Hemorrhagic Infarction (HI) has long been recognized as a potential complication of embolic stroke. Fisher and Adams postulated that downstream migration of the embolus after its initial impact leads to extravasation of blood via reflow into damaged vessels of the proximally infarcted zone.¹

The exact role of anticoagulants in the causation of hemorrhage into infarcted brain tissue remains unknown. Moreover, recent studies have emphasized the efficacy of early anticoagulation (AC) in the prevention of recurrent embolic stroke.²⁻⁵ Knowledge of the risks versus benefits of such treatment decisions and the prognosis of HI is now possible with the advent of high resolution computerized tomography (CT) capable of visualizing macroscopic brain hemorrhage.⁶ Serial CT scanning allows direct observation of the effect of AC on the evolution of embolic infarcts.

We have retrospectively analyzed our experience with patients in whom the diagnosis of HI was made by CT during a period of two years. The study sought to clarify the roles of anticoagulation and embolism in producing HI and to explore the clinical significance of hemorrhagic transformation of bland infarction.

**Methods**

The CT scan reports of all patients studied during the years 1983 and 1984 in two tertiary hospitals were surveyed, and the hospital records reviewed for all cases in whom the diagnosis of HI was made. All scans were reviewed again by one of two neuroradiologists without knowledge of the clinical picture and a neurologist to verify the original diagnosis and tabulate the characteristics of each HI.

The radiologic diagnosis of HI was defined as an area of low attenuation conforming to a vascular territory within which a single non-homogeneous area or multiple areas of high attenuation were present with characteristic blood density. Infarct size was described as large if the entire vascular territory of a major vessel (anterior, middle, or posterior cerebral artery) was involved; moderate if a major division of that territory was involved; and small if only a minor branch territory was involved. The extent of hemorrhage was described as severe if greater than 50% of the infarct was of blood density; mild if having the appearance of scattered punctate hemorrhages; and moderate for those of intermediate degree.

Cases were classified as "probably cardiac embolism" if 1) the symptoms appeared suddenly and rapidly achieved maximal intensity and 2) there was an associated cardiac source, which included atrial fibrillation, rheumatic heart disease, infective endocarditis, prosthetic heart valve, acute myocardial infarction within the prior six weeks, or severe cardiomyopathy. A case was considered "possibly cardiac embolism" if 1) the clinical course was that of embolic cases, and 2) one or more other cardiac diseases were present, including other ectopic arrhythmias, acute subendocardial myocardial infarction within the prior six weeks, myocardial infarction earlier than six weeks, congestive heart failure, or conduction block.

Of the five cases classified as "carotid thrombosis," four had angiographic evidence of severe carotid stenosis or occlusion, and one had non-invasive studies indicating severe carotid artery stenosis. The remaining cases were classified as "unknown" when the cause of the stroke could not be ascertained from the record.

Based on the results of prothrombin time (PT), activated partial thromboplastin time (APTT), and other coagulation studies, patients were classified as having normal coagulation, coagulopathy, or on anticoagulant therapy. Of the latter, therapeutic anticoagulation was defined as a PT between 1.5 and 2.5 times control values or APTT between 45 and 70 seconds simultaneous with or preceding the diagnosis of HI. Excessively anticoagulated patients were those having a maximum PT or APTT beyond these limits during the same time period.

**Results**

Forty-four patients were included in the study. The composition of the group categorized according to co-
agulation status and stroke etiology is given in table 1. There were 23 males and 21 females; ages ranged from 22 to 89, with a median age of 70. The majority of patients (73%) were regarded as having probable or possible cardiac embolic strokes.

Of the five cases with carotid thromboembolism, angiograms showed complete occlusion of the internal carotid artery in two patients, high grade stenosis of the internal carotid artery in one patient, and high grade stenosis of the common carotid with moderate stenosis of the internal carotid artery in another. In the fifth patient, non-invasive studies showed high grade stenosis of the internal carotid artery ipsilateral to the infarct. Figures 1 and 2 illustrate cases of carotid occlusion and carotid embolism respectively.

No differences in age, sex, or race were observed between different groups except for the coagulopathy group which had a median age of 59, compared to 70 for the group as a whole.

The presence and degree of hypertension at stroke onset and during the hospital course were similar between different subgroups. History of hypertension was present in seven of eight (88%) of excessively anticoagulated patients compared to a 50% rate for the other three groups.

The infarct sizes were similar in all subgroups of patients, whether defined by stroke etiology or coagulation status, with a total of 35 (80%) being of moderate to large size. Hemorrhage severity was similar among the stroke etiology subgroups; however, 67% of hemorrhages were severe in the non-AC patients compared to 45% in the AC patients. Hemorrhage severity was similar between the therapeutically and excessively coagulated patients.

The majority of patients (55%) were not receiving either heparin or coumadin prior to or at the time that hemorrhagic infarction was diagnosed. Of these 24, there were 14 cases of probable or possible embolic stroke, including five cases of infective endocarditis.
Figure 2. 66 y.o. man with six month history of transient left arm weakness and numbness, and retinal artery embolization on the right. Presented with multiple episodes of left arm symptoms which did not clear. Exam revealed hypesthesia and mild weakness of left arm. CT scan (a) shows gyral hemorrhage in right superior posterior frontal lobe. Angiogram (b) shows plaque in distal common carotid and proximal right internal carotid, internal carotid stenosis, and a small ulceration.

Figure 3 illustrates such a case of HI in infective endocarditis.

Among the non-AC patients, other potential risk factors for hemorrhage were sought. The patients with apparent coagulopathies included those with lupus anticoagulant (2 patients), acute lymphocytic leukemia with chemotherapy-induced thrombocytopenia and endocarditis, multiple myeloma with chemotherapy-induced thrombocytopenia, severe uremia with prolonged bleeding time and endocarditis, and disseminated intravascular coagulation (one patient each). Among the 18 other non-AC patients, three were on aspirin; one on indomethacin; one on ibuprofen; three had infective endocarditis; and one had a presumed coagulopathy secondary to active ulcerative colitis. Thus, 15 of 24 patients had relative risk factors for hemorrhage other than AC therapy.

Hemorrhage infarction were found to occur predominantly in patients not receiving AC therapy and in patients who were neurologically stable at the time of the transformation (see table 2). The diagnosis was made in asymptomatic patients on the basis of CT scans ordered for other reasons such as documentation of the extent or location of infarction following a previously normal or equivocal study. Of the 20 patients who were on anticoagulant drugs at the time HI was diagnosed, ten were receiving intravenous heparin, four coumadin, and six both drugs.

Twenty cases (45%) of HI were diagnosed during the first 24 hours following stroke onset. Most of these patients were not receiving AC therapy (85%). Of the entire group of anticoagulated patients, 15% of HI were diagnosed in the first 24 hours; whereas, of the non-anticoagulated patients, 71% were diagnosed within this period of time. Of the entire group of embolic stroke patients, 41% were diagnosed as having HI within 24 hours.

Of the twenty-four cases of HI diagnosed after the first day of stroke onset 19 had an initial CT scan which was normal or showed bland infarction. These are referred to as hemorrhagic transformations. Seventeen of these initial scans were performed on day one, and in these patients the transformation time was in the range of 18 hours to 60 days. Hemorrhagic transformation was documented to occur within nine days in one half of the cases. A patient who transformed after 60 days is illustrated in figure 4.

All seven patients who showed neurologic deterioration at the time that hemorrhagic transformation was found on CT were receiving AC therapy. Six of these patients had moderate to large sized infarcts, of whom three showed severe hemorrhage.

There were eight deaths during the hospitalization for stroke. All had moderate or large sized infarcts. Five had massive infarctions contributing to death. One patient died of fungal sepsis; two others died from complications of endocarditis. Five of these eight were not on AC, and four of these had severely hemorrhagic infarcts. Three out of the seven patients with symptomatic hemorrhagic transformation died, one of whom had a severely hemorrhagic infarct.

Management decisions at the time of diagnosis of HI were examined (see table 3). Of the twenty patients who were fully anticoagulated at the time of diagnosis of HI, AC therapy was discontinued and never resumed in ten; resumed in 11 to 35 days in four; and continued without interruption in six others. Two patients not on AC had AC instituted 12 and 23 days later, while two other patients not on AC had full AC instituted within 24 hours of the diagnosis of HI. Of the
FIGURE 3. 26 y.o. male with history of tetralogy of Fallot presented with fever and dyspnea secondary to endocarditis. He developed acute hemiparesis and focal seizures three days after hospitalization. CT scans show hemorrhage with a gyral configuration in the right parietal lobe, within a low absorption region extending medially toward the right lateral ventricle.

Discussion

It is evident from reviewing this series of patients that the clinical and radiologic diagnosis of HI involves a spectrum of stroke etiologies, severity, CT scan appearances and prognosis. The high prevalence of anti-coagulation therapy and other coagulation disorders suggests a contribution of these factors in the development of HI.

There was a high incidence of potential risk factors, other than the presence or degree of AC therapy, for hemorrhagic complications among this group of patients. The presence of hypertension has been identified as a risk factor for intracerebral hemorrhage. Among anticoagulated patients, intracerebral hemorrhage has been related to age greater than 65 years and length of treatment in one study, age greater than 50 years and hypertension in a second study, and age greater than 65 years, hypertension, excessive AC, and diabetes in a third study. Distinction of risk for primary intracerebral hematoma from hemorrhagic infarction was not made in these studies. The Sixty Plus Reinfarction Study found no relationship of bleeding risk to age or duration of therapy among AC and non-AC elderly patients. In comparing a series of patients with HI to a similar group without HI, the Cerebral Embolism Study Group found that average blood pressure, age, PTT values, and embolic source did not appear to be risk factors, whereas there was a high prevalence (80–86%) of large infarcts among the HI patients. Although our study lacks a control population, it is notable that there was a wide range of ages, with the majority being elderly patients. Hypertension was similar in incidence among the different subgroups, with the exception of chronic hypertension being found more commonly in association with excessive anti-coagulation. Although our system of grading infarct size differed, the 80% incidence of moderate to large infarcts in our series is comparable to the findings of the Cerebral Embolism Study Group.

Neither the degree nor the presence of AC appeared to influence the hemorrhage severity. In fact, hemorrhages were more severe among the non-AC patients, suggesting that other factors may be of greater importance in the pathogenesis of HI.

Severe hemorrhage was a characteristic finding in the patients with endocarditis. Experimental evidence in dogs has shown that inflammation-producing emboli significantly increase the severity of hemorrhage.

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<tr>
<th>TABLE 2: Clinical and Anticoagulant Status at the Time of Diagnosis of HI by CT</th>
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<tr>
<td>HI on initial CT*</td>
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<td>Hemorrhagic transformation with deterioration</td>
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<td>Hemorrhagic transformation without deterioration</td>
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*Not all cases had CT scans on the first day.
FIGURE 4. 74 y.o. female with chronic atrial fibrillation and previous strokes had recently developed aphasia. CT scan (a) shows low absorption areas in right frontal and left parietal lobes. Chronic coumadin therapy was continued. Two months later she presented with one day history of confusion and progressive impairment of consciousness. PT 23 seconds; APTT 44.6. CT scan (b) shows massive hemorrhage, both parenchymal and intraventricular. The question of a new stroke cannot be resolved by the scan.

compared to bland emboli, supporting the contention that embolic stroke secondary to endocarditis carries a significant risk for HI. In addition, these patients are at risk for hemorrhage secondary to mycotic aneurysm rupture. The risk versus benefit of AC in patients with endocarditis remains controversial. In none of our cases was AC used before or after the diagnosis of HI.

Other underlying diseases represented in this series have been reported in association with HI. Cerebral venous thrombosis has been proposed as an etiology of HI in leukemic patients. Chemotherapy-induced thrombocytopenia may have contributed to hemorrhage in one of our patients with leukemia and one with myeloma. Heparin-induced thrombocytopenia, although reported in association with intracerebral hemorrhage, did not play a role in any of our patients. Inhibition of platelet function by nonsteroidal anti-inflammatory drugs or uremia may have been contributory in six patients. Disseminated intravascular coagulation has been reported with HL, and was found here in one case. Cerebral venous thrombosis as a complication of ulcerative colitis and hypercoagulability may have been a factor in another case. Two patients in our series had evidence of lupus anticoagulant, a circulating procoagulant inhibitor that has generally been associated with a thrombotic state but also reported in associated with HI and subdural hematoma.

The occurrence of HI in clinical studies such as ours is underdiagnosed due to the limitations of CT scanning and spinal fluid examination for detecting blood. Non-visualization on CT may occur as the result of averaged normal attenuation values in an area of admixed hemorrhage and necrosis. Isolated petechial hemorrhages may be too small to distinguish from surrounding tissue. Contrast enhancement has been advocated to demonstrate small areas of petechial hemorrhage in a region of gray matter infarction, or to predict patients at risk for developing HI. In our experience, contrast scans were done too infrequently to draw any conclusions about their usefulness in this situation.

Since many of the hemorrhages involve cortical gray matter, lumbar puncture could be a potentially

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<th>Management Decisions in Anticoagulated Patients at the Time of Diagnosis of HI</th>
<th>Number of patients</th>
<th>Days after diagnosis of HI</th>
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<tbody>
<tr>
<td>AC discontinued and not resumed</td>
<td>10</td>
<td>—</td>
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<tr>
<td>AC discontinued and later resumed</td>
<td>4</td>
<td>11, 18, 22, 35</td>
</tr>
<tr>
<td>AC started after diagnosis of HI</td>
<td>4</td>
<td>1, 1, 12, 23</td>
</tr>
<tr>
<td>AC continued despite diagnosis of HI</td>
<td>6</td>
<td>—</td>
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more sensitive technique than CT for demonstrating microscopic or petechial hemorrhage. In one autopsy series, 75% of cases with intracerebral hemorrhage, 10% of cases with HI, and no cases with ischemic infarction who had lumbar punctures showed grossly bloody or xanthochromic fluid. In studies comparing CT scan with lumbar puncture in the diagnosis of HI, 10 to 17% of patients with HI on CT had apparently bloody or xanthochromic fluid. Since red cell counts less than 1,000 may result in clear fluid, attention to the number of red cells may be a more sensitive discriminator. Lee et al found a 26% incidence of absent red cells in HI. Although none of our patients with HI had absent red cells, of eleven spinal fluid examination only three had numbers sufficiently high to be observed as bloody in appearance. Thus lumbar puncture cannot be relied upon to rule in or out the presence of HI, although the presence of red cells, even in low numbers, may raise one's suspicion for the diagnosis. Furthermore, differentiation between bland infarction with traumatic lumbar puncture and hemorrhagic infarction with a spinal fluid containing a small number of red cells is difficult.

Reports of catastrophic HI associated with AC have recently emphasized this complication in the face of adequately controlled PT and PTT measurements, supporting the belief that caution should be exercised in the use of AC during the acute stage of non-septic cerebral embolism. Five of our eight fatal cases were not receiving AC therapy. In the other three cases, whether or not AC produced a more adverse outcome than if they had not received AC cannot be concluded from our data. The fact that all of them had large or moderate sized infarcts suggests that in these patients a conservative therapeutic approach should probably be taken during the acute stage.

The development of HI generally occurs within the first week of stroke onset and often within the first 24 hours. The development of HI during chronic AC therapy, as in our patient (number 4), should raise the possibility that a new embolic event has occurred rather than the appearance of hemorrhage into the site of an old infarct.

It is relevant to note that hemorrhagic transformation was diagnosed most often in patients who were neurologically stable or improving. This observation is consistent with the experience of Hakim, et al who found that all of three hemorrhagic transformations were asymptomatic, and the experience of the Cerebral Embolism Study Group who found eleven of nineteen transformations to be asymptomatic. The higher prevalence of hemorrhagic transformation among anticoagulated patients probably in part reflects the tendency of physicians to use CT scanning more frequently in these cases to monitor therapy and changes in neurologic condition, while the higher prevalence of HI on
initial CT scan among non-anticoagulated patients likely reflects the use of the study to screen patients prior to AC therapy. The observation that so many hemorrhagic infarcts occurred in non-anticoagulated patients raises the possibility that HI usually reflects the natural development of some embolic infarcts rather than an unusual complication of therapy. Although the majority of hemorrhagic transformations were asymptomatic, it is also apparent from our data that AC therapy may contribute to clinical deterioration at the time that hemorrhage develops in some patients.

In other series of patients with HI, ten cases have been briefly mentioned in whom AC was instituted early or continued despite the finding of HI on CT scan, none of whom subsequently deteriorated. This has also been our experience. Although AC can be successfully continued or instituted early during the course of HI in patients having strong indications for therapy and asymptomatic transformation, recommendations for selecting out those patients most likely to have a poor prognosis can only be based on the presently limited data about relative risk factors mentioned previously.

In those cases associated with AC therapy, management decisions are most soundly based on knowledge of the natural history of HI and cerebral embolism, and on the risk factors for poor prognosis rather than solely on the appearance or potential appearance of blood on CT scan. Symptomatic hemorrhage, severe systemic illness, and large infarct size appear to adversely affect prognosis. Avoidance of anticoagulation in patients with infective endocarditis or large infarcts and avoidance of excessive anticoagulation in hypertensive patients is probably warranted.

The precise sequence of events leading to hemorrhagic infarction is still imperfectly understood. Pathology studies of HI have revealed a characteristic appearance, which includes primary involvement of the cerebral gray matter with necrotic brain tissue that is interspersed with congested blood vessels and multiple petechial hemorrhages that may become confluent. Both anemic and hemorrhagic infarction may coexist in the same lesion. In the cerebral cortex, the hemorrhage is most prominent in the depths of sulci. Approximately 65% of post-mortem cerebral embolism cases show evidence of HI compared to 19% of thrombotic cases. Venous thrombosis accounts for a minority of cases. Our series also supports the observation that embolism is the most common etiology of these strokes, implying that a cardiac or arterial source of embolism should be sought in such cases.

Reflow of blood into damaged tissue after embolus migration remains a tenable explanation of pathogenesis. In cases of middle cerebral or carotid artery occlusion, early recanalization of the vessel with reflow may explain the development of HI. A similar reflow mechanism probably explains the occurrence of HI following carotid revascularization procedures during the acute stroke period.

The chemical environment of infarcted brain tissue itself may have a significant effect on the presence and severity of secondary hemorrhage. Brain is among the richest sources of the procoagulant, tissue thromboplastin, in the body. Furthermore, thromboplastin has been shown experimentally to inhibit the anticoagulant activity of heparin. Local release of this factor into infarcted tissue could thus explain our observation that AC therapy and degree of elevation of PT and PTT in the systemic circulation did not appear to affect hemorrhage severity, nor did it adversely affect the outcome in those patients who continued to receive AC despite HI found on CT scan.

The activities of tissue thromboplastin in gray and white matter have been shown to be similar, indicating that other factors such as capillary density may have a greater role in determining the relative localization of hemorrhage to gray matter areas in HI.

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