Unstable Angina
— Clinical Course and Medical Management Including Antiplatelet Treatment —

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One hundred patients with unstable angina who were treated medically were classified into 2 groups of non-crescendo and crescendo angina and reviewed regarding their clinical course for 24 months on the average. Thirty-four patients with non-crescendo angina had an occurrence of recurrent angina in 7 patients (21%), myocardial infarction in 2 (6%) and death in none, while 66 patients with crescendo angina had a significantly higher occurrence of recurrent angina in 29 (44%) and myocardial infarction in 14 (21%), p < 0.05 in both angina and infarction. There were 4 (6%) deaths in patients with crescendo angina in spite of similar clinical backgrounds. Modern medical treatments of unstable angina include nitrates, beta blockers, calcium antagonists as well as antiplatelet and thrombolytic therapy. We conclude that our patients under active medical treatment have more favorable prognosis than once thought and that classification of unstable angina into non-crescendo and crescendo angina according to the early clinical course appears to be useful both for a selection of treatments and for an assessment of prognosis.

Unstable angina has been considered to represent a potentially hazardous situation which may presage the development of myocardial infarction and death. Evaluation of the syndrome, however, demonstrates a broad spectrum of coronary artery disease as shown by arteriography and variable results of progress. This makes appropriate management of this type of angina difficult, chiefly because of the different criteria of this syndrome and the general lack of homogeneity of the patients studied.

Accordingly, the present investigation was designed to identify a subgroup of patients with a higher risk of morbidity/mortality and to evaluate some of the new antiplatelet treatments in this category of unstable angina.

PATIENTS AND METHODS
All patients studied were admitted with unstable angina to the CCU at Kyoto University Hospital or at Kyoto Takeda Hospital and subsequently underwent cardiac catheterization. The patients who did not undergo cardiac catheterization were excluded.

One hundred patients (85 men and 15 women, ranging in age from 41 to 75 years with an average of 57.6) who fulfilled the criteria of unstable angina as defined by the American Heart...
## TABLE I  CLINICAL AND FOLLOW-UP DATA OF UNSTABLE ANGINA

<table>
<thead>
<tr>
<th>Unstable angina (100 cases)</th>
<th>Risk F.</th>
<th>OMI</th>
<th>CAG</th>
<th>Follow-up</th>
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<td>New E.A.</td>
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<tr>
<td>Non-crescendo 15</td>
<td>1.7</td>
<td>2</td>
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<td>Crescendo 15</td>
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<td>Changing</td>
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<td>New R.A.</td>
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<td>Non-crescendo 19</td>
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<td>Crescendo 6</td>
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AMI = acute myocardial infarction; AP = angina pectoris; CAG = coronary arteriography; number of stenosed arteries; E.A. = angina of effort; R.A. = angina at rest; Risk F. = number of risk factors

Fig. 1. Cardiac events during an average follow-up period of 24 months. Cresc = crescendo. Other abbreviations are the same as in Table I.

Association (AHA) were included in the study. Patients with any history or evidence of recent myocardial infarction and with valvular or congenital heart disease were not included in this study. Follow-up data was available on all patients for periods of an average of 24.5 months at the time of this investigation.

We classified the patients into 2 groups according to symptoms: 1) patients with chronic angina who complained of recent deterioration of symptoms with pain at rest and patients with new onset of angina with progressive deterioration of pain at rest (crescendo angina) and 2) patients with new onset of pains without progressive deterioration (non-crescendo angina).

Each patient was examined for coronary risk factors of hypertension (160/90 at least 3 occasions during hospitalization), diabetes mellitus, hypercholesterolemia, hyperuricemia and cigarette smoking (≥ 20 pack-year continued until at least 3 years prior to this study).

Selective coronary arteriography was performed using the Sones technique in almost all patients except a few who were examined using the Judkins technique. The studies were performed using a Philips 6.5 inch image intensifier and coronary arteries were reviewed at several projections. Significant obstruction of the coronary artery was considered to be 75% or greater narrowing of luminal diameter of major coronary vessels. Left main coronary artery narrowing was considered to be two-vessel disease for statistical purposes. In patients found to have insignificant coronary narrowing (< 75% obstruction) and without electrocardiographic evidence of variant angina (ST elevation) in spite of resting angina, provocation with ergonovine maleate was performed. Fourteen out of 100 patients had normal arteriography, 33 had one-vessel involvement, 53 two- or three-vessel involvement. Eleven out of 14 patients who had insignificant coronary artery disease, nevertheless, developed spontaneous anginal attacks with ST elevation or had positive ergonovine tests with chest pain.

Platelet aggregation was measured with the method described previously. Blood was taken from the patients and platelet-rich plasma was obtained by centrifugation at 300 x g for 15 min. The remaining blood was centrifuged at 2000 x g for 15 min to obtain platelet-poor plasma. Platelet aggregation in response to addition of
bypass grafting was performed in 5 patients for symptomatic relief of persistent pain and these patients were considered lost to follow-up at the time of surgery.

Statistical analysis was performed using unpaired Student t and chi-square tests.

RESULTS

Classification of Unstable Angina and Morbidity/Mortality

Clinical data of 100 patients and morbidity and mortality are shown in Table I. According to the classification of the AHA, patients were divided into 3 groups: 1) 30 patients with new angina of effort (EA), 2) 45 patients with changing pattern and 3) 25 patients with new angina at rest (RA). Among the 3 groups no significant difference was present in age (58.0 ± 8.1, 56.1 ± 14.0 and 58.9 ± 7.8 years, respectively), sex (male/female: 25/5, 39/6 and 21/4, respectively) and a mean follow-up period (23.6, 25.5 and 22.0 months, respectively). The EA group included 30 patients, whose average number of risk factors was 1.4. Four out of these 30 patients (13%) had a history of old myocardial infarction, and the average number of stenosed coronary arteries per patient was 1.84 (± 0.96) for the whole group. The changing pattern group had an average risk factor of 1.5, included 5 cases (11%) of old myocardial infarction and had 1.66 (± 1.10) stenosed coronary arteries on the average. The RA group, including 2 (8%) of old myocardial infarction, averaged 1.6 risk factors and 1.34 (± 0.91) stenosed arteries. There was no significant difference in

Platelet Aggregation (T.O. 70 y.o. male; ADP 0.8 µM)

![Platelet Aggregation](image)

Fig.3. Platelet aggregation at the time of symptom free, anginal attack and after sublingual administration of nitroglycerin. M.A. = maximum aggregation
and 15 cases (23%), respectively), ejection fraction on a left ventriculogram (average 65% and 62%, respectively) and a mean follow-up period (25.3 and 22.4 months, respectively). Incidence of angina pectoris, myocardial infarction and death during the follow-up period is shown in Fig. 1. The crescendo group demonstrated a significantly higher incidence of recurrent angina and myocardial infarction. There was no death in the non-crescendo group.

**Medical Treatment of Unstable Angina**

Beta blockers were less often used in RA (24%; 44% in EA and 40% in changing pattern) and less effective in RA (33%; 77% in EA and 61% in changing pattern). Calcium channel blockers are now used most frequently in all groups of unstable angina. Efficacy (control of angina and prevention of myocardial infarction and death) of drug treatment was not different among the EA (57%), the changing pattern (56%) or the RA group (56%).

Various drugs and drug efficacy in non-crescendo and crescendo angina are shown in Fig. 2. In the non-crescendo angina group overall drug efficacy was 79%, while in the crescendo group it was 44% and was significantly lower than the non-crescendo group in spite of a higher incidence of multiple drug administration (55% vs 18%).

**Antiplatelet Treatment**

Some of the patients with unstable angina pectoris demonstrated distinctly abnormal platelet aggregation which was suppressed by nitroglycerin administration (Fig. 3). Figure 4 shows recurrent anginal attacks and elevation of platelet aggregation which was temporarily controlled by sublingual nitroglycerin.

Prostacyclin (PGI₂) was infused intravenously in a dosage of 22 ng/kg/min in a patient whose anginal attacks were controlled in association with a definite suppression of platelet aggregation. Prolonged suppression of platelet aggregation could be attained by an administration of ticlopidine at 300–600 mg/day. Some of the patients with RA demonstrated a good response to this drug and relief of angina pectoris.

Twenty-three out of 27 patients who underwent emergency coronary arteriography within 10 hours after the onset of myocardial infarction demonstrated occurrences of total occlusion in an artery and 18 of these responded successfully.
to intracoronary infusion of urokinase together with the reopening of the totally occluded coronary artery.

**DISCUSSION**

Unstable angina may be a clinical manifestation of a temporary period in the course of coronary artery disease in which a dynamic imbalance exists between myocardial blood supply and demand, resulting in profound clinical instability, and has been considered a prodromal syndrome of myocardial infarction and sudden death. Vakil has observed acute myocardial infarction in 41% of the patients within 3 months after the onset of the syndrome. Wood has recorded 22% incidence of infarction within 2 months, and Fulton et al have documented infarction in only 15% over a period of 3 years. The Cooperative Study Group has reported the overall inhospital mortality rate of 2% for the medical group and 3% for the surgical group and nonfatal myocardial infarction of 10% for the medical and 13% for the surgical group. At 2 years, the respective survival rate for medically and surgically treated patients were 91 and 90%. Therefore, the natural history of unstable angina varies probably due to dissimilar patient population and varying pathology. Even the AHA classification of unstable angina does not represent a homogeneous group of patients in regard to either their clinical history or their prognosis. For example, unstable angina of the present study as defined by the AHA happened to include patients with variant type of angina with normal coronary arteriography in the RA group. Persistent pain under treatment has been reported to be associated with a less favorable long-term outcome? Accordingly, we classified the patients into 2 groups: non-crescendo angina and crescendo angina (including changing pattern). Cardiac morbidity and mortality were significantly higher in the latter group than in the former in spite of similar risk factors and underlying coronary artery disease. It is clinically useful to group patients in this way for evaluating the prognosis of unstable angina.

The present study demonstrated that overall one-year rate of infarction and cardiac death was 8 and 2%, respectively. These results compare favorably with the previous reports of medical treatment as well as surgical intervention. This suggests that emergency surgical revascularization is rarely required in the early stage of medical managements in patients with unstable angina.

Since the advent of calcium antagonists and various forms of nitrates, beta blockers appear to be used less often than before. Among drugs, calcium blockers are most useful in treating patients with unstable angina. In spite of these multiple drug administrations crescendo angina is less responsive and less favorable in the prognosis.

In addition to the conventional drug treatment new antiplatelet treatment may play a role in the treatment of unstable angina. There has been several reports suggesting that coronary thrombosis may be related to genesis and/or extension of myocardial ischemia and infarction. However, the significance of coronary artery thrombosis in the pathophysiology of ischemic heart disease remains controversial. There is autopsy evidence that patients who died suddenly had platelet emboli in the coronary microcirculation frequently. Fulton and Sumner have shown using radiofibrinogen have shown central radionegative cores in occlusive thrombi in coronary arteries supplying areas of acute infarction, and this finding suggests that the thrombi were formed early and may have preceded the infarction. Other authors have disputed this causal relation and have maintained that the thrombus occurs as a result of infarction. Support for this argument rests on the findings of a low incidence of coronary artery thrombosis in fatal subendocardial or transmural infarction and the increase in frequency of thrombosis with increasing time between the onset of acute ischemic symptoms and death. In patients with sudden cardiac death the incidence of coronary artery thrombosis is considerably lower, occurring in less than one-third of the cases. In the present study 18 out of 27 patients who underwent emergency coronary arteriography demonstrated occurrences of total occlusion of artery. Eighteen patients (67%) who responded successfully to intracoronary infusion of urokinase had strong evidence of coronary thrombosis in the arteries responsible for myocardial infarction. Recently DeWood et al have also reported that 87% of patients with acute myocardial infarction had coronary arterial thrombi during the first 4 hours after the onset of symptoms of myocardial infarction. This suggests a role for coronary thrombosis in the genesis of most transmural infarction though relation between cause and result is still highly controversial. The usual
clinical course with unstable angina of acute onset also suggests the possibility that the thrombus may have been responsible for the abrupt change in clinical condition or may at least have been a contributing factor in the patients' history. Recent studies document that thromboxane B₂, a product of platelets with a potent vasoconstricting and platelet-aggregating action, rises in the coronary sinus during ischemia and that atherosclerotic vessels have a reduced ability to produce prostacyclin, a powerful vasodilating substance synthesized in the endothelium of blood vessels through the prostaglandin endoperoxide pathway. These metabolites of arachidonic acid are also associated with recent angina episodes in patients with unstable angina pectoris. Should prostaglandin and thromboxanes prove important in ischemic vascular disease, attention will be directed to the correction of their pathologic imbalance. Drugs which decrease platelet aggregability may have a definite clinical value in treatment of unstable angina, especially crescento type of RA.

Thrombolytic agents are given systematically and/or intracoronary to patients with acute myocardial infarction with good short-term results. Thrombolytic therapy in cases of unstable angina showed variable results but this relatively easy and safe procedure should be taken into consideration prior to surgical intervention.

In conclusion, unstable angina should be classified into non-crescento or crescento angina according to the clinical course for the assessment of morbidity and mortality. In a case of crescento angina active medical treatments including antiplatelet and thrombolytic therapy are advisable prior to any surgical intervention considering that this syndrome has a relatively lower incidence of morbidity and mortality than previously thought.

REFERENCES


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