unstable E+R: II! Three subgroups of E=E+R, R=E+R, E+R→(E+R)↑ were classified according to their clinical courses. E = effort angina; R = rest angina; E+R = effort and rest angina; III = group III (changing pattern); E=E+R = development to E+R from E; R=E+R = development to E+R from R; E+R→[E+R]↑ = E+R, which remained with the same pattern but the frequency and/or the intensity of the attack increased.
**Clinical Course of Unstable E+R-III and CAG Findings**

A changing pattern in effort and rest angina of the unstable type (E+R-III) was subdivided into 3 subgroups according to their clinical courses, i.e., from E to E+R (E→E+R), from R to E+R (R→E+R) and E+R, which remained with the same pattern but increased the frequency and/or the intensity of the attack (E+R→[E+R]↑). At the initial stage of the disease, E→E+R had effort angina, R→E+R had rest angina and E+R→(E+R)↑ had both effort and rest angina.

There were no significant differences among 3 groups except that group E→E+R showed a significantly higher incidence of multi-vessel disease than group R→E+R (p < 0.04) and group E+R→(E+R)↑ showed significantly higher incidence of spontaneous spasm than group E→E+R (p < 0.02) (Figs. 8, 9 and 10). However, there were no significant differences in the incidence of subtotal stenosis among 3 groups.

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Types of Unstable Angina and ECG Findings

Among 48 patients with E, 40 (83%) showed an ST depression and 8 (17%) showed an ST elevation during attack (Fig. 11). On the other hand, among 31 patients with R, 21 (68%) showed an ST elevation, 7 (23%) an ST depression and 3 (9%) an ST elevation or depression during attack. Among 50 patients with E+R, 23 (46%) revealed an ST depression, 23 (46%) an ST elevation and 4 (8%) an ST elevation or depression during attack. Positive exercise test was observed in 45 (94%) patients with E (Fig. 12). However, it was negative in 7 patients (23%) with R and 7 (14%) with E+R and variable
Fig. 13. Coronary angiographic findings in a patient with unstable angina of E-I. Upper figure: RCA (LAO view). Lower figure: LCA (RAO view).

Case 33049 : 39y M

Control

During Attack (Ergometer Exercise)

Fig. 14. Coronary angiographic findings in a patient with unstable angina of E+R-I. Upper figure: LCA (LAO view). Lower figure: LCA (LAO view) recorded during an anginal attack induced by ergometer exercise.

Fig. 15. Coronary angiographic findings in a patient with unstable angina of R-I during a spontaneous anginal attack. Upper figure: RCA (LAO view). Lower figure: LCA (LAO view).

Case 33214 : 66y F

During Attack

Fig. 16. Coronary angiographic findings in a patient with unstable angina of R-I (the same patient as in Figure 15) after a nitroglycerin administration. Upper figure: RCA (LAO view). Lower figure: LCA (LAO view).

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in 2 (4%) with E+R. There were no significant differences in ST changes during the attack and the incidence of a positive treadmill test among groups I, II and III in E, E+R and R.

Case 1: A 66-year-old female with unstable angina of E-III (Fig. 13). A CAG revealed a 99% stenosis of the proximal RCA, a 90% stenosis of the proximal LAD and a 75% stenosis of the mid-distal LCX with collateral vessels from the conus branch to the distal RCA.

Case 2: A 39-year-old male with unstable angina of E+R-III (Fig. 14). A CAG revealed a 90% stenosis of the proximal LAD. Coronary spasm was provoked at the site of a stenotic plaque in the LAD during ergometer exercise with an ST elevation in V3.

Case 3: A 50-year-old male with unstable angina of R-I (Figs. 15 and 16). A CAG showed spontaneous vasospastic occlusion of the RCA at the site of the minor stenosis and generalized diminution in diameter of the LCA due to spasm (Fig. 15). Spasm was relieved by an administration of sublingual nitroglycerine, however, coronary artery showed not uniform dilation with the development of collateral vessel from the LCA to the RCA (Fig. 16).

DISCUSSION

The term “unstable angina” is usually applied to a spectrum of acute myocardial ischemic pain syndrome interposed between stable angina and myocardial infarction1-7. However, the pathophysiology of unstable angina is not completely understood. It has been recognized that lesions in unstable angina are somewhat more proximal and more severe than those of stable angina. Most studies, however, have shown that the distribution and severity of coronary atherosclerosis in patients with unstable angina is similar to those in patients with stable angina.8,10,13,14,16 Unstable angina defined by the AHA Committee Report1 includes several types of angina pectoris, which makes the etiologic consideration complicated. Therefore, we classified the unstable angina into several subgroups according to the clinical spectrum and studied the etiology of the unstabilization of the symptom.

No significant differences were found in the degree of severe narrowing of the coronary artery between patients with stable angina and unstable angina in our study. However, the incidence of spasm is higher in unstable rest angina (R) and effort and rest angina (E+R) than stable R and E+R, respectively. Maseri et al11,12,14 have summarized the occurrence of the coronary artery spasm as an important pathophysiologic mechanism in unstable angina pectoris. We demonstrated coronary artery spasm angiographically in a high percentage of patients with unstable R and E+R. Unstable angina with frequent attacks (the so-called impending infarction) was associated with a high frequency of severe narrowing of the proximal coronary artery in E+R and of coronary spasm in R than those without frequent attacks. However, no significant difference in the severity of coronary atherosclerosis was observed between unstable E with frequent attacks and that without frequent attacks. It is considered that coronary spasm as well as severe coronary atherosclerotic lesions may be responsible for the unstabilization of angina pectoris in patients with R and E+R. We analyzed patients with E+R of group III (changing pattern) according to their clinical course. There were no significant difference in the severity of coronary stenosis among 3 subgroups (E→E+R, R→E+R, E+R→(E+R))1), although the incidence of multiple vessel disease was significantly higher in E→E+R than in R→E+R. However, incidence of spasm was significantly higher in R→E+R and E+R→(E+R)1) than in E→E+R.

It is clear that aggressive medical therapy is the initial treatment of choice of unstable angina2,16. All patients in our study received vigorous medical therapy including one or more of the following: bed rest, sublingual and topical nitroglycerin, long-acting nitrates, propranolol, Ca-antagonists, heparin and sedation. With early optimal medical management, the majority of patients, who were hospitalized with unstable angina, rapidly became asymptomatic. Only 2 of 129 patients with unstable angina developed myocardial infarction. Patients with unstable angina, who are refractory to medical therapy, should undergo emergency CAG and a revascularization procedure2,17-20

REFERENCES
1. AHA Committee Report: Circulation 51 (4): (page 5) 1975
5. BERTOLASI CA, TRONGE JE, MON GA, TURRI


