Intracerebral Hemorrhage in Stroke Patients Anticoagulated With Heparin

Viken L. Babikian, MD, Carlos S. Kase, MD, Michael S. Pessin, MD, Bo Norrving, MD, and Philip B. Gorelick, MD

To characterize the clinical features of patients with acute cerebral infarction who sustained intracerebral hemorrhage related to heparin anticoagulation, we describe 10 patients and review reports of 16 cases. Cardiac-source embolism was identified in seven (70%) of the 10 patients and consisted of atrial fibrillation in six of the seven. The middle cerebral artery territory was affected in nine patients (90%), with moderate-sized or large infarcts by clinical and computed tomographic criteria. The interval between stroke onset and intracerebral hemorrhage was <72 hours in 80% of the patients. Intracerebral hemorrhage occurred <24 hours after the time heparin was started in 80% of the patients. The activated partial thromboplastin time closest to the time of intracerebral hemorrhage was >2xcontrol in seven patients. Our findings in the 10 patients are similar to those of the 16 cases previously reported and suggest that heparin-related intracerebral hemorrhage occurs early after stroke onset, usually with moderate-sized or large infarcts, and with excessive anticoagulation in some patients. (Stroke 1989;20:1500-1503)

Patients with progressing stroke and cerebral embolism of cardiac origin are frequently anticoagulated with intravenous heparin to prevent further neurologic events. By binding to antithrombin III, heparin helps inhibit the conversion of fibrinogen to fibrin and prevents clot formation but also increases the risk of systemic and intracranial bleeding. Intracerebral hemorrhage (ICH) related to anticoagulation in patients with acute ischemic stroke has been associated with advanced age, hypertension, and large infarcts. This information, however, is derived from studies presenting only a few patients at times treated simultaneously with heparin and warfarin or heparin and dextran. In some instances, reports date from before computed tomography (CT scan), thus introducing uncertainty about the original diagnosis of cerebral infarction.

To further clarify the clinical features of ICH in heparin-anticoagulated patients with acute cerebral infarction, we describe 10 patients and review the cases of 16 others from previous reports.

Subjects and Methods

We reviewed stroke service records at our respective hospitals for patients with the clinical diagnosis of transient ischemic attacks (TIAs) or cerebral infarction who had intracerebral bleeding while receiving intravenous heparin. These patients were not selected as part of a prospective study and represent only a collection of case presentations. All 10 patients had CT scans on admission consistent with the diagnosis of cerebral ischemia; follow-up CT scans or postmortem examinations showed ICH in all. Patients were excluded if the admission CT scan showed intracerebral or subarachnoid hemorrhage, hemorrhagic infarction, trauma, brain tumor, or arteriovenous malformation. Patients were also excluded if they had known bleeding disorders, were being treated with warfarin at the time of ICH, had septic embolism, or did not satisfy the following laboratory criteria on admission: 1) prothrombin time within 1 second of control, 2) activated partial thromboplastin time (aPTT) within 3 seconds of control, 3) platelet count between 150,000 and 450,000/mm³, and 4) serum glutamic-oxaloacetic transaminase (SGOT) and alkaline phosphatase levels <2xcontrol. Cases from the literature also satisfied these criteria.

Data on the 10 patients were collected according to the following guidelines: 1) infarct or hemorrhage...
size was estimated according to the criteria outlined by the Cerebral Embolism Study Group: 1) cardiac function was assessed with electrocardiography in all and with echocardiography in two; 3) time of ICH was estimated by reviewing the medical record for the time of onset of new symptoms, which was taken to represent the onset of hemorrhage (when in doubt, the longest interval from stroke onset to ICH was chosen); and 4) aPTT closest to ICH was that obtained immediately before or after ICH diagnosis, depending on the available information. Neurologic and cardiac diagnoses were verified at postmortem examination in five of the 10 patients. The same guidelines were applied to the 16 cases from the literature.

Our 10 patients are analyzed in the following sections, and pertinent findings from all 26 patients are summarized in Table 1.

Results
Mean age of the 10 patients (four men, six women) was 68 (range 28–89) years. Eight patients (80%) had a history of hypertension. Blood pressure readings closest to ICH onset were >140/90 mm Hg in nine patients (90%), but only three patients (30%) had readings of >200/105 mm Hg. One patient’s blood pressure was 150/90 mm Hg when recorded 2 hours before onset of ICH symptoms, but it had increased to 200/110 mm Hg by 1 hour after onset of ICH.

All 10 patients sustained cerebral infarction, nine in the middle cerebral and the other in the posterior cerebral artery territory. Based on neurologic deficits and brain CT findings, the infarcts were estimated to be large in four patients (40%) and medium-sized in the other six. No patient presented with only TIAs.

A cardiac source for cerebral embolism was identified in seven patients (70%), consisting of nonvalvular atrial fibrillation in six and a patent foramen ovale concurrent with deep-vein thrombosis in the other. The remaining three patients had normal cardiac examinations and electrocardiograms. A two-dimensional echocardiographic study in one of the three and postmortem cardiac examination in another showed no cardiac sources for embolism.

The interval between stroke onset and ICH symptoms (Table 1) was <72 hours in eight patients (80%). For the other two, intervals of 4 and 6 days were recorded. The interval between onset of heparin anticoagulation and ICH was <24 hours in eight patients (80%). The remaining two bled 4 and 5 days after the onset of anticoagulation.

The method of heparin anticoagulation included an initial bolus of 5,000 or 7,000 units in seven patients, and anticoagulation in one patient was started with an intravenous drip without a preceding bolus. Information concerning the method of heparinization was not available in the other two patients. aPTTs closest to ICH were >2x control in seven patients (70%, Table 1). Evidence of systemic bleeding was detected in four patients: two had microscopic hematuria, one had mild epistaxis, and the other had guaiac-positive vomitus. None of these four patients required blood transfusions.

Noncontrast CT scans on admission showed hypodense areas or sulcal effacement consistent with cerebral infarction in two patients, but scans were either normal or showed no evidence of infarction in eight patients (80%). ICH, as documented by follow-up CT scan or postmortem examination, occurred in the areas of cerebral infarction in all 10 patients. The hematomas were large in seven patients (70%) and of moderate size in the other three. Intraventricular or subarachnoid extension of the hemorrhage was noted in six patients.

All 10 patients deteriorated neurologically following the onset of ICH. Medical management included treatment with protamine sulfate and discontinuation of heparin as well as measures to control intracranial pressure. Two patients had surgical evacuation of their hematomas, and both survived. Six patients (60%) died as a result of the ICH, five 1–3 days after onset. The sixth patient died on Day 8 after the stroke.

Discussion
ICH associated with heparin anticoagulation occurred ≤72 hours after stroke onset in eight (80%) of our 10 patients and in 11 (73%) of 15 cases from the literature (Table 1). Few patients bled after Day 3, but ICH occurred even after 11 days of treatment (Table 1). Our results also indicate that in a similarly high proportion of our patients (80%) and of previously reported cases (67%, Table 1), bleeding took place ≤24 hours after heparin was started, further emphasizing the relation between ICH and heparin anticoagulation. An increased incidence of ICH in stroke patients anticoagulated soon after symptoms of cerebral ischemia has been recognized, but the exact time of this complication after stroke onset was uncertain. After a review of personal cases and reports from the literature, Shields et al calculated that the mean interval from initiation of anticoagulant therapy to hemorrhage was approximately 6.6 days and suggested delaying the onset of anticoagulation for at least 4 days. Others have also reported delayed ICH after stroke and have recommended waiting 3 weeks before starting anticoagulation. Our results suggest, however, that the interval between cerebral infarction and ICH is shorter in the majority of patients with this complication.

All patients selected for this study presented with cerebral infarction. We did not identify patients with only TIAs who had ICH at our centers or on review of the literature. The infarcts were of moderate or large size in all patients, and ICH occurred predominantly in areas of infarcted brain tissue. Cerebral embolism was the stroke mechanism in seven (70%) of our 10 patients and in all 16 previously reported cases (Table 1). It should be noted,
however, that the Cerebral Embolism Study Group selected only patients with cardioembolic strokes. Embolic infarcts are known to undergo hemorrhagic transformation as part of their natural history, but their association with ICH is less well established. Fisher and Adams suggested that hemorrhagic infarction occurs after fragmentation and distal migration of the embolus, exposing damaged proximal capillary beds to reperfusion and resulting in extravasation of erythrocytes into infarcted tissue. Angiograms obtained early after cerebral embolism show that emboli undergo lysis and that arteries recanalize during the days following stroke onset. The conversion from pale to hemorrhagic infarct occurs ≤4 days after onset of symptoms in the majority of nonanticoagulated patients with cardioembolic embolism, an interval similar to the one we observed in our patients with ICH. We believe that hemorrhagic transformation of embolic infarction probably covers a wide spectrum of severity, with ICH representing its extreme form.

The 30-day mortality rate following spontaneous or hypertensive ICH has been estimated to be 20–30%. Six (60%) of our patients and nine (56%) of 16 previously reported cases died of complications of ICH. High mortality and morbidity rates and limitations of effective treatment once ICH has occurred highlight the need to identify potential risk factors for this complication of anticoagulant treatment. A history of hypertension and medium-sized or large infarcts were shared by the majority of our patients. These features have also been associated with ICH in previous studies.

### TABLE 1. Clinical and Laboratory Data for 26 Cases of Intracerebral Hemorrhage Associated With Heparin Anticoagulation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Infarct Size</th>
<th>Vascular territory</th>
<th>Cardiac findings</th>
<th>History of hypertension</th>
<th>CT findings at admission</th>
<th>Interval to intracerebral hemorrhage (hr)*</th>
<th>From stroke onset</th>
<th>From onset of anticoagulation</th>
<th>aPTT†</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>MM</td>
<td>Med MCA</td>
<td>AF</td>
<td>Yes</td>
<td>Negative</td>
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<td>7</td>
<td>3.9</td>
<td>Died</td>
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<td></td>
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<tr>
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<td>Lg MCA</td>
<td>AF</td>
<td>Yes</td>
<td>Negative</td>
<td>17</td>
<td>14</td>
<td>2.7</td>
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<tr>
<td>JV</td>
<td>Med MCA</td>
<td>AF</td>
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<td>Negative</td>
<td>22</td>
<td>6</td>
<td>4.7</td>
<td>Survived</td>
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<tr>
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<tr>
<td>PS</td>
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<td>AF</td>
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<td>Negative</td>
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<td>16</td>
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<td></td>
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<tr>
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<td>AF</td>
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<td>1.0</td>
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<tr>
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<td>AF</td>
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<td>84</td>
<td>2.6</td>
<td>Survived</td>
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<tr>
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<td>Med MCA</td>
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<td>Yes</td>
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<td>19</td>
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<tr>
<td>HF</td>
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<td>AF</td>
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<td>7</td>
<td>2.6</td>
<td>Died</td>
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<td></td>
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**From the literature**

- CESG 1
- CESG 6
- CESG 7
- CESG 4
- CESG 5
- CESG 6
- CESG 7
- CESG 8
- CESG 9
- Shields et al
- Drake and Shin
- Phillips and Heffman

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Infarct Size</th>
<th>Vascular territory</th>
<th>Cardiac findings</th>
<th>History of hypertension</th>
<th>CT findings at admission</th>
<th>Interval to intracerebral hemorrhage (hr)*</th>
<th>From stroke onset</th>
<th>From onset of anticoagulation</th>
<th>aPTT†</th>
<th>Outcome</th>
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<td>Med MCA</td>
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<td>3.9</td>
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<td>Lg MCA</td>
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<td>Died</td>
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<td>JV</td>
<td>84/M</td>
<td>Med MCA</td>
<td>AF</td>
<td>Yes</td>
<td>Negative</td>
<td>22</td>
<td>6</td>
<td>4.7</td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NW</td>
<td>65/M</td>
<td>Med PCA</td>
<td>AF</td>
<td>Yes</td>
<td>Negative</td>
<td>47</td>
<td>23</td>
<td>3.4</td>
<td>Survived</td>
<td></td>
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<tr>
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<td>28/F</td>
<td>Lg MCA</td>
<td>PFO</td>
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<td>Negative</td>
<td>27</td>
<td>16</td>
<td>1.9</td>
<td>Died</td>
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<tr>
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<td>Lg MCA</td>
<td>AF</td>
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<td>Negative</td>
<td>33</td>
<td>20</td>
<td>1.0</td>
<td>Died</td>
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<tr>
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<td>Positive</td>
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<td>124</td>
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<td>Died</td>
<td></td>
<td></td>
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<tr>
<td>TB</td>
<td>66/F</td>
<td>Med MCA</td>
<td>Normal</td>
<td>Yes</td>
<td>Negative</td>
<td>96</td>
<td>84</td>
<td>2.6</td>
<td>Survived</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF</td>
<td>65/M</td>
<td>Med MCA</td>
<td>AF</td>
<td>Yes</td>
<td>Negative</td>
<td>25</td>
<td>19</td>
<td>1.1</td>
<td>Survived</td>
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<td>MM</td>
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<td>Lg MCA</td>
<td>Normal</td>
<td>Yes</td>
<td>Positive</td>
<td>15</td>
<td>7</td>
<td>2.6</td>
<td>Died</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**From the literature**

- CESG 1
- CESG 6
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- CESG 4
- CESG 5
- CESG 6
- CESG 7
- CESG 8
- CESG 9
- Shields et al
- Drake and Shin
- Phillips and Heffman

**CT**, computed tomographic; F, female; M, male; Med, medium; Lg, large; MCA, middle cerebral artery; PCA, posterior cerebral artery; AF, atrial fibrillation; PFO, patent foramen ovale; RHD, rheumatic heart disease; MVP, mitral valve prolapse; AMI, acute myocardial infarction; MVS, mitral valve stenosis.

*In Cerebral Embolism Study Group (CESG) studies* to computed tomogram with bleeding were provided.

†aPTT, activated partial thromboplastin time closest to onset of intracerebral hemorrhage expressed as patient to control ratio.
Excessively intense anticoagulation characterized by aPTT values >2×control was noted in seven (70%) of our 10 patients and in at least 11 (69%) of the 16 cases from the literature, but excessively intense anticoagulation was not associated with hemorrhagic transformation and clinical worsening in a previous report. At present, however, these factors (hypertension, large infarct, and prolonged aPTT) are not of sufficient predictive power to identify patients eminently at risk for ICH, even if anticoagulation is regulated to a less excessive range, since many patients with acute embolic stroke share these features. We also found that although admission CT scans were helpful in identifying hemorrhagic infarcts, a negative CT scan did not eliminate the risk of later bleeding, as seen in eight (80%) of our 10 patients. The key element may be in determining whether large arteries occluded by an embolus regularly recanalize early, allowing reperfusion. The uncommon occurrence of ICH in embolic stroke suggests that recanalization of large arteries such as the middle cerebral artery is uncommon, at least early after infarction. Future work could test this hypothesis by noninvasive serial evaluation for recanalization with transcranial Doppler studies.

Our data suggest that 1) in most patients with embolic cerebral infarcts, heparin-related ICH occurs early in the course of the stroke, usually ≤72 hours after stroke onset and ≤24 hours after onset of heparinization; 2) ICH may follow heparinization in patients with moderate-sized or large cerebral infarcts who have been anticoagulated to >2×control aPTT values; and 3) the time course of these hemorrhages suggests that their pathogenesis is related to the phenomenon of hemorrhagic transformation of embolic cerebral infarcts.

References


Key Words • cerebral hemorrhage • cerebral infarction • heparin
Intracerebral hemorrhage in stroke patients anticoagulated with heparin.
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Stroke. 1989;20:1500-1503
doi: 10.1161/01.STR.20.11.1500

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