Hematologic Abnormalities Occur in Both Cortical and Lacunar Infarction

Trevor J. Kilpatrick, MB, BS, PhD, FRACP; Zelco Matkovic, MB, BS; Stephen M. Davis, MD, FRACP; Catherine M. McGrath, MB, BS, FRCPA; Raymond J. Dauer, BAppSc

Background and Purpose: Primary hematologic abnormalities are a rare but established cause of ischemic stroke. In addition, activation of hemostatic parameters is often present during the acute phase of stroke. However, it is uncertain whether these abnormalities occur in both cortical and lacunar infarction; this study aimed to further assess this issue.

Methods: Hematologic parameters (prothrombin, activated partial thromboplastin, thrombin clotting, and euglobulin lysis times; and fibrinogen, fibrinopeptide A, antithrombin III, protein C, protein S, and plasminogen levels) were measured in 19 patients within 48 hours of the onset of acute cerebral infarction. These patients included 10 with cortical infarcts and 9 with lacunar infaracts, as determined by standard clinical and radiological criteria.

Results: Five patients with lacunar infarction and 7 patients with cortical infarction demonstrated raised fibrinopeptide A levels, indicating enhanced thrombin activity. Fibrinolysis, assessed by the euglobulin lysis time, was impaired in 6 of 9 patients with lacunar infarction and in 2 of 10 patients with cortical infarction. Lupus anticoagulants were detected in 3 patients with lacunar infarction and in 1 patient with cortical infarction. Three patients in each group displayed decreased antithrombin III function, and 1 patient with a lacunar infarction had a low protein C level.

Conclusions: Primary hematologic disorders and secondary hemostatic derangements may occur in patients with either cortical or lacunar infarction. (Stroke. 1993;24:1945-1950.)

Key Words • cerebral infarction • hemostatics • lacunar infarction

O f the recognized subtypes of ischemic stroke, cortical infarction is the most common and is usually caused by atherothrombosis or thromboembolism, due chiefly to large-vessel and cardiac disease. In contrast, lacunar infarction, which accounts for approximately 15% of ischemic strokes, is due to occlusion of single, deep penetrating branches of the large cerebral arteries and is widely postulated to be caused by either lipohyalinosis or microatheroma. However, the etiology of lacunar infarction remains controversial, and occasionally either small emboli,dissection of a small artery, or hemodynamic factors have been implicated.

In adults, an estimated 1% to 4% of cases of ischemic stroke are due to primary hematologic disorders. These include the antiphospholipid antibody syndrome, hereditary deficiencies of coagulation inhibitors, abnormalities of fibrinolysis (plasminogen deficiency, abnormalities of tissue plasminogen activation, dysfibrinogenemia), thrombocytosis and qualitative platelet abnormalities, and erythrocyte disorders including polycythemia and paroxysmal nocturnal hemoglobinuria. Although these primary hematologic disorders are uncommon causes of ischemic stroke, other hemostatic derangements, which have often been assumed to occur as secondary phenomena, have been more frequently identified. These abnormalities include enhanced fibrin formation (enhanced thrombin activity), abnormal fibrinolysis, and disturbed platelet function. Although these abnormalities could also be relevant to the etiology of ischemic stroke, enhanced thrombin activity also occurs in cerebral hemorrhage, suggesting that the enhancement may be caused by the nonspecific release of procoagulants from damaged cerebral tissue. Whatever its cause, enhanced thrombin activity may influence the progression of ischemic stroke by inducing the propagation of thrombus at the site of vascular occlusion. Moreover, the magnitude of the hemostatic abnormalities identified after a stroke may reflect the extent of tissue damage and likely prognosis.

It is uncertain whether the same spectra of hemostatic derangements occur in all types of ischemic stroke and, specifically, in both cortical and lacunar infarction. Previous studies suggest that these derangements may be confined to cortical infarction, although in some of these studies the comparison was based on post hoc analysis. In one prospective comparison, cross-linked d-dimer levels were raised at 48 hours in patients with lacunar infarction in comparison to control subjects, raising the possibility of an imbalance between

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thrombotic activity and fibrinolysis in this stroke subtype, but the difference did not reach statistical significance. Thus, further study of this issue is warranted, and its clarification could have implications for the application of therapeutic strategies, such as thrombolytic therapy, in the various subtypes of ischemic stroke. Given this background, we assessed hemostatic function in a group of 19 patients presenting with either acute lacunar or cortical infarction.

Subjects and Methods

Nineteen consenting, nonconsecutive patients with acute cerebral infarction admitted to the Royal Melbourne Hospital were studied during 1988 to 1990. Patients with transient ischemic attacks were excluded from the study.

A detailed history, including time of stroke onset, prior history of smoking, hypertension, diabetes, myocardial infarction, malignancy, and surgery, was obtained (Tables 1 and 2). Preexisting therapy with either antiplatelet agents or warfarin was recorded. A full neurological examination was performed. Cerebral computed tomography (CT) was performed in all patients and was reported by a neuroradiologist. Cerebral digital subtraction angiography, carotid Doppler ultrasound, and echocardiography were performed when clinically appropriate.

Strokes were classified according to accepted clinical and radiological criteria, as assessed by two neurologists and a neuroradiologist, as either lacunar or cortical cerebral infarcts. A diagnosis of lacunar infarction was made if the clinical deficit consisted of pure motor hemiplegia, pure sensory stroke, motor-sensory stroke, ataxic hemiparesis, or the dysarthria–clumsy hand syndrome, in the absence of visual field defects or abnormal cortical signs (see below) and with cerebral CT either normal or compatible with a small (less than 15 mm) deep infarct. A diagnosis of cortical cerebral infarction was made if there were cortical signs such as either apraxia, aphasia, cortical sensory function abnormalities, or neglect and if cerebral CT was either normal or showed features of acute cortical infarction. Patients who had intracranial hemorrhage were excluded from the study. In addition, patients with a history of either myocardial infarction, surgery in the 6 months before the stroke, or malignancy were excluded. The clinical features of patients with either infarct type are compared in Tables 1 and 2; other clinical differences between the two groups (for example, differences in blood pressure at presentation) were not observed. The patients studied represented a random sample of the 45 patients with lacunar infarcts and 240 patients with cortical infarcts who were admitted to the Royal Mel-

<table>
<thead>
<tr>
<th>Table 1. Clinical Features of Patients With Cortical Infarcts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt/Age, y/Sex</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>1/15/F</td>
</tr>
<tr>
<td>2/41/F</td>
</tr>
<tr>
<td>3/81/M</td>
</tr>
<tr>
<td>4/90/F</td>
</tr>
<tr>
<td>5/55/M</td>
</tr>
<tr>
<td>6/75/F</td>
</tr>
<tr>
<td>7/80/M</td>
</tr>
<tr>
<td>8/63/M</td>
</tr>
<tr>
<td>9/62/F</td>
</tr>
<tr>
<td>10/85/F</td>
</tr>
</tbody>
</table>

Pt indicates patient; DM, diabetes mellitus; HT, hypertension; CT, computed tomography; OC, oral contraceptive; MVD, mitral valve disease; AF, atrial fibrillation; MS, mitral stenosis; MCA, middle cerebral artery; DSA, digital subtraction angiography; IV, intravenous; and NAD, no abnormality detected.
Kilpatrick et al  Hemostatic Function in Cerebral Infarction  1947

Table 2. Clinical Features of Patients With Lacunar Infarcts

<table>
<thead>
<tr>
<th>Pt/Age, y/Sex</th>
<th>Past History</th>
<th>Neurological Findings</th>
<th>Head CT Scan (Timing of CT)</th>
<th>Other Investigations and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/60/M</td>
<td>- + +</td>
<td>Left pure motor hemiparesis</td>
<td>Lacune in anterior limb of internal capsule (day 1)</td>
<td>...</td>
</tr>
<tr>
<td>2/92/M</td>
<td>- + +</td>
<td>Right pure motor hemiparesis</td>
<td>Bilateral deep white matter low-attenuation areas (day 3)</td>
<td>...</td>
</tr>
<tr>
<td>3/78/F</td>
<td>- + +</td>
<td>Dysarthria–clumsy right hand</td>
<td>Bilateral deep white matter low-attenuation areas (day 2)</td>
<td>...</td>
</tr>
<tr>
<td>4/63/M</td>
<td>- + +</td>
<td>Right hemichorea</td>
<td>Left caudate nucleus infarct (day 1)</td>
<td>Aspirin and clonazepam</td>
</tr>
<tr>
<td>5/80/M</td>
<td>- + +</td>
<td>Left pure motor hemiparesis</td>
<td>Bilateral lacunar infarcts (day 3)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>6/58/F</td>
<td>- + +</td>
<td>Left pure motor hemiparesis</td>
<td>Bilateral lacunar infarcts (day 1)</td>
<td>IV heparin followed by aspirin</td>
</tr>
<tr>
<td>7/61/F</td>
<td>+ + -</td>
<td>Dysarthria, right ataxic hemiparesis</td>
<td>Normal (day 2)</td>
<td>Aspirin</td>
</tr>
<tr>
<td>8/80/F</td>
<td>- - +</td>
<td>Left pure motor hemiparesis</td>
<td>Normal (day 1)</td>
<td>Carotid Doppler: left internal carotid artery, 50% stenosis</td>
</tr>
<tr>
<td>9/56/M</td>
<td>+ + +</td>
<td>Left pure motor hemiparesis</td>
<td>Lacunes bilaterally in posterior limb of internal capsule (day 2)</td>
<td>Carotid Doppler: NAD</td>
</tr>
</tbody>
</table>

Pt indicates patient; DM, diabetes mellitus; HT, hypertension; CT, computed tomography; IV, intravenous; and NAD, no abnormality detected.

Bourne Hospital within the study period and who met the entry criteria.

Hemostatic function was measured within 48 hours of admission to the hospital (Table 3) before the use of antithrombotic agents; for selected patients, it was repeated 1 week later. Blood samples were obtained between 9 AM and 12 noon to control for possible circadian fluctuation in hemostatic function. Blood was drawn from an antecubital vein via a 21-gauge butterfly needle. The first 5 mL of blood was discarded. Venous blood (4.5 mL) was added to tubes containing either 0.5 mL of 3.8% trisodium citrate or a solution that also contained citrate 32 g/L, heparin 1000 U/mL, and aprotonin 1000 U/mL and was then mixed. A blood pressure cuff was then applied to the opposite arm, and a pressure midway between systolic and diastolic pressure was maintained for 10 minutes, after which an additional 5-mL venous blood sample was obtained. The specimens were centrifuged for 15 minutes at 3000 rpm at 5°C. The supernatant plasma was pipetted into a 5-mL plain tube and either analyzed directly or stored at −70°C before analysis. All laboratory tests were performed without access to the clinical data.

The euglobulin lysis time (ELT) was performed on specimens both before and after venous occlusion. The remaining coagulation tests were performed on precocclusion specimens and included the prothrombin time, activated partial thromboplastin time, thrombin clotting time, and fibrinogen concentration. Plasminogen levels were obtained with the Stachrom-PLG kit.

To detect the lupus anticoagulant, the activated partial thromboplastin time was performed on filtered plasma specimens, and, if abnormal, mixing tests were performed. The dilute thromboplastin test (tissue thromboplastin inhibition test) and dilute Russell’s viper venom time were also performed. The kaolin clotting time was performed if the above lupus screen was equivocal. The concentration of protein S in plasma was quantitatively measured by electroimmunodiffusion using the Assera-plate (STAGO) Protein S kit.

Protein C was measured using the chromogenic assay (Stachrom Protein C kit) and, if abnormal, a protein C antigen assay was performed (Assera-plate Protein C kit). Similarly, antithrombin III functional activity was measured by a chromogenic assay (Dade Baxter antithrombin III), and, if abnormal, an antigen assay was determined by radial immunodiffusion (Behring). Fibrinopeptide A (Fpa) levels were determined quantitatively by an enzyme immunoassay using the Asserachrom Fpa kit. Bentonite treatment was performed to remove all the fibrinogen from the plasma.

The hemostatic parameters for each patient were compared with the normal reference range used at the Royal Melbourne Hospital. These reference values were derived from analysis of blood taken from laboratory staff and normal blood donors (n>50), with the
CT showed a discrete, small acute infarct in the contralateral caudate nucleus. This infarct occurred in a territory supplied by a small, penetrating artery and has been considered to represent a likely lacunar syndrome.\textsuperscript{30} Six of the other patients had lacunar infarcts on CT scanning (multiple in 4 patients), and 2 had normal CT scans. One patient with a stuttering onset of hemiplegia received heparin therapy. Four patients were treated with aspirin. No other specific therapy was administered.

Laboratory testing detected hemostatic abnormalities in 16 patients. FpA values above 3 ng/L were considered abnormal and indicative of enhanced thrombin activity. Five patients with lacunar infarction had abnormal FpA levels on initial testing (4 with levels of 10 or greater), and the mean level was also significantly elevated (mean±SD, 14.9±12.2 ng/L). Four of the patients with abnormal values had repeat testing 1 week after infarction, and 3 had persistently elevated levels (mean±SD, 5.0±2.5 ng/L). Abnormal FpA values were also detected in 7 of the patients with cortical infarcts (mean±SD, 13.3±17.2 ng/L). After 7 days, FpA values were reassessed for 3 of these 7 patients, and the levels were still elevated (mean±SD, 17.2±12.9 ng/L). The initial FpA levels were similar in both infarct types (P=.86) and were significantly different from the published reference range (0.5 to 2.5 ng/L; n=25; P<.05).\textsuperscript{29} It remained theoretically possible, however, that FpA levels were also elevated in age-matched control subjects in comparison to the literature reference range. To address this possibility, we analyzed FpA levels in 9 age-matched control subjects and found the mean±SD value to be 2.9±2.1 ng/L; 4 patients with lacunar infarcts and 6 with cortical infarcts had elevated FpA values outside this range. The differences between the mean FpA level for the control group and the lacunar and cortical infarct groups also approached statistical significance (P=.09).

The ELT (after occlusion) was used as a marker of impairment of fibrinolysis. On initial testing, 6 of 9 patients with lacunar infarction and 2 of 10 patients with cortical infarction had increased ELT. The mean values for the two cohorts were not significantly different (lacunar infarct group, 138.3±84 minutes; cortical infarct group, 84±60 minutes; P=.12). Of the 4 patients with abnormal fibrinolysis on initial testing who were reevaluated, 2 had repeat levels within the normal range 1 week after infarction and 1 had a normal level by 6 weeks after infarction.

Lupus anticoagulants were detected in 3 patients with lacunar infarcts and in 1 patient with a cortical infarct. Three patients with lacunar infarcts and 3 patients with cortical infarcts had decreased antithrombin III function. One patient with a lacunar infarct, who was not given warfarin, had a low protein C level, and plasminogen deficiency was detected in 1 patient.

**Discussion**

A number of previously reported studies have documented aberrations of hemostatic parameters in acute stroke. Shah et al\textsuperscript{113} documented raised levels of the platelet release proteins platelet factor 4 and β-thromboglobulin in patients with cortical infarction. Feinberg et al\textsuperscript{114} reported elevated concentrations of FpA and cross-linked d-dimer in the first month after cortical

### Table 3. Results of Hemostatic Function on Admission in Patients With Acute Cerebral Infarction

<table>
<thead>
<tr>
<th></th>
<th>Normal Range</th>
<th>Lacunar Infarction (n=9)</th>
<th>Cortical Infarction (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PT, s</strong></td>
<td>11.0-15.0</td>
<td>13.3±1.8</td>
<td>12.6±1.1</td>
</tr>
<tr>
<td><strong>APTT, s</strong></td>
<td>26.0-37.0</td>
<td>29.4±3.0</td>
<td>29.9±3.7</td>
</tr>
<tr>
<td><strong>TCT, s</strong></td>
<td>11.0-14.0</td>
<td>13.4±1.5</td>
<td>14.6±1.3</td>
</tr>
<tr>
<td><strong>Fibrinogen, g/L</strong></td>
<td>2.0-5.0</td>
<td>3.9±1.1</td>
<td>4.1±1.2</td>
</tr>
<tr>
<td><strong>Antithrombin III, %</strong></td>
<td>80-120</td>
<td>88.5±14.6</td>
<td>93.0±25.6</td>
</tr>
<tr>
<td><strong>Plasminogen, %</strong></td>
<td>80-120</td>
<td>100.0±17.3</td>
<td>113.6±12.1</td>
</tr>
<tr>
<td><strong>Protein C function, %</strong></td>
<td>50-150</td>
<td>77.8±48</td>
<td>79.1±25</td>
</tr>
<tr>
<td><strong>Protein S antigen, %</strong></td>
<td>70-140</td>
<td>115.5±18</td>
<td>122.6±20.4</td>
</tr>
<tr>
<td><strong>ELT prestress, min</strong></td>
<td>120-240</td>
<td>193±83</td>
<td>205±68</td>
</tr>
<tr>
<td><strong>ELT poststress, min</strong></td>
<td>40-120</td>
<td>138.3±84</td>
<td>84±60</td>
</tr>
<tr>
<td><strong>Fibrinopeptide A, ng/L</strong></td>
<td>&lt;3</td>
<td>14.9±12.2t</td>
<td>13.3±17.2t</td>
</tr>
</tbody>
</table>

Values in patients are mean±1 SD. Hemostatic parameters were measured, as described in “Subjects and Methods,” in patients with either cortical or lacunar infarction within 48 hours of stroke onset. PT indicates prothrombin time; APTT, activated partial thromboplastin time; TCT, thrombin clotting time; and ELT, euglobulin lysis time.

*One patient with a high protein C level (380%) was excluded from this analysis.

1P<.05 significantly different from reference laboratory range for both lacunar and cortical infarction groups.

Results

There were 10 patients with cortical cerebral infarction: 4 men and 6 women, with a mean age of 64.7 years (range, 15 to 90 years) (Table 1). One patient had a prior stroke. Clinical neurological deficits indicated cortical cerebral infarction in all of these patients. In the 5 patients with abnormal CT scans, the sites of the acute infarcts identified were consistent with the clinical deficit. In the 5 patients with normal CT scans, the procedure was performed within 24 hours of admission and was not repeated.

Cardiogenic cerebral embolism was diagnosed in 3 patients, all of whom had atrial fibrillation and mitral valve disease. Two of these patients received heparin initially and later warfarin. Three patients, on the basis of either digital subtraction angiography or carotid Doppler ultrasonography, were diagnosed as having cerebral infarction due to large-vessel atherosclerotic disease. They were all treated with aspirin. Of one of these patients also had a carotid endarterectomy. For 3 patients, the cause of cerebral infarction remained undetermined.

A diagnosis of lacunar infarction was made in 9 patients (Table 2): 5 men and 4 women with a mean age of 69.8 years (range, 56 to 92 years). Six patients had pure motor hemiplegia, 1 had ataxic hemiparesis, and 1 had the dysarthria–clumsy hand syndrome. The ninth patient presented with acute hemichorea, and cerebral
infarction, and Fisher and Francis reported acutely elevated FpA and d-dimer levels in some patients. These studies did not, however, report hemostatic abnormalities in patients with lacunar infarcts. Recently, Takano et al. found that a majority of patients with either atherothrombotic or lacunar stroke exhibited plasma hypercoagulability, which was partially related to an increase in factor VII activity. However, in a subsequent study, it was found that thrombotic and fibrinolytic activities in patients with lacunar infarction did not differ significantly from those of control patients in the first 30 days after cerebral infarction.

Our data confirm that abnormalities of hemostatic function occur in cortical stroke but also suggest that enhanced thrombin activity may occur in lacunar infarction. We have identified elevated levels of FpA in patients with both cortical and lacunar infarction, and the results suggest that the activation of thrombin activity in lacunar infarction is at least as great as in cortical infarction. The reason why our study detected enhanced thrombin activity in patients with lacunar infarction, but previous studies have not, is not immediately apparent. It is possible that average infarct size differed between the studies, but previous reports have suggested that, at least for cortical infarction, there is no relation between stroke volume and FpA levels. The extent of the clinical neurological deficit and the stroke risk factor profile were not detailed in previous studies, but these factors are unlikely to explain the recorded differences. It has, however, been hypothesized that the pathogenesis of lacunar infarcts might reflect heterogeneous mechanisms, and this could potentially explain the variable results reported in these studies. For example, it could be that some lacunar infarcts arise secondarily to small emboli, and secondary thrombus could form around the occlusion site. Further, if hemodynamic factors are implicated, thrombus formation may represent the initial occlusive event. Alternatively, the release of thromboplastin from damaged parenchymal tissue may lead to enhanced thrombin activity if infarct size were to reach a critical volume. This is not to say that enhanced thrombotic activity is a phenomenon unique to ischemic stroke, as alterations in FpA levels have also been noted in post–acute myocardial infarction populations. Further, it is theoretically possible that some of the observed hemostatic abnormalities found in our study could have reflected the presence of comorbid vascular disease, for example, occult thrombotic disease such as deep venous thrombosis. This possibility cannot be absolutely excluded, but subjects were carefully selected to exclude those patients with a recent history of overt thrombotic events, which could have complicated the interpretation of the results.

We have also documented abnormal fibrinolytic activity in cerebral infarction, thus confirming previous studies that have established that thrombin activity outweighs fibrinolytic activity during the acute phase of ischemic stroke. However, in contrast to previously reported results, we identified abnormalities in fibrinolysis in patients with lacunar infarction as well as those with cortical infarction. The demonstration of abnormalities of fibrinolysis in stroke does not imply that they are specific to cerebral ischemia, because they have also been demonstrated in patients with myocardial infarction. These abnormalities have been previously attributed to either deficient levels of plasminogen activators or to the presence of plasminogen activator inhibitors, but without clear confirmatory evidence.

Significant abnormalities of both FpA and ELT levels were detected in some patients at 1 week after infarction. These results contrast with those documented after myocardial infarction, in which abnormal hemostatic parameters have been shown to normalize within 48 hours. This raises the possibility that infarcted brain itself may be responsible for the continued hemostatic activation that we and others have identified in stroke. However, these analyses were performed on a subset of those patients studied, and definitive conclusions with regard to this point await further, more extensive study.

The detection of the lupus anticoagulant and of protein C deficiency in some of the patients with lacunar infarction raises the possibility of primary hematologic abnormalities in these patients. However, given the small numbers of patients involved, it remains uncertain as to whether these abnormalities are positively associated with lacunar infarction.

These findings are of potential therapeutic significance. The role of thrombolytic therapy, aimed at inducing the reperfusion of acute infarcts, is currently under intensive study. The appropriate deployment of this pharmacologic intervention in stroke requires an understanding of the pathogenesis, the etiology, and the abnormalities of hemostasis that occur in the various subtypes of ischemic stroke. Our results indicate that hemostatic abnormalities may occur not only in cortical infarction but also in lacunar infarction. Thus, we recommend further study of hemostatic parameters in patients with lacunar infarction; to do so appropriately, it will be necessary to assess large numbers of patients and to compare the values obtained with appropriate control groups. These groups should include age-, sex-, and also risk factor–matched control subjects in addition to patients with systemic ischemic disease (eg, myocardial infarction or peripheral vascular disease) to further delineate how and when abnormalities of hemostasis are generated. If the findings of the current study are confirmed, they may indicate that enhanced thrombin activity is implicated in the pathogenesis, if not the underlying etiology, of lacunar infarction and hence may be an important determinant in the selection of patients for thrombolytic therapy.

Acknowledgments

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References


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