Exact Mechanisms Contributing to Instability and Refractoriness to Therapy in Patients with Unstable Angina:
Coronary Arteriographic Evaluation

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Ninety one patients with unstable angina were evaluated by clinical and angiographic study. Of 91 patients, 42 (46%) responded poorly to the intensive medical treatment. Emergency coronary arteriography was then performed on these patients. The important pathoanatomical mechanisms contributing to instability of angina pectoris and/or refractoriness to the intensive medical treatment were observed in 19 of 42 patients (45%).
These include: 1) More severe disease with left main lesion; 2) Refractory coronary spasm; 3) Coronary dissection; 4) Rapid progression of atherosclerosis; 5) Ulcerating plaque and 6) Coronary thrombus.

Our results presented here suggest that an appropriate knowledge regarding pathophysiology might improve the approach to treatment.

Patients with unstable angina are at high risk of myocardial infarction and sudden death. Therefore, in an attempt to understand the pathophysiology of unstable angina and plan appropriate therapy for these patients, many cardiologists have recommended immediate coronary arteriography, if feasible.

Our angiographic observations in patients with unstable angina might establish the exact mechanisms accounting for the instability and/or refractoriness to the therapy.

Key words:
Unstable angina
Refractory coronary spasm
Ulcerating plaque
Coronary dissection
Coronary thrombus

METHOD
Selection of patients
Ninety one patients showing clinical symptoms of unstable angina pectoris for period of two years were evaluated by clinical and angiographic studies. Unstable angina pectoris in this study was defined as shown in Fig. 1. Myocardial infarction was excluded after an observation period of at least 24 but usually 48 hours.

Initial treatment
Patients were admitted to either coronary care unit (CCU) or post CCU and treated with bed rest, O2 inhalation, isosorbide dinitrate or nitroglycerin sublingually and nifedipine sublingually for their pain episodes. If patients were

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Clinical Presentation Subgrouping of Unstable Angina

Angina of Effort
- Recent onset (initial)
- With previous symptoms (crescendo pattern)

Angina at Rest
- Recent onset
- With previous symptoms

Both Angina at Rest and Angina of Effort
- Recent onset
- With previous symptoms

Fig.1. The term “unstable angina” comprises of a spectrum of acute myocardial ischemic pain syndromes that may be divided into six categories, using two clinical features: (1) the circumstances under which the symptoms occur (effort only, rest only, or both), and (2) the time elapsed since the onset of ischemic symptoms (recent onset or a more prolonged history of symptoms). Recent onset is defined for symptoms developing within four weeks.

| CCU Admission
| --- |
| Intensive Medical Treatment
| A. Treating episodes of ischemic pain
| 1) Sublingual nitroglycerin
| 2) Sublingual nifedipine
| 3) Intravenous morphine sulfate
| B. Preventing further episodes of ischemia
| Long-acting nitrates (Oral, Topical) plus
| Beta blockers and/or
| Calcium blockers
| maximize anti-ischemic regimen

If symptom refractory

- Additional Treatment
- IV Nitroglycerin
- IABP

Emergency CAG

Fig.2. Management of patients with unstable angina.

not taking β-blockers or calcium blockers, one or both of these agents were added. Accordingly, treatment with orally administered propranolol or metoprolol was initiated with use of a small dose that was gradually increased to a maximal dose of 120 mg daily. Long-acting nitrate 60 mg daily and/or calcium blocker (nifedipine) 30 mg daily, was used in most instances. Pharmacological therapy was individualized and patients with unstable angina were then treated aggressively as shown in Fig. 2 in an attempt to prevent further ischemic episodes.

Angiography
Patients who, after 48 hours observation under the intensive medical therapy in the CCU, still persisted in having recurrent ischemic episodes were given emergency coronary arteriography (CAG) using the Judkins technique. Emergency CAG was performed 2 to 76 hours (mean 52 hours) after CCU admission. CAGs were performed without nitroglycerin (control), following the administration of sublingual nitroglycerin (0.3 mg) and subsequently intracoronary nitroglycerin (0.2 mg). Thereafter, intracoronary urokinase (24–96 x 10^6 units) was administered and CAG was repeated if thrombus was strongly suggested or had been recognized.
TABLE I ARTERIOGRAPHIC DISTRIBUTION OF OCCLUSIVE CORONARY ARTERY DISEASE IN 91 PATIENTS WITH UNSTABLE ANGINA

<table>
<thead>
<tr>
<th></th>
<th>Responder (49)</th>
<th>Non-responder (42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple vessel disease</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Main left</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Double vessel disease</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Main left</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>&quot;normal&quot; arteries</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Fig. 3. Coronary arteriographic findings in 42 non-responders.

Fig. 4. A case of NTG-induced vasoconstriction in the left anterior descending artery. Arrow indicates the site of vasoconstriction.

RESULTS
During intensive medical therapy (Fig. 2), forty two of 91 patients (46%) in this study continued to have recurrent ischemic episodes in the CCU (non-responder). The mean age of the patients was 56 years. Thirty four patients men and eight were women. Forty nine of 91 patients (54%) responded to the intensive medical therapy and were free from ischemic episode (responders: mean age 54 years, 37 men, 12 women).

Coronary arteriographic findings

A. Arteriographic distribution of coronary lesions
Arteriographic distribution of coronary lesions is shown in Table I. Approximately two thirds of both responders and non-responders had multivessel disease (at least 70 percent luminal narrowing). There was no significant difference in the distribution of occlusive coronary artery disease in both groups. However, seven of the 42 patients (17%) in the non-responder group had greater than 50 percent stenosis of the left main coronary artery. Four of 91 patients (three responders and one non-responder) had normal coronary arteriograms. These patients presented with a history of angina at rest. One patient responded poorly to nitrates and calcium blocker.

B. Multiple spectrum of coronary lesions accounting for the instability of angina and refractoriness to the therapy
The characteristic features of coronary arterio-

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grams were observed in 19 of 42 nonresponders (45%). These features were not observed in responders. As shown in Fig. 3, superimposed spasm was seen in 8 patients (refractory spasm in 6 patients, which was relieved by only intra-coronary nitroglycerin and nitroglycerin-induced vasoconstriction in 2 patients), coronary dissection in 3 patients, rapid progression in 2 patients, ulcerating plaque in 3 patients and coronary thrombus in 3 patients.

Representative case reports

Case 1 (Fig. 4): A 46-year-old male presented with a history of rest angina responded poorly to nitrates. Coronary arteriogram showed nitroglycerin-induced vasoconstriction, indicated by an arrow.

Case 2 (Fig. 5): A 54-year-old male with a previous history of myocardial infarction was given coronary arteriograms because of postinfarction angina. Injections of the left and right coronary artery 6 months before are shown in the upper. Coronary arteriograms for the evaluation of postinfarction angina are shown in the lower. High grade stenotic lesions of the first diagonal branch and right coronary artery are observed and indicate rapid progression.

Case 3 (Fig. 6): A 64-year-old male with a history of worsening effort angina was admitted for coronary arteriography. The coronary arteriogram showed a subintimal dissection involving the proximal segment near the site of the high grade stenosis.

Case 4 (Fig. 7): A 62-year-old male patient presented with a history of effort and rest angina, which responded poorly to intensive medical treatment. Emergency coronary arteriography was carried out and percutaneous transluminal coronary angioplasty (PTCA) was subsequently performed on a high grade lesion with an ulcerating plaque.

Case 5 (Fig. 8): Left coronary arteriograms in a 38-year-old male patient presenting with a history of worsening effort angina showed a floating thrombus in the proximal portion of the left anterior descending artery indicated by an arrow. Coronary thrombolysis with urokinase (48 x 10^4 units) resulted in complete lysis.
Case 6 (Fig. 9): Left coronary arteriograms in a 48-year-old male patient revealed lysis of non-occlusive or mural thrombus in the left circumflex artery by intracoronary administration of urokinase $48 \times 10^4$ units.

Follow-up management and clinical outcome

As shown in Fig. 10, 49 patients in the responder group received intensive medical therapy and became asymptomatic during hospitalization. However, 19 patients were potential candidates for myocardial revascularization. Among 19 of 49 patients (39%), elective PTCA was performed in 12 patients and elective coronary artery bypass graft (CABG) was performed in 7 patients.

Myocardial revascularization such as CABG, PTCA and coronary thrombolysis as a therapeutic option offers a great deal in non-responder group. CABG was clearly indicated in 17 of 42 patients (41%), PTCA in 11 of 42 patients (26%) and coronary thrombolysis in 3 patients (7%).

OKY-046 (thromboxane A$_2$ synthetase inhibitor) was added to the conventional therapy (modified medical therapy), for treating patients who were not indicated for myocardial revascularization.

All the patients had follow-up for 3 to 24 months (average 14 months) following therapy. In the responder group, 2 of the medically treated patients had an uncomplicated myocardial infarction, and sudden death occurred in 1 medically treated patient during hospital stay. Two medically treated patients had recurrent angina.

In the non-responder group, 2 of the patients receiving modified treatment had uncomplicated myocardial infarction. One

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Fig. 8. A case of a floating thrombus in a 38-year-old male patient. Left coronary arteriogram shows a filling defect in the proximal portion of left anterior descending artery, which had disappeared following administration of urokinase.

Fig. 9. A case of mural thrombus in the left circumflex artery. Urokinase administration resulted in lysis accompanied by a complete relief from ischemic pain.

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patient died from myocardial infarction, and two from renal failure after surgery. Sudden death occurred in one modified medically treated patient. Four patients had recurrent angina, all within 6 months after PTCA. Eight of the eleven patients receiving modified medical therapy reported symptomatic improvement.

**DISCUSSION**

The clinical syndrome of unstable angina causes great concern because of the high risk of progression to myocardial infarction. Some patients with unstable angina continue to present with symptoms of persistent ischemia, despite intensive medical therapy. In 20 to 50 percent of patients, unstable angina is refractory to initial medical therapy, and anginal episodes are continuous or recur within 24 to 48 hours after admission to CCU.\(^4\) The intensive medical therapy often takes several days and has an associated myocardial infarction rate of approximately 10% and a death rate of 3% during the initial hospitalization. Most patients continued to be trouble by angina and many have surgery within a few weeks.\(^5\)

Urgent coronary angiography is required in such patients, with a view to performing emergency myocardial revascularization including thrombolysis, PTCA and coronary bypass surgery if anatomically feasible.

However, before deciding on a particular treatment, the spectrum of pathophysiology and mechanisms responsible for the instability of angina pectoris and/or refractoriness to the intensive medical therapy in patients with unstable angina should be analysed. Analysis should be based on a grouping of patients into low- and high-risk subsets (i.e. responder and non-responder). An appropriate knowledge regarding pathophysiology might improve the approach to treatment.

The histological studies by Fuster et al.\(^6\) revealed that rupture, cracking or ulceration of atherosclerotic plaques on coronary arteries or a combination of all these lesions, is a very common finding at autopsy in patients with unstable angina pectoris. Our present study shows that the characteristic features of emergency coronary arteriography, particularly those performed on patients with unstable angina refractory to the intensive medical therapy, emphasize the most important cause of unstable angina. The exact mechanism accounting for the instability and/or refractoriness to the therapy remains unclear. However, a number of possibilities have been considered. Coronary arteriographic characteristics in our study include rapid progression of atherosclerotic lesions, rupture of atherosclerotic plaques, refractory coronary spasm, coronary thrombus, coronary dissection or various combinations of these factors. Ateriographic evidence of intracoronary thrombus was present in 7 percent of our patients refractory to the intensive medical therapy. Zack et al.\(^7\) reported the occurrence of arterio-
graphically detected intracoronary thrombus in patients undergoing cardiac catheterization for unstable angina but showing no signs of myocardial infarction. Falk\textsuperscript{8,9} reported that in cases of unstable angina, 73% of autopsies revealed the presence of small fragments of microemboli and/or recent microinfarcts in the myocardium, distal to evolving coronary thrombi. This indicates that thrombus material may break off and be transported in the blood (peripheral embolization). The frequency of intracoronary thrombus in our study was found to be lower than found previously.

On the basis of postmortem angiographic and pathologic correlations by Levin and Fallon\textsuperscript{10}, stenoses with irregular borders are indicative of plaque rupture or partially occlusive thrombi. Ambrose et al.\textsuperscript{11} characterized an eccentric lesion with irregular borders in coronary artery stenosis in patients with unstable angina. These eccentric lesions were present in 29 of 41 arteries in patients with unstable angina compared with 4 of 25 arteries in those with stable angina, probably representing ruptured atherosclerotic plaques or partially occlusive thrombi, or both. These eccentric lesions were also documented in a large number of our patients in conjunction with other lesions such as typical ulcerating plaques and superimposed dissection.

Patients with severe coronary atherosclerosis and multiple high grade stenosis often follow a stable clinical course for many years. However, such individuals develop unstable angina which is often associated with the characteristic arteriographic features that we demonstrated. The lesions could also account for patients with unstable angina who are refractory to intensive medical therapy. Disruption of coronary atherosclerotic plaques might be the result of coronary vasospasm, resulting in decreased coronary blood flow and increased platelet aggregation\textsuperscript{12}.

On the hypothesis that platelet aggregation causes a release of vasoactive substances, such as thromboxane A\textsubscript{2}, which induce the spasm\textsuperscript{13} This then results in further vasospasm or plaque disruption. These cycles of aggregation followed by spasm perpetuate finally resulting in coronary thrombosis. Under such situations prudence should be applied in the adoption of a more aggressive therapy.

Our study indicates that many patients with unstable angina, refractory to intensive medical therapy, require immediate myocardial revascularization. Patients who responded to intensive medical therapy are those patients with unstable angina who became completely asymptomatic during the initial hospitalization. For some of these patients (38%), however, elective CABG or PTCA is required within months of hospitalization. On the other hand, it is also evident in our study that patients responded poorly to intensive medical therapy required coronary thrombolysis and emergency CABG or PTCA. The anatomical status of the coronary artery, in fact, determines the course of optimal therapy. Thus, our results highlight the need for a more aggressive modalities in angiographic evaluation and subsequent treatment.

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