Thromboelastographic Studies in Cerebral Infarction

BY MILTON G. ETTINGER, M.D.

Abstract: Thromboelastographic Studies in Cerebral Infarction

Blood coagulability in patients following cerebral infarction was studied utilizing the thromboelastograph (TEG). Cerebral infarction patients from two separate institutions were studied within 24 to 48 hours after onset of stroke. Ninety-four stroke patients from one institution and 109 from another yielded a total stroke population of 203 patients for this study. Fifty-nine age-matched normals were used as a control group. Frequency distribution curves were determined for a TEG ratio of ma/(r + k). The 59 controls exhibited a normal frequency distribution between the values of 1.6 and 4.0. Both groups of stroke patients revealed an increased number of patients with a ratio exceeding 4.0, suggesting a hypercoagulable state exists following cerebral infarction in approximately 29% to 38% of the patients studied.

Additional Key Words
- Clot lysis
- Hypercoagulability
- Fibrinolysis
- Platelet function
- Cerebrovascular disease

Our laboratory has been investigating abnormalities of blood clotting, clot lysis and platelet function in various categories of cerebrovascular disease. One of our objectives has been to identify a simple, reliable and clinically relevant test of blood or plasma which accurately identifies the overall consequences of the separate, yet simultaneously occurring reactions, which collectively result in the balance between clot formation and clot dissolution. A number of "global" tests of coagulation have been described, including the plasma recalcification test, partial thromboplastin time (PTT), the activated partial thromboplastin time, and the whole blood clotting time. All have their limitations with respect to reliability, sensitivity, and lack of correlation with clinically significant clotting or bleeding events. A somewhat different approach to a laboratory measurement of overall coagulation and fibrinolysis, which also is sensitive to platelet dysfunction, has been the development of the thromboelastograph.

The thromboelastograph (TEG) provides a continuous recording of the process of blood coagulation and subsequent clot retraction. The instrument is capable of analyzing three blood samples simultaneously (fig. 1). Stainless steel sample containers maintained at 37°C are set in motion around a vertical axis. A cylindrical dragbar is lowered into the slowly oscillating metal containers and remains immobile as long as the blood or plasma sample is fluid. As the clot forms, the dragbar, suspended by the torsion wire, becomes dynamically coupled to the cup resulting in transmission of the oscillatory rotation of the cup to the cylinder. The cylinder then oscillates with an amplitude governed by the specific mechanical properties of the clot (fig. 2). A mirror, coupled to the cylinder torsion wire, reflects light from an internal source, both to a graduated scale and to a constant-speed photographic film. The spot of light reflected from the mirror moves from left to right of the initial stationary (unclotted) position, the distance traveled in each direction being related to the oscillation of the cylinder. The photographic paper, activated at a point in time prior to the appearance of any oscillatory movement, gives rise to a "tuning fork" silhouette of a developed thromboelastogram (fig. 3).

The following measurements can be made from the resulting thromboelastogram: reaction time (r), clotting speed (k), and maximum amplitude (ma). Hypercoagulability is associated with smaller values for r and k and an increase in ma. Our results are reported as a ratio [ma/(r + k)]; thus larger values, as compared with controls or normals, reflect hypercoagulability (fig. 4).

Methods

This study of thromboelastography in patients with cerebral infarction was performed in two separate populations of stroke patients who were compared with an age-matched "control" group. One hundred nine patients with cerebral infarction were studied at the Hennepin County General Hospital and 94 patients with cerebral infarction were drawn from successive admissions to the University of Minnesota Hospitals (Minneapolis, Minnesota). The "old" normals were from the control group of patients being utilized as age-
Hemorrhage, were excluded, as were patients suspected of harboring hematomas and/or hemorrhagic infarctions. The blood samples were drawn from an antecubital vein in the morning following admission and with the patient in a fasting state. Citrated plasma (0.3 cc) was introduced by a siliconized pipette into a TEG cuvette and allowed to warm for one minute. Then 0.1 cc of 1.29% calcium chloride was added by means of a tuberculin syringe. The pin was adjusted and the cuvette covered with one drop of paraffin oil to avoid evaporation and the sample was run for 24 hours. Timing began with the addition of the calcium chloride. Results were reported as measured values for r, k, and ma, as well as the value of the ratio of ma/(r + k).

The age distribution of the control group and the two stroke groups were analyzed (table 1). It can be noted that the University stroke patients contained a slightly larger number of younger patients (under 55 years) than the other two population groups, but they were reasonably comparable with respect to distribution of age.

**Results**

The values for the TEG ratio of ma/(r + k) were analyzed with respect to frequency distribution between the range of 1.5 and 4.0 (table 2). These values indicate a larger number of stroke patients in both stroke groups with values exceeding 4.0 (29% and 38%), as contrasted with the 12% incidence exceeding a value of 4.0 in the control group. This study suggests that the TEG identified a hypercoagulable state in 29% to 38% of patients with cerebral infarction during the first few days following the ictus.

The difference between the control values and each Stroke Group was statistically significant (table 2).

**Discussion**

Patients with cerebral infarction have been studied with a variety of tests in an attempt to identify specific abnormalities of coagulation, lysis and platelet function. The credibility of the test method utilized in this investigation is a matter of singular importance. Since the first publication on thromboelastography by Hartert in 1947, TEG has been extensively utilized by coagulation laboratories throughout the world. In a
study of patients receiving 600 mg of aspirin, Hawkins\(^1\) made the following statement: "The results indicate that the thromboelastograph may provide a measure of hemostasis comparable to that provided by the small puncture wounds in bleeding time tests. Bleeding time tests are comparatively crude, the scatter of results from one healthy individual is large, and the tests are not sensitive to minor disorders. Standardization of the procedures is often difficult and the results depend upon operator technique. Thromboelastography is a more easily standardized procedure and reproducible results can be obtained." Brewer,\(^2\) in a study of 76 patients on long-term anticoagulation, observed: "Because of the difficulty in assaying each element which is altered by a drug therapy (anticoagulation), and because we are interested in the summary effect of all these changes on the coagulation mechanism, thromboelastography appears to be the ideal tool for evaluation of the one-stage prothrombin time as an adequate measure for the control of this anticoagulant therapy. The thromboelastograph designed by Hartert provides more information from fibrin formation than does any other method. This instrument can record continuously and simultaneously fibrin formation of three blood or plasma specimens and provide a permanent record photokymographically." Other studies utilizing thromboelastography for the study of overall coagulation abnormalities are reported by Rosato et al.,\(^3\) Sicuteri and co-workers,\(^4\) and Fisch and his colleagues.\(^5\) Kimche and Eisenkraft\(^6\) had sufficient confidence in the clinical relevance of the TEG data to administer a proteinase inhibitor and low-molecular-weight dextran for the treatment of postoperative thromboemboli on the basis of abnormal TEG data, and to utilize daily TEG studies as an index of adequate treatment.

The literature contains a mixture of negative and positive reports concerning attempts to identify abnormalities of coagulation in the systemic circulation in patients with cerebral infarction. Examples of negative reports include an analysis of plasma fibrinolytic activity following cerebral infarction in 20 patients who were studied 16 to 48 hours after onset of illness. In marked contrast to patients with myocardial infarction where the same authors had previously described an elevated plasma fibrinolytic activity five to eight hours after myocardial infarction, which was depressed 16 to 48 hours following onset of illness, the acute studies of fibrinolytic activity in these stroke patients did not differ significantly from controls.\(^7\) Gaston et al.\(^8\) described abnormalities in blood fibrinogen, factor VIII, prothrombin, platelet factor 3, and PTT tests. He felt that these abnormalities were of no clinical significance because similar changes could be noted in the blood of healthy subjects of essentially the same age range. The most recent negative study was presented by Todd and colleagues,\(^9\) who reported on coagulation studies in 87 normal controls, 33 patients with thrombotic stroke, and 55 patients.

### Table 1

#### Age Distribution in Control and Patient Groups

<table>
<thead>
<tr>
<th>Age</th>
<th>'Old' normals</th>
<th>HCGH CVA pts.</th>
<th>Univ. CVA pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 55</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>55 - 59</td>
<td>3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>60 - 64</td>
<td>4</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>65 - 69</td>
<td>17</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>70 - 74</td>
<td>19</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>75 - 79</td>
<td>9</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>80 - 84</td>
<td>3</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>85 +</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

*HCGH = Hennepin County General Hospital.
†Univ. = University of Minnesota Hospitals.

### Table 2

#### Distribution of TEG Ratio \(\text{na}/(r + k)\) in Control and Patient Groups

<table>
<thead>
<tr>
<th>TEG values</th>
<th>Controls</th>
<th>HCGH pts.</th>
<th>Univ. pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>&lt; 1.5</td>
<td>5</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>1.5 - 1.9</td>
<td>6</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>2.0 - 2.4</td>
<td>7</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>2.5 - 2.9</td>
<td>18</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>3.0 - 3.4</td>
<td>9</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>3.5 - 3.9</td>
<td>7</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>4.0 +</td>
<td>7</td>
<td>12</td>
<td>41</td>
</tr>
</tbody>
</table>

*HCGH = Hennepin County General Hospital.
†Univ. = University of Minnesota Hospitals.
\(\text{IP} < 0.001.\)
\(\text{II} < 0.01.\)
with diabetes mellitus in the same age distribution (50 to 80 years). They identified no significant differences in their test values imposed by sex or age variables. Twenty-seven tests of clotting were performed on each blood specimen. Significant differences were detected between normals and patients with stroke in the following studies: fibrinogen level, glass clotting time, silicone clotting time, heparin tolerance, platelet count, and retarded thromboplastin generation tests (TGT). Significant differences between normals and diabetics were noted in the following tests: prothrombin time, silicone clotting time, platelet count, TGT, and retarded TGT. The clinical significance of these differences is not of practical value in the diagnosis or as a guide to therapy of stroke, in the opinion of the authors.

In contrast, both Hume and Mathur and colleagues noted elevations in fibrinogen and low fibrinolytic activity in patients with cerebral infarction, which they consider of clinical significance. Bang and McDowell have reported 22 patients who had been studied by in vitro coagulation tests. Ten of these patients revealed evidence of accelerated coagulation in all three phases of intrinsic clotting tests. Thromboembolic episodes, thrombophlebitis, or pulmonary embolus were apparent or suspected on clinical grounds in six of these patients. The remaining 12 patients exhibited the paradoxical picture of bleeding tendency with clinical in vitro evidence of defibrinogen.

Mittal et al. reported on 19 patients with cerebral infarction, all of whom were studied within 72 hours of onset of symptoms. Plasma fibrinogen levels were characteristically elevated after an acute episode of cerebral infarction and were noted to rise from the second day on reaching peak values by the sixth or seventh day and thereafter declining toward normal. Values for fibrinogen are generally lower than those observed following myocardial infarction, but significantly higher than controls. The blood fibrinolytic activity was significantly lower in patients with cerebral infarction than in controls or in myocardial infarction patients.

Recently Bilger and colleagues have described abnormalities of soluble fibrinogen, plasminogen, plasminogen activator, fibrinogen, partial thromboplastin time, generation of thromboplastin, and fibrin degradation products in a group of 406 patients suffering from recent ischemic-thrombotic cerebrovascular disease. These patients were compared with an age-matched group of 115 for risk factors which would separate the stroke-prone individuals from the healthy population. Utilizing four primary risk factors (thromboplastin time, soluble fibrin, fibrinogen, and plasminogen activator) in a discriminate function analysis, 93.2% of the patients were correctly classified, suggesting that abnormalities of coagulation and lysis are indeed possible parameters of significance in prospective and retrospective studies of cerebrovascular disease.

This study demonstrates that thromboelastographic values in patients with recent cerebral infarction suggest a hypercoagulable state exists for some period of time in 29% to 38% of the stroke patients, as contrasted with 12% of the age-matched normal control group. The next phase of this study is assessment of the possible clinical relevance of these observations. If, as is suggested by others, these TEG abnormalities do correlate with clinically significant vascular events, such as thrombophlebitis, pulmonary embolism, etc., then a relatively simple and reliable laboratory test to identify patients who are in danger of developing these complications has been identified. Appropriate therapy to prevent the clinical complications noted is available and can be utilized in a prophylactic sense as described in the paper by Kimche and Eisenkraft.

Summary

The thromboelastograph was used to study coagulation abnormalities in patients with acute cerebral infarction. The two study groups consisted of 94 and 109 stroke patients. These were compared with 59 age-matched normals who were used as a control group. Frequency distribution curves were determined for the TEG ratio of ma/(r + k) in all three groups. The controls demonstrated 12% with a ratio in excess of 4.0 and a normal distribution of values between 1.5 and 4.0. Both stroke groups revealed an increased frequency of patients with a ratio exceeding 4.0 and a skewed curve toward the higher values, suggesting a hypercoagulable state existed following cerebral infarction in 29% to 38% of the patients studied, during the period of study. The possible therapeutic implications of such observations have been discussed and will be explored in future studies.

Acknowledgments

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References

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