FIBRINOLYSIS IN PATIENTS WITH ISCHEMIC HEART DISEASE
(IN RELATION TO THE ETIOLOGIC FACTOR
OF MYOCARDIAL INFARCTION)

HIROMI SASSA, TAKEHITO TOYO TAKI, TOYOO NIWA, AND EJI MATSU

Coronary artery sclerosis and thrombosis are the major etiologic factors in acute myocardial infarction. Intravascular coagulation or thrombus formation is suggested to occur easily in the state of decreased plasma fibrinolytic activity in atherosclerotic patients. Several studies have recently shown that the defective plasma fibrinolysis and the higher plasma fibrinogen concentration were frequently found in the patients with ischemic heart disease, especially with acute myocardial infarction.

From this point of view, the impaired plasma fibrinolytic system might be possible etiologic basis for coronary artery thrombosis, although some reports indicate that it seems to be the secondary process due to myocardial infarction. These findings inspired us to commencing the relationship between the plasma fibrinolytic system and myocardial infarction.

The present study was designed to elucidate the etiologic significance of the abnormal plasma fibrinolysis in myocardial infarction.

Patients

Ninety in- and outpatients with ischemic heart disease and 25 subjects with essential hypertension (mean age 52.9 years) as control were studied. The diagnosis was angina pectoris on effort in 13 (mean age 57.2 years), intermediate type in 28 (mean age 51.7 years), acute myocardial infarction in 16 (mean age 59.9 years) and old myocardial infarction in 33 (mean age 61.3 years). Any control subjects showed no ischemic signs in the resting and post-exercise electrocardiograms. The criteria required for coronary patients were as follows: (1) Angina pectoris on effort: those with past history of anginal pain on exercise and who showed positive Master's double step test. (2) Intermediate type: those with anginal pain at rest or of longer duration than 15 minutes. (3) Acute myocardial infarction: those with clinical and electrocardiographic evidence of acute episode of myocardial infarction within 30 days. (4) Old myocardial infarction: those of 31 days or more after the onset of myocardial infarction.

Laboratory Determinations

Bovine fibrinogen was obtained from N.B.C., thrombin (50 u/ml) from Mochida, plasmin (2 u/ml) from Novo and streptokinase from Lederle. All other compounds were obtained from commercial sources.

(1) Plasma lipids: Total cholesterol was measured by Ferro-Ham's method, triglyceride by nephometer and β-lipoprotein by immunological method.

(2) Plasma fibrinolytic activity: Samples of venous blood (4.5 ml) were obtained with 3.8% sodium oxalate (0.5 ml) from patients and control subjects preprandially. Plasma fibrinogen was estimated by Biuret's method. Apparatus of N.C.U.M-type was used for the determination of plasma euglobulin lysis time which is considered to express the spontaneous fibrinolytic activity in the sample. The measurement of whole plasmin, euglobulin + streptokinase and antiplasmin was carried out by fibrin plate method. Whole plasmin values, estimated on the standard plate, shows a summation of the activity of

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proactivator, activator, plasminogen and inhibitors. The value of euglobulin + streptokinase on the standard plate exhibits the activity of proactivator and plasminogen, and those on the heated plate, the activity of plasminogen in the sample. Antiplasmin value was expressed as percentage of inhibiting ability of the sample of the control.

RESULTS

(a) Plasma lipids.

Fig. 1 shows the levels of the plasma lipids in the respective groups. Although, all four groups of coronary patients did not differ from controls significantly, the level of triglyceride was slightly decreased in the patients with acute myocardial infarction and the level of β-lipoprotein was slightly increased in the patients with old myocardial infarction.

(b) Plasma fibrinolytic activity.

Fig. 2 and Table I show the plasma fibrinolytic activity in coronary patients and controls. In the patients with acute myocardial infarction, the values of plasma fibrinogen (p<0.01), euglobulin lysis time (p<0.01), whole plasmin (p<0.01), euglobulin + streptokinase on standard plate (p<0.01) and euglobulin + streptokinase on heated plate (p<0.05) were significantly higher than controls. Also in the patients with intermediate type, euglobulin lysis time was significantly prolonged (p<0.001), compared with controls. While, there were no considerable differences in the patients with angina pectoris on effort and with old myocardial infarction. The patients who died of acute and old myocardial infarction showed the highest values in plasma fibrinogen, euglobulin lysis time and antiplasmin among the respective groups. However, the levels of whole plasmin, euglobulin + streptokinase on standard and heated plates in those patients were similar to mean levels in the corresponding groups.

DISCUSSION

The plasma fibrinolytic activity seems to be influenced by many factors. Especially, the age and the plasma lipids are supposed to be the factors of considerable importance. The patients with essential hypertension, whose ages were remarkably similar to those of coronary patients, were appointed for control subjects in the present study. There were no apparent differences between control subjects and coronary patients in the plasma lipids, too. Therefore, the influences of the age and the plasma lipids to fibrinolysis could be excluded in this study.

Fig. 3 shows the summary of the plasma fibrinolytic activity in each group of coronary
Fig.2. Plasma fibrinolytic activity of coronary patients and controls. (mean value ± S.E.M.).

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TABLE 1  PLASMA FIBRINOLYTIC

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Fibrinogen (mg/dl ± SEM)</th>
<th>E. L. T. (hrs ± SEM)</th>
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<tr>
<td>Control</td>
<td>25</td>
<td>264.4 ± 19.24</td>
</tr>
<tr>
<td>Angina on Effort</td>
<td>13</td>
<td>235.8 ± 19.85</td>
</tr>
<tr>
<td>Intermediate Type</td>
<td>28</td>
<td>272.5 ± 18.21</td>
</tr>
<tr>
<td>Acute Myocardial Infarction</td>
<td>16</td>
<td>389.2 ± 29.04</td>
</tr>
<tr>
<td>Old Myocardial Infarction</td>
<td>33</td>
<td>274.7 ± 12.34</td>
</tr>
</tbody>
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![Table](attachment:image)

Fig. 3. Summary of plasma fibrinolytic activity of coronary patients.

E.L.T.: Euglobulin lysis time,
Eug.+S.K. (standard): Euglobulin + streptokinase on standard plate,

patients. In intermediate type, euglobulin lysis time was significantly prolonged. In acute myocardial infarction, the remarkably higher plasma fibrinogen level and prolonged euglobulin lysis time were observed, as previously described by other investigators. The plasma proactivator and plasminogen activities were, as indicated by the values of whole plasmin and euglobulin + streptokinase on standard and heated plates, elevated in contrast with our presumption. Namely, from the fact that the activities of the plasminogen proactivator was high, though the plasma fibrinolytic activity was low, it is suggested that an imbalance exists between the plasma procoagulants and the plasma fibrinolytic activity in the patients with acute myocardial infarction and possibly with intermediate type.

This imbalanced plasma fibrinolysis may be secondary to the process of infarction, or it may be one of the etiologic factors in coronary artery thrombosis. Although a prospective study can solve this problem, it is clinically difficult to
Fibrinolysis in Patients with Ischemic Heart Disease

ACTIVITY OF CORONARY PATIENTS AND CONTROLS

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<tr>
<td>(mm² ± SEM)</td>
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<td>(mm² ± SEM)</td>
<td>(%) ± SEM</td>
</tr>
<tr>
<td>852.9 ± 38.29</td>
<td>524.6 ± 28.84</td>
<td>68.0 ± 11.00</td>
<td>52.8 ± 2.76</td>
</tr>
<tr>
<td>876.7 ± 24.56</td>
<td>513.9 ± 31.16</td>
<td>73.4 ± 11.79</td>
<td>46.9 ± 4.19</td>
</tr>
<tr>
<td>888.3 ± 25.90</td>
<td>567.0 ± 19.16</td>
<td>74.9 ± 7.70</td>
<td>49.9 ± 3.17</td>
</tr>
<tr>
<td>1039.7 ± 43.25</td>
<td>634.5 ± 28.12 (p &lt; 0.01)</td>
<td>94.7 ± 12.65 (p &lt; 0.05)</td>
<td>54.4 ± 4.88</td>
</tr>
<tr>
<td>898.9 ± 23.18</td>
<td>559.7 ± 25.94</td>
<td>67.0 ± 7.41</td>
<td>55.3 ± 1.00</td>
</tr>
</tbody>
</table>


estimate plasma fibrinolytic activity in the patients with myocardial infarction before the onset.

An important result from this study is that, defective plasma fibrinolysis was observed in the patients with intermediate type, who are usually supposed to be the forerunner of myocardial infarction. The defective plasma fibrinolysis in the patients with intermediate type would not seem to be the secondary event due to anodal attack, because the blood sample was obtained at non-anginal period and the patients with angina on effort showed no significant changes of plasma fibrinolysis.

From these observations, the lower activity of plasma fibrinolysis, which was demonstrated in the patients with intermediate type, might represent an etiologic contribution to coronary thrombosis and resultant acute myocardial infarction.

It was indicated by Astrup that plasma fibrinolysis was in a dynamic equilibrium with the fibrin-depositing coagulation process. According to the author, small amounts of fibrin which are being constantly deposited are removed by plasma fibrinolytic system as rapidly as they were formed in healthy organism, and the fibrin deposits ensue in the arterial wall in the organism with an imbalanced plasma fibrinolytic system. In addition to this view, Rokitansky and Duguid argued previously that the deposits of fibrin caused atherosclerosis. The above concepts suggest that the defective plasma fibrinolysis seems to play a role in the progression of coronary artery sclerosis and thrombosis.

More prominent imbalance of plasma fibrinolytic system was shown in the patients who died of myocardial infarction in the present study. This fact suggests that the prognosis of myocardial infarction is influenced by the degree of the impairment of plasma fibrinolysis, as well as other risk factors.

**CONCLUSION**

Thirteen patients with angina pectoris on effort, 28 with intermediate type, 16 with acute myocardial infarction, 33 with old myocardial infarction and 25 with essential hypertension as control were studied.

In the patients with acute myocardial infarction, the levels of plasma fibrinogen, whole plasmin, euglobulin + streptokinase on standard plate and euglobulin + streptokinase on heated plate were significantly elevated, and euglobulin lysis time was markedly prolonged. Significantly prolonged euglobulin lysis time was also found in the patients with intermediate type.

The patients with angina pectoris on effort and with old myocardial infarction showed no significant changes in these values.

We conclude that there may exist an imbalance between the plasma procoagulants and the plasma fibrinolytic activity in the patients with acute myocardial infarction and possibly with intermediate type, and that the imbalanced lower activity of plasma fibrinolysis leads to accelerate the progression of coronary insufficiency and results in myocardial infarction.

**REFERENCES**

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