Plasma Fibrinogen Patterns in Patients with Coronary Atherosclerosis

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THE PLASMA FIBRINOGEN concentration has been observed to be relatively constant for a healthy individual. An elevation in the concentration, however, is one of the most frequent responses of the organism to a variety of noxious stimuli. Among these stimuli is acute myocardial infarction following coronary thrombosis. The fibrinogen level has been shown to rise quickly and remain elevated for several days after a myocardial infarct. The hypothesis that fibrin is laid down on the vascular endothelium at all times but that the inherent blood fibrinolytic system which normally holds this process in check is inhibited in the individual who ultimately develops a thrombus has been stated by Astrup. He has suggested that the plasma fibrinogen level reflects the balance of the various procoagulant and lytic factors in the blood since it is elevated after thrombosis and lowered by activation of the fibrinolytic system. The present study concerns a comparison over time of plasma fibrinogen concentration of individuals with known coronary artery disease and apparently healthy individuals of the same age and sex.

Methods

Data were obtained from 46 patients who had had one or more myocardial infaracts as documented by clinical history and electrocardiogram. These data were compared with data from 49 individuals with no evidence of coronary artery disease who served as controls. There were 10 female and 36 male patients and 13 female and 36 male controls. The average age of both groups of subjects was 57 years with a range from 32 to 79. Plasma fibrinogen levels were determined by the micro-Kjeldahl assay. Duplicate samples varied from 0 to 51 mg/100 ml and had a mean difference of 13.86 (SD ± 13.09). The data included intermittent measurements of fibrinogen over a period of about 33 months from October 3, 1961, through June 6, 1964. Mean fibrinogen levels were calculated for comparison of the patients to the controls, and the groups were further examined by decades to correct for the effects of age on the fibrinogen levels.

For purposes of statistical analysis it appeared permissible to assume that repeated measurements in the same patient or control individuals were independent in the probability sense and that the values for each patient or control represented a random selection from a normally distributed population. With these assumptions, it was possible to derive an estimator for the common variance of the patient group and of the control group. The tests of fibrinogen concentration in milligrams per 100 ml were arranged in chronological order for each person in the study. Subjects having the same number of fibrinogen measurements (that is, three to seven) for a selected period of time were used. The shortest intervals to obtain the given number of tests are shown in table 1. These intervals were selected by obtaining the maximum data available within the time period which kept the distribution between tests as equal as possible. The variance

<table>
<thead>
<tr>
<th>Tests completed</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0-150</td>
</tr>
<tr>
<td>4</td>
<td>100-250</td>
</tr>
<tr>
<td>5</td>
<td>200-700</td>
</tr>
<tr>
<td>6</td>
<td>200-600</td>
</tr>
<tr>
<td>7</td>
<td>300-500</td>
</tr>
</tbody>
</table>
was then calculated from the individual measurements, the running mean, and the number of tests. Therefore, the variance of those individuals who required more than 150 days to complete the first three tests were eliminated from the comparison. Similarly, the range of days for upward of three tests was kept closely comparable for the two groups.

Data collected during episodes of bleeding, infection, or surgery, or all three, were not included in the first comparison of patients to controls. A second comparison was made, however, after measurements of fibrinogen made during these episodes were added for all individuals who had completed at least six tests. There were nine episodes of bleeding, infection, or surgery in the patient group and 13 in the control group. These data were then compared with another group of patients who were receiving anticoagulant drugs orally which had prolonged their one-stage pro-
thrombin times to approximately twice that of the controls.

**Results**

In the comparison of the mean levels of plasma fibrinogen, which are shown in figure 1, it can be seen that higher levels were obtained in the older individuals of the control group. The plasma fibrinogen of the younger patient group, on the other hand, ranged almost 100 mg% higher than the fibrinogen levels in the younger control individuals. Follow-up determinations of plasma fibrinogen during asymptomatic periods were not always elevated in the individuals with evidence of coronary artery disease. Frequently the values were even below the mean value. The striking difference was the variability of the fibrinogen level in the coronary group as compared to controls. The common fibrinogen variance in the two groups after three to seven tests are shown in table 2. This comparison of variances excluded all measurements during episodes of infection, bleeding, and surgery occurring in both patients and controls. The variance is greater in the patient group and continues to be so even after seven tests have been completed. The variance of five measurements in the patient and control groups were tested for equality of their median values by using the median test. Table 3 summarizes the results of this test and shows that the two groups are significantly different. Fibrinogen measurements during episodes of bleeding, infection, or surgery were then added to the data, and the variance of patient and control groups was again compared. This comparison of the mean variance with six tests is made in table 4. The patient variance was still greater. When the fibrinogen variance was higher.

![Influence of age on fibrinogen levels](image)

*Figure 1*

Coronary artery disease appears to superimpose an elevation of fibrinogen in the younger patients with myocardial infarction.

| Table 2 |

| Fibrinogen Variance in Healthy Control Individuals Is Compared to That in Patients with Evidence of Coronary Artery Disease |
|---|---|---|---|---|
| No. of tests | Variance | No. of controls | Variance | No. of patients |
| 3 | $4.42 \times 10^3$ | 15 | $7.83 \times 10^3$ | 22 |
| 4 | $3.75 \times 10^3$ | 13 | $8.70 \times 10^3$ | 15 |
| 5 | $4.36 \times 10^3$ | 21 | $8.40 \times 10^3$ | 26 |
| 6 | $2.45 \times 10^3$ | 12 | $12.00 \times 10^3$ | 21 |
| 7 | $2.15 \times 10^3$ | 4 | $9.69 \times 10^3$ | 10 |

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Table 3
Comparison of the Fibrinogen Variance after Five Measurements Is Made Between Patients and Controls Using the Median Test

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Patients</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below Median</td>
<td>14</td>
<td>9</td>
<td>23</td>
</tr>
<tr>
<td>Above Median</td>
<td>7</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>26</td>
<td>47</td>
</tr>
</tbody>
</table>

*P < 0.001; two groups are significantly different.

Table 4
Mean Fibrinogen Variance after Six Measurements Is Contrasted with Control and the Two Groups of Patients, One of Which Was Receiving Anticoagulants

<table>
<thead>
<tr>
<th>No.</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>49</td>
</tr>
<tr>
<td>Patients</td>
<td>46</td>
</tr>
<tr>
<td>Taking anticoagulants</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 5
Contrasting the Variance of the Fibrinogen Levels in Patients with Coronary Artery Disease Some of Whom Have Died from Recurrent Coronary Events and Some of Whom Have Survived

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>No. of tests</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>54</td>
<td>Man</td>
<td>6</td>
<td>1.87 × 10^3</td>
</tr>
<tr>
<td>64</td>
<td>Man</td>
<td>6</td>
<td>2.97 × 10^3</td>
</tr>
<tr>
<td>69</td>
<td>Man</td>
<td>6</td>
<td>5.86 × 10^3</td>
</tr>
<tr>
<td>68</td>
<td>Woman</td>
<td>4</td>
<td>1.66 × 10^3</td>
</tr>
<tr>
<td>61</td>
<td>Man</td>
<td>6</td>
<td>4.57 × 10^3</td>
</tr>
<tr>
<td>68</td>
<td>Man</td>
<td>6</td>
<td>7.65 × 10^3</td>
</tr>
<tr>
<td>69</td>
<td>Man</td>
<td>4</td>
<td>7.72 × 10^3</td>
</tr>
<tr>
<td>65</td>
<td>Woman</td>
<td>4</td>
<td>4.37 × 10^3</td>
</tr>
</tbody>
</table>

of this group of patients was compared to that of the smaller group who were receiving oral anticoagulants, it appeared that the anticoagulants had not influenced the patients' greater variance. Four patients, three men and one woman, died of recurrent coronary events while the study was being conducted. The fibrinogen variances of four tests in these patients were then compared with variances of four surviving patients of similar age and sex in table 5. Although this represents a small number of patients, it is interesting to note that each variance was consistently greater for the individuals who died than for those who survived.

Discussion

More than 100 years ago Rokitansky postulated that a primary pathological process in atherogenesis is the deposition of fibrin on the endothelial wall of the affected artery. His hypothesis was revived 10 years ago by Duguid. The theory proposes that the vascular endothelial cells are stimulated to overgrow the fibrin deposits. As this layering process proceeds, lipid is deposited in the mural substance.

Astrup's data have suggested the hypothesis that the dynamic process of production, endothelial coating, and the final breakdown by the inherent fibrinolytic system is altered in the direction of fibrin formation in atherosclerosis and that the plasma level of fibrinogen at any given moment may reflect a balance between the two opposing processes.

Atencio and Reeve found a relatively rapid rate of fibrinogen catabolism in animals which was proportional to their ages with the younger animals having an increased rate. McFarlane and co-workers, on the other hand, observed a relatively constant catabolic rate of fibrinogen in man even in the presence of wide pathological fluctuations in the circulating mass of the protein. He included, however, no individuals with coronary artery disease in his study.

The observation that fibrinogen levels in individuals without coronary artery disease increased with age has been confirmed by this study. The documentation of a previous myocardial infarction in our patients appeared to impose a further elevation of the mean fibrinogen level irrespective of their age. The absolute difference in mean fibrinogen levels between the coronary group and the healthy group was greatest among patients less than 50 years of age.

Anticoagulation of the coronary patients did not significantly lower the greater mean variance in the patient group. Lewis and associates did not find any changes in the
plasma disappearance of fibrinogen in dogs receiving anticoagulant therapy. Nakamura and associates\textsuperscript{12} investigated the plasma fibrinogen levels in a group of patients with coronary thrombosis who were receiving long-term anticoagulant therapy and found that the therapy did not affect the raised fibrinogen level which follows a myocardial infarction.

Amris and Amris\textsuperscript{13} in their study of the turnover and distribution of human fibrinogen in a group of patients included one woman with coronary occlusion. They found that her "fibrin pool" was greater than that of any other patient studied. The "fibrin pool" represented the sum of total fibrinogen plus fibrin generated in an individual from zero time and appeared to correlate well with the rate of turnover. They suggested that the greater the "fibrin pool" the longer before equilibrium of the plasma fibrinogen level is reached.

The variability of the fibrinogen level in addition to reflecting an unstable balance of the coagulation mechanism may also be of prognostic significance. Four patients who died of documented recurrent coronary events during the 3-year period of observation had fibrinogen variances greater than those of patients of comparable age and sex who survived.

Summary

Plasma fibrinogen determinations in 46 coronary patients and 49 healthy individuals were made over a period of about 33 months. The mean fibrinogen levels were calculated and shown to increase with age. The fibrinogen levels in the younger patient group were elevated and resembled the levels of the older control subjects. The statistical test of the variance was significantly greater in the patient group. The inclusion of episodes of infections, bleeding, and surgery, all of which are known to raise the plasma fibrinogen levels, did not significantly alter the greater fibrinogen variance in the patient group. Comparison of a group of patients receiving anticoagulant orally to a group not receiving the drugs failed to indicate that the anticoagulants restored the lower variance seen in the controls. Of the four patients whose deaths were documented as due to recurrent coronary events, all had greater fibrinogen variances than a comparable group of patients who survived. The fibrinogen variance may not only reflect an unstable clotting mechanism in patients with coronary thrombosis but may also have prognostic significance for the recurrence of myocardial infarction.

References

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