Anticoagulant-Related Hemorrhage in Acute Cerebral Embolism

ROBERT W. SHIELDS, JR., M.D.*, ROBERT LAURENO, M.D.,† TIM LACHMAN, M.D.,‡ AND MAURICE VICTOR, M.D.*

SUMMARY Five patients with nonseptic cerebral embolism of cardiac origin are reported in whom early anticoagulant therapy resulted in clinical deterioration or death from frank hemorrhage into the acute infarct. In each patient an initial CT scan excluded the presence of intracerebral hemorrhage and a second CT scan, after clinical deterioration had occurred, documented frank hemorrhage into the infarcted zone. All five patients had large infarctions in the right middle cerebral artery territory and three patients were mildly hypertensive. Four patients received heparin within 36 hours of their stroke and one was on warfarin anticoagulant therapy. Clinical deterioration occurred after intervals of several hours (2 cases), 5-6 days (2 cases) and 30 days (1 case). In only 2 patients was anticoagulant activity excessive at time of clinical deterioration. This report illustrates the danger of early anticoagulant therapy of acute nonseptic cerebral embolism, particularly in the setting of large infarction.

NONSEPTIC CEREBRAL EMBOLISM of cardiac origin is a common cause of stroke accounting for nearly one third of all cerebral infarctions.1 Despite this high incidence the correct management of this disorder remains uncertain. Although chronic anticoagulation therapy has proven to be effective in decreasing the incidence of recurrent arterial embolism of cardiac origin,2-4 its use in the setting of acute embolic cerebral infarction remains controversial.5-8 At issue is whether the potential benefit of anticoagulants in reducing the risk of early recurrent embolism outweighs their potential danger of inducing massive hemorrhage into the infarcted tissue. The concern that anticoagulation therapy may lead to frank hemorrhage in acute embolic cerebral infarcts has been based largely upon pathologic observations that such infarcts are often stippled with small petechial hemorrhages.9 There have been only a few well documented examples of intracerebral hematoma following the administration of anticoagulants to patients with acute cerebral embolism.10-14 The rarity of these reports has fostered the view that such an event is extremely uncommon and that early use of anticoagulants is uniformly safe.8 15-17 Our experience contradicts this view, and for this reason we are reporting five patients who developed catastrophic cerebral hemorrhage following anticoagulant therapy of nonseptic cerebral embolism.

Case Reports

The following five cases were extracted from a retrospective analysis of 51 consecutive patients with acute nonseptic cerebral embolism of cardiac origin, seen on the Neurology services of The Cleveland Metropolitan General Hospital, Cleveland, Ohio, The

References

Washington Hospital Center, Washington, D.C., and the Lankenau Hospital, Philadelphia, Pa., during a three-year period (1978 to 1981). Twenty-eight of the 51 patients were treated with anticoagulants at some time following the cerebral embolism, and in 5 of the treated cases anticoagulation therapy appeared to induce hemorrhage into the acutely infarcted tissue.

Case 1

A 69-year-old man was brought to the hospital after the abrupt onset of right frontal headache, difficulty swallowing, garbled speech, and left-sided weakness. These symptoms had their onset while he was eating dinner. Past medical history was unremarkable.

On admission to the hospital, blood pressure was 140/90 mmHg, pulse 80/min and irregular and respirations 24/min. The patient was afebrile. General physical examination disclosed no abnormalities except for a grade 3/6 harsh systolic apical murmur. The patient was lethargic, spoke only a few words, and followed only simple commands. There was a right gaze preference and a left supranuclear facial paresis. The tongue deviated to the left on protrusion. There was a dense left hemiparesis with intermittent spontaneous decerebrate posturing of the left limbs. Deep tendon reflexes were hyperactive and the plantar reflexes were extensor bilaterally. The patient could not cooperate for sensory or cerebellar testing.

Laboratory tests including CBC, electrolytes, BUN, blood glucose, prothrombin time and partial thromboplastin time were normal. ECG revealed atrial fibrillation with occasional premature ventricular contractions. Chest films disclosed borderline cardiomegaly. An emergency CT scan showed no abnormalities (fig. 1a).

The patient was transferred to the Intensive Care Unit where blood pressure was 180/110 mmHg. After application of nitroglycerin ointment, the blood pressure decreased to 160/100 mmHg. Within 8 hours from the onset of the stroke, heparin was administered intravenously, beginning with a loading dose of 5000 units and continuing as a constant infusion at a rate of 1000 units per hour. Within 4 hours of initiation of heparin therapy a guaiac positive vomitus was noted. One hour later the patient was found comatose. At this time the right pupil was 3 mm and the left 2 mm; both were unreactive to light. Oculocephalic and corneal reflexes were absent. Deep tendon reflexes were hyperactive and the plantar reflexes were extensor bilaterally. A CT scan disclosed a large hemorrhage into the presumed zone of acute infarction in the right hemisphere (fig. 1b). Partial thromboplastin time (PTT) was 57 sec. (control 35 sec.). Heparin was discontinued and solumedrol was administered intravenously. The patient remained comatose and expired on the fourth day of his illness.

Pathologic Findings

The pertinent findings were in the cardiovascular and central nervous systems. The heart weighed 580 gm. and showed biventricular hypertrophy. The right atrium was dilated but free of thrombus. The left atrial...
appendage was dilated and contained a mural thrombus 4 cm in diameter. Prolapse of the mitral valve was also present. The brain weighed 1340 gm. The subarachnoid space was blood stained throughout, especially over the right frontal lobe. The right frontal lobe contained a large hemorrhage, extending medially to the thalamus and laterally to the cortex where it had ruptured into the subarachnoid space. There was evidence of both tonsillar and right uncal herniation.

Comment

The abrupt development of left hemiparesis, left supranuclear facial paresis, and left gaze paresis in the setting of atrial fibrillation was strongly suggestive of embolic cerebral infarction in the distribution of the right middle cerebral artery. When the initial CT scan showed no evidence of intracerebral bleeding, the patient was treated with heparin, to prevent recurrent arterial embolism. Within hours of the initiation of anticoagulant therapy the patient developed a massive intracerebral hemorrhage into the presumed area of acute embolic infarction.

Case 2

A 49-year old white man was admitted to the hospital for the management of congestive heart failure and recent onset atrial flutter with 2:1 block. During the preceding year, he had been treated for essential hypertension with thiazide diuretics. Six weeks prior to admission treatment of congestive heart failure with digoxin and furosemide was begun.

On admission, blood pressure was 135/95 mmHg, apical pulse 120/min and irregular, respirations 16/min and temperature 37°C. General physical examination was unremarkable except for signs of mild congestive heart failure. The neurologic examination disclosed no abnormalities.

Routine laboratory tests including CBC, platelet count, serum electrolytes, BUN, blood glucose and urinalysis were normal. Chest films showed cardiomegaly and prominent vascular markings. ECG disclosed atrial flutter with an atrial rate of 250/min and a 2:1 block.

On the first hospital day, treatment with quinidine gluconate was begun. Electrocardioversion was accomplished on the third hospital day, resulting in a normal sinus rhythm. A few hours after cardioversion the patient suddenly became drowsy and developed a frank left hemiparesis, with left supranuclear facial weakness. Additional neurologic findings included a left homonymous hemianopia, a left hemisensory deficit to pinprick and a left Babinski sign. A CT scan disclosed no abnormalities at this time (fig. 2a). Approximately four hours later, a loading dose of 7500 units of heparin was administered intravenously followed by a continuous infusion of heparin at a rate of 625 units/hour. Partial thromboplastin time (PTT) was 34 sec (control 26 sec.). On the fourth hospital day, blood pressure rose to 190/120 mmHg. Intravenous nitroprusside was administered, and the dosage was adjusted to keep the blood pressure below 150/100 mmHg. On the seventh hospital day, PTT was 32 sec. (control 27 sec.) and the heparin dosage was increased to 834 units/hour. The next day the patient was alert and oriented but there was little improvement in the left hemiparesis. A loading dose of 15 mg. of warfarin

FIGURE 2a. Unenhanced CT scan from Case 2, obtained a few hours after embolic infarction in the right middle cerebral artery distribution. No evidence of infarction or hemorrhage is present. Figure 2b. Unenhanced CT scan from Case 2, obtained soon after clinical worsening while on therapeutic anticoagulant therapy. A small intracerebral hemorrhage is present in a zone of infarction involving the basal ganglia and frontal and temporal lobes of the right cerebral hemisphere.
was administered. On the ninth hospital day the patient appeared lethargic. PTT was 49 sec. (control 26 sec.). On the following day, a CT scan was repeated and disclosed a zone of hemorrhage in the area of acute infarction (fig. 2b). Heparin and warfarin were discontinued and I.V. dexamethasone was administered. The neurologic state stabilized but there was little resolution of the left hemiparesis over the ensuing several months.

Comment
The abrupt development of a left hemiparesis, hemisensory deficit and homonymous hemianopia within a few hours after electrocardioversion for atrial flutter indicated the occurrence of embolic infarction in the territory of the right middle cerebral artery. When the initial CT scan disclosed no evidence of intracerebral bleeding, heparin was administered to prevent recurrent embolism. After 6 days of anticoagulation therapy the patient became lethargic, at which time a second CT scan demonstrated the presence of frank hemorrhage into the presumed zone of acute infarction.

Case 3
A 77-year old woman was brought to the hospital after she suddenly slumped to her left side while eating supper. She was lethargic and could not move her left arm or leg. She had not seen a doctor in many years and was not known to have diabetes, hypertension, heart disease or any other medical disorder.

On admission to the hospital blood pressure was 120/78 mmHg, pulse rate 90/min, and irregularly irregular, respirations 24/min, and the temperature 37°C. The patient was lethargic, but was oriented to name and date although not to place. She denied that her left arm was her own. She could remember three items for five minutes. Speech was dysarthric, but language function was intact. A right gaze preference was noted.

There was a dense, flaccid, left hemiplegia and a left supranuclear facial paresis. Deep tendon reflexes were symmetrical but the left plantar reflex was extensor. Strength, sensation, finger to nose and heel to shin testing on the right were normal.

Routine laboratory tests including CBC, platelet count, serum electrolytes, BUN, blood glucose, prothrombin time, PTT and urinalysis were normal. Chest films showed pulmonary congestion. ECG revealed atrial fibrillation and a vertical axis. A CT scan of the head, obtained at the time of admission, disclosed no abnormalities (fig. 3a).

The patient remained stable during the first hospital day. On the next day a continuous intravenous infusion of heparin at 1000 units per hour was begun. Blood pressure was 150/100 mmHg. Five hours later PTT was 125 seconds (control 35 sec.). Three hours later she was found unresponsive, with decerebrate posturing and bilateral Babinski signs. Blood pressure had

![Figure 3a](http://stroke.ahajournals.org/)

**Figure 3a.** Unenhanced CT scan from Case 3, obtained a few hours after embolic infarction in the right middle cerebral artery distribution, and prior to anticoagulant therapy. No evidence of infarction or hemorrhage is present. **Figure 3b.** Unenhanced CT scan from Case 3, obtained soon after clinical worsening while on anticoagulant therapy. A large hemorrhage is present in the right cerebral hemisphere causing a marked shift of midline structure to the left.
rissen to 230/130 mmHg. Heparin was discontinued and mannitol and dexamethasone were administered intravenously. A CT scan now showed an intracerebral hemorrhage in the right hemisphere with marked shift of the midline structures to the left (fig. 3b). The patient expired on the third hospital day. Permission for autopsy was denied.

Comment
The abrupt development of a severe right frontoparietal deficit in a setting of atrial fibrillation was strongly suggestive of embolic infarction in the distribution of the right middle cerebral artery. The normal CT scan on admission was consistent with this diagnosis and excluded an intracerebral hemorrhage. Within 8 hours of the institution of heparin therapy, hemorrhage occurred into the presumed area of acute infarction. A single PTT estimation made a few hours after a standard initial dose of heparin, indicated an excessive degree of anticoagulation, which probably contributed to the development of the hemorrhage.

Case 4
A 64-year old white woman was admitted to the hospital with a one-year history of exertional syncope. Ten years earlier essential hypertension had been discovered and the patient was treated with antihypertensive medication. A few years later she discontinued this medication without the advice of her physician. She also had mild osteoarthritis of the cervical spine, for which she took ibuprofen. There was no prior history of cardiopulmonary disease, and no history of rheumatic fever.

On admission to the hospital, blood pressure was 150/74 mmHg, pulse 92/min and regular, respirations 18/min, and temperature 37° C. General physical examination showed only a grade 2/6 late systolic murmur along the left sternal border with radiation into the neck and axilla. Neurologic examination was entirely normal.

Laboratory tests including CBC, urinalysis, serum electrolytes, BUN, and blood glucose were normal. Prothrombin time was normal. ECG showed a regular sinus rhythm at a rate of 75/min, LVH with strain, and p mitrale.

On the second hospital day a cardiac catheterization was performed, revealing a calcific aortic valve, a 50–70 mmHg pressure gradient across the aortic valve and high grade stenosis of the proximal left anterior descending coronary artery. On the sixth hospital day, the patient underwent aortic valve replacement and a coronary artery bypass. She did well postoperatively except for an episode of mild hypotension which was controlled by dopamine and occasional premature ventricular contractions, which were treated with lidocaine. On the ninth hospital day, treatment with warfarin was begun. Four days later the patient had two episodes of clonic movements of the left arm and head, each lasting about 15 minutes. She was slow to respond and had a mild left facial droop and a left hemiparesis. Prothrombin time was in the therapeutic range (1½ to 2 times control values) and remained in this range for the next 2 days. On the 15th hospital day, a CT scan showed an area of decreased attenuation in the right hemisphere, lateral to the anterior horn of the lateral ventricle (fig. 4a). The left-sided focal seizures recurred and she was noted to be in atrial fibrillation. On the following day, prothrombin time was 2.8 times the control value. On the 18th hospital day, the patient became lethargic and developed a dense left hemiplegia with tonic deviation of the eyes to the right. CT scan now revealed hemorrhage into the area of previous infarction (fig. 4b). Prothrombin time was 3.5 times the control value. Vitamin K was administered but after several hours the patient became comatose and developed fixed dilated pupils and bilateral extensor plantar reflexes. She expired on the 21st hospital day. Permission for postmortem examination was denied.

Comment
The abrupt development of a right hemispheric neurologic deficit, heralded by focal seizures and associated with aortic valve replacement and recent onset atrial fibrillation was indicative of embolic cerebral infarction. The infarction developed during therapeutic anticoagulation. The initial CT scan documented the presence of infarction in the territory of the right middle cerebral artery, but disclosed no evidence of intracerebral hemorrhage. Five days after the onset of stroke the neurologic status deteriorated and a second CT scan demonstrated a hemorrhage in the zone of the acute infarct. The hemorrhage occurred when the prothrombin activity was excessive (3.5 times the control value). In this case frank hemorrhage developed in an ischemic embolic infarction during excessive anticoagulation therapy.

Case 5
A 41-year old woman was admitted to the hospital because of the sudden onset of headache and weakness of the left face, arm and leg. She was known to have mitral stenosis secondary to childhood rheumatic fever and had a commissurotomy of the mitral valve at age 21. There were no recent cardiopulmonary symptoms and no history of cardiac arrhythmias, hypertension, or diabetes mellitus. The patient was taking no medications.

On admission to the hospital, blood pressure was 108/79 mmHg, pulse 90/min and irregular, respirations 16/min, and temperature 37° C. General physical examination was unremarkable except for a soft diasstolic murmur over the left sternal border. The patient was slightly lethargic and had a dense left hemiplegia and a right gaze preference.

Laboratory tests including CBC, platelet count, prothrombin time, urinalysis, serum electrolytes, BUN and blood glucose were normal. Left atrial enlargement was evident on the chest film and the ECG disclosed atrial fibrillation. A CT scan obtained shortly after admission revealed an area of decreased attenuation in the right hemisphere with mild mass effect
FIGURE 4a. Unenhanced CT scan from Case 4, obtained 2 days after embolic infarction in the right middle cerebral artery distribution. A small zone of infarction is present in the right hemisphere lateral to the basal ganglia. FIGURE 4b. Unenhanced CT scan from Case 4, obtained soon after clinical worsening while on anticoagulant therapy. A large intracranial hemorrhage is present in the right basal ganglia and surrounding tissue.

The CSF was under an opening pressure of 120 mmHg. The fluid was clear, colorless and acellular, with a protein content of 22 mg% and a glucose of 75 mg%.

After the CT scan and lumbar puncture revealed no evidence of hemorrhage, treatment with heparin and warfarin was instituted. By the 3rd hospital day the prothrombin time was in the therapeutic range (1½ to 2 times control) and by the 6th hospital day, the patient was fully alert. Heparin was discontinued after 3 days and the patient was maintained on warfarin. The hemiparesis improved gradually until the 30th hospital day when the patient complained of the sudden onset of severe headache and became lethargic. A second CT scan now revealed gross hemorrhage in the area of previous infarction with extension into the right lateral ventricle (figs. 5a, 5b, 5c). Prothrombin time was 2 times the normal control value. Warfarin was discontinued and Vitamin K and dexamethasone were administered. The patient’s condition stabilized but she was left with a dense left hemiparesis.

Comment

The abrupt onset of left hemiparesis in a setting of mitral stenosis and the recent onset of atrial fibrillation was indicative of embolic cerebral infarction in the distribution of the right middle cerebral artery. Both the CT scan and lumbar puncture at the time of admission disclosed no evidence of hemorrhage, and the patient was treated with heparin and warfarin to prevent recurrent arterial embolism. After 30 days of therapeutic anticoagulant treatment, frank hemorrhage developed in the zone of infarction.

Discussion

The five patients reported here illustrate the potential danger of administering anticoagulants in the setting of acute cerebral embolism. In each patient, the administration of anticoagulants was followed by the development of frank hemorrhage in the zone of infarction. Analysis of these five cases disclosed several other features which were remarkably uniform from one patient to the next.

In each patient the clinical finding suggested that the cerebral infarct was large. In three patients (cases 1, 2, 3) this was confirmed by CT scanning, while in the other two patients (cases 4, 5) the initial CT scan was obtained too soon after the stroke to detect an abnormality. In none of the patients, however, did the initial CT scan disclose evidence of hemorrhage.

In each patient, the interval between the onset of stroke and the institution of anticoagulation therapy was brief, less than 12 hours in Cases 1, 2, and 5, and 36 hours in case 3. In case 4, cerebral embolism occurred during anticoagulation therapy. In 4 of the 5 patients hemorrhage into the infarcted area occurred soon after anticoagulation therapy was initiated, within 8 hours in two patients (cases 1 and 3) and within 5 and 6 days in two others (cases 2 and 4). In Case 5, however, hemorrhage occurred after 30 days of anticoagulation therapy and thus its relationship to immediate anticoagulation therapy is doubtful.
In three patients the anticoagulant activity was therapeutic when the hemorrhage developed, while in the other two patients (Cases 3 and 4), anticoagulant activity was excessive and thus may have played a role in the development of the hemorrhage. These cases, however, reflect the inherent difficulties in assessing and controlling anticoagulant activity, especially during the initial period of anticoagulation. Two of the five patients (cases 1 and 3) were mildly hypertensive when anticoagulation therapy was begun, however, one (case 3) became severely hypertensive following the hemorrhage. A third patient (case 2) who was initially normotensive became mildly hypertensive after anticoagulants were administered. The modest degree of hypertension noted in these 3 patients, may still have influenced the occurrence of hemorrhage, as hy-
Hypertension has been associated with an increased risk of intracerebral hemorrhage in patients taking anticoagulants for other reasons.  

Review of Literature  
Although there are numerous reports of apparent anticoagulant-induced bleeding into a zone of acute nonseptic embolic cerebral infarction, there are only a few in which the clinical events are described in sufficient detail to be certain that the initial stroke represented an embolic infarct and that the clinical deterioration which followed anticoagulation therapy resulted from hemorrhage into the infarcted tissue.  

These reports describe nine patients.  

The clinical features of these 9 patients and of the 5 reported in this study are remarkably similar and are summarized in Table 1. There were 6 men and 8 women ranging in age from 41 to 79 years, with a mean age of 60 years. Seven of the 14 patients were mildly or moderately hypertensive; however, the remaining seven were normotensive. Cerebral infarction occurred in the territory of the right middle cerebral artery in 9 cases, and of the right posterior cerebral artery in 2 others. There were only 2 cases with infarction in the left middle cerebral artery territory and only one in which the vertebrobasilar system was involved. There is no apparent biologic reason to account for the preponderance of anticoagulant-related hemorrhage in right hemispheric infarctions. It is possible that patients with large dominant hemispheric lesions were not as aggressively managed with anticoagulants as those with nondominant hemispheric lesions. Findings on CT scan and/or clinical features suggested large infarctions in half of the patients. It is noteworthy that hemorrhage was not observed in patients in whom anticoagulation therapy was delayed, but was noted only in those patients treated within the first 3 days after the cerebral embolism. Five patients were taking anticoagulants at the time of their cerebral embolism. In the remaining 9 patients, anticoagulants were started after delays of 4 hours to 3 days, with 7 of the patients treated within the first 24 hours. Hemorrhage developed in most cases soon after anticoagulants were given. The interval between initiation of anticoagulant therapy and the development of hemorrhage ranged from 8 hours to 30 days, with a mean of 6.6 days. It is also noteworthy that anticoagulant activity was excessive at the onset of cerebral hemorrhage in only 3 patients. In 9 patients the anticoagulant activity was in the therapeutic range and in the remaining 2 patients, the level of anticoagulant activity at the time of the hemorrhage was unknown. Seven patients died as a result of their hemorrhage, and of the seven that survived, two had severe persistent deficits.  

Some authors have attributed the occurrence of massive intracerebral hemorrhage following anticoagulation therapy for apparent embolic cerebral infarction to enlargement of a small primary cerebral hemorrhage that had been misdiagnosed as embolic infarction. Small hemorrhages confined to the cerebral white matter may mimic cerebral infarction syndromes clinically and may not be reflected in cerebrospinal fluid...
TABLE 1  Clinical Summary of Cases of Anticoagulant-Related Hemorrhage in Acute Infarction

<table>
<thead>
<tr>
<th>Author/cases</th>
<th>Age</th>
<th>Sex</th>
<th>HTN*</th>
<th>Cardiac diagnosis</th>
<th>Neurologic diagnosis</th>
<th>AC-delay†</th>
<th>Delay-hemorrhage‡</th>
<th>AC activity§</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Groch et al</td>
<td>66</td>
<td>M</td>
<td>+ none</td>
<td>R-PCA++ thrombosis</td>
<td>large</td>
<td>3 days</td>
<td>14 days</td>
<td>PT-therapeutic¶</td>
<td>mortality</td>
</tr>
<tr>
<td>Castleman</td>
<td>67</td>
<td>F</td>
<td>+ A. fib.</td>
<td>R-MCA§§ embolism</td>
<td>large</td>
<td>1 day</td>
<td>10 days</td>
<td>PT-therapeutic</td>
<td>mortality</td>
</tr>
<tr>
<td>Liberman et al</td>
<td>51</td>
<td>F</td>
<td>A. fib.</td>
<td>L-MCA embolism</td>
<td>On therapy</td>
<td>2 days</td>
<td>15 days</td>
<td>not available</td>
<td>mortality</td>
</tr>
<tr>
<td>Drake &amp; Shin</td>
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<td>M</td>
<td>none</td>
<td>L-MCA thrombosis</td>
<td>On therapy</td>
<td>5 days</td>
<td>PT-therapeutic</td>
<td>recovery</td>
<td></td>
</tr>
<tr>
<td>Rinaldi et al</td>
<td>51</td>
<td>F</td>
<td>A. fib.</td>
<td>VBJ</td>
<td></td>
<td>VB</td>
<td>On therapy</td>
<td>3 days</td>
<td>PT 3.5 x control</td>
</tr>
<tr>
<td>case 3</td>
<td>58</td>
<td>M</td>
<td>PHV</td>
<td>R-PCA embolism</td>
<td>On therapy</td>
<td>1 day</td>
<td>PT-therapeutic</td>
<td>mild deficit</td>
<td></td>
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<tr>
<td>case 4</td>
<td>79</td>
<td>F</td>
<td>A. fib.</td>
<td>L-MCA embolism</td>
<td>On therapy</td>
<td>1 day</td>
<td>PT-therapeutic</td>
<td>recovery</td>
<td></td>
</tr>
<tr>
<td>Shields et al</td>
<td>59</td>
<td>M</td>
<td>A. flut.</td>
<td>R-MCA embolism</td>
<td>large</td>
<td>24 hrs.</td>
<td>1 day</td>
<td>not available</td>
<td>mortality</td>
</tr>
<tr>
<td>case 2</td>
<td>44</td>
<td>F</td>
<td>RHD</td>
<td>R-MCA embolism</td>
<td>24 hrs.</td>
<td>1 day</td>
<td>PTT-therapeutic***</td>
<td>recovery</td>
<td></td>
</tr>
<tr>
<td>case 1</td>
<td>69</td>
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<td>A. fib.</td>
<td>R-MCA embolism</td>
<td>large</td>
<td>8 hrs</td>
<td>6 hrs</td>
<td>PT-therapeutic</td>
<td>mortality</td>
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<tr>
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<td>49</td>
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<td>A. flut.</td>
<td>R-MCA embolism</td>
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<td>6 days</td>
<td>PTT-therapeutic</td>
<td>severe deficit</td>
</tr>
<tr>
<td>case 3</td>
<td>77</td>
<td>F</td>
<td>A. fib.</td>
<td>R-MCA embolism</td>
<td>large</td>
<td>24 hrs.</td>
<td>8 hrs</td>
<td>PTT 3.6 x control</td>
<td>mortality</td>
</tr>
<tr>
<td>case 4</td>
<td>64</td>
<td>F</td>
<td>PHV</td>
<td>R-MCA embolism</td>
<td>large</td>
<td>On therapy</td>
<td>5 days</td>
<td>PT 3.5 x control</td>
<td>mortality</td>
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<tr>
<td>case 5</td>
<td>41</td>
<td>F</td>
<td>A. fib.</td>
<td>R-MCA embolism</td>
<td>large</td>
<td>24 hrs.</td>
<td>30 days</td>
<td>PT-therapeutic</td>
<td>severe deficit</td>
</tr>
</tbody>
</table>

* = hypertension; † = interval from stroke to anticoagulation therapy; ‡ = interval from anticoagulation therapy to hemorrhage; § = anticoagulant activity; | = atrial fibrillation; ¶ = rheumatic heart disease; ** = prosthetic heart valve; †† = atrial flutter; ‡‡ = posterior cerebral artery; §§ = middle cerebral artery; || = vertebrobasilar; ¶¶ = prothrombin time 1.5-2.0 x control; *** = partial thromboplastin time 1.5-2.0 x control.

Fisher and Adams have proposed a mechanism to account for the spontaneous hemorrhagic component of embolic cerebral infarcts. These authors have theorized that hemorrhagic infarction develops when an embolus that had occluded an artery fragments and migrates distally in the arterial tree, allowing blood to seep through the damaged arterial wall(s) into the zone of acute infarction. In their view, the reconstitution of blood flow into a zone of acute infarction is the essential factor in the development of hemorrhagic infarction. This theory has been supported by a variety of clinical and experimental observations.

There is additional evidence that reconstitution of blood flow into an acute cerebral infarct may result not only in hemorrhagic infarction but also intracerebral hemorrhage.
hemorrhage. Laurent et al.\textsuperscript{40} using an experimental model of cerebral infarction in monkeys, produced hemorrhagic infarction in 1 to 4 day old cerebral infarcts by elevating the mean arterial pressure, thus increasing blood flow to the infarcted area via collaterals. Intracerebral hemorrhage was produced in 4 day old infarcts by enhancing cerebral blood flow with hypercapnia. Thus, in monkeys with acute cerebral infarction, manipulation of the mean arterial pressure and cerebral blood flow produced either hemorrhagic infarction or frank hemorrhage into the infarction. In man, endarterectomy, performed soon after complete hypercapnia. Thus, in monkeys with acute cerebral infarction appears to be the primary mechanism.

A number of observations support the concern that anticoagulation therapy in patients with embolic infarcts contribute to the development of hemorrhagic infarction or intracerebral hemorrhage. Several experimental studies of cerebral infarction in dogs have shown that anticoagulants increase the severity of hemorrhagic infarction\textsuperscript{41-49} and occasionally produce intracerebral hemorrhage.\textsuperscript{48, 50} In a primate model of cerebral infarction, Meyer demonstrated that the administration of anticoagulants caused increased perivascular hemorrhage, and in one animal which received a large dose of anticoagulant, frank hemorrhage occurred.\textsuperscript{51} In a large autopsy series, Jorgensen and Torvik noted that use of anticoagulants increased the degree of hemorrhage in cases of hemorrhagic infarction.\textsuperscript{52} One may deduce from these observations that the risk of anticoagulant-related hemorrhage into a zone of acute infarction is greatest in the setting of hemorrhagic infarction. This observation is supported by the fact that nearly all reported instances of anticoagulant-related hemorrhage into cerebral infarction, have involved embolic infarctions, two-thirds of which are spontaneously hemorrhagic in the absence of anticoagulants.\textsuperscript{9}

Therapeutic Considerations

Recognition of the potential hazard of anticoagulation therapy in patients with acute embolic cerebral infarction creates a therapeutic dilemma. One must weigh the risk of inducing hemorrhage into the acute infarct against the potential benefit of decreasing the incidence of early recurrent embolism. This dilemma has produced a divergence of opinion regarding the proper management of such patients.

Most authors recommend that early anticoagulation therapy be avoided in patients with hemorrhagic infarction.\textsuperscript{16, 53-56} Although hemorrhagic infarction is frequently noted at autopsy in patients with cerebral embolism it is difficult to detect clinically. CT scan and lumbar puncture may not be helpful in establishing the presence of hemorrhagic infarction.\textsuperscript{31, 39, 59-61} Particularly when these procedures are done early, before the hemorrhagic aspect of the infarct has time to develop. The hemorrhagic component of the infarction probably evolves over several days following the onset of the stroke.\textsuperscript{36, 37} and it follows that the diagnostic value of lumbar puncture and CT scan would be enhanced if they were obtained after a delay of a few days.\textsuperscript{36} Recently it has been proposed that delayed high dose contrast CT scans may be helpful in identifying patients at risk for developing hemorrhagic infarction.\textsuperscript{36} This method may eventually aid in identifying patients at high risk for anticoagulant-related bleeding into acute cerebral infarction but its value in selecting patients for anticoagulation therapy has not yet been established by a controlled trial.

Many authors suggest that the risk of early recurrent embolism is so great that patients should be treated with anticoagulants immediately after intracerebral hemorrhage has been excluded by CT scan and/or lumbar puncture.\textsuperscript{1, 15, 16, 54, 62-67} This opinion is based upon the assumption that early recurrent arterial emboli are common and that anticoagulation therapy can prevent such early recurrences. Although there is a considerable risk of recurrent arterial embolism in the weeks that follow the initial embolus,\textsuperscript{63-67} the precise risk of recurrence during the days immediately following an embolus is unknown. We did not encounter a high incidence of early recurrent emboli in our patients. There were 23 patients in this study who did not receive anticoagulants following their cerebral embolism. Each of these patients was followed during their acute hospitalizations for an average of 22 days and no recurrent emboli were noted. Of the 23 patients who were treated with anticoagulants who did not develop cerebral hemorrhage, 6 were fully anticoagulated at the time of their cerebral embolism or were treated within the first 24 hours, and 17 were treated after a delay of 2 to 21 days (mean 7.6 days). Two recurrences occurred in the group that received delayed therapy. One patient had an embolus to the radial artery seven days after his cerebral embolism while the other patient developed transient signs of spinal cord dysfunction three days after his cerebral embolism.

Although the value of chronic anticoagulation therapy in decreasing the risk of recurrent arterial emboli has been amply demonstrated,\textsuperscript{2, 68-72} the efficacy of immediate anticoagulant therapy in preventing early recurrent arterial embolism has not. All studies supporting early anticoagulation therapy have reported small numbers of patients\textsuperscript{15-17, 73} and either did not employ randomized controlled methodology\textsuperscript{15-17} or reported statistically insignificant results.\textsuperscript{73} Some data even suggest that anticoagulants are much less effective in reducing the risk of recurrent embolism in the first six weeks following the initial embolus.\textsuperscript{69} In a recent study,\textsuperscript{17} 2 of 21 patients with acute cerebral embolism had recurrent cerebral emboli during the first 10 days following their stroke despite immediate anticoagulant therapy. This recurrence rate is close to that reported for untreated patients.\textsuperscript{63-67, 73} Thus it remains to be established what benefit is afforded patients treated with anticoagulants in the days immediately following the initial embolism.

Many authors recommend waiting for variable periods of time, ranging from three days to three weeks, before starting anticoagulation therapy.\textsuperscript{6, 54, 57-58} This
delay is believed to decrease the risk of anticoagulant-related hemorrhage in the acute infarct. This contention is supported by the fact that in 4 of our 5 patients and in the majority of similar cases reviewed in the literature the hemorrhage occurred during the first several days after early anticoagulation therapy.

The exact benefits and risks of immediate anticoagulation therapy of acute cerebral embolism are unknown. The clinical data presented in this report, however, indicate that immediate anticoagulation therapy of nonseptic cerebral embolism carries a substantial risk of catastrophic hemorrhage into the infarct. Our observations suggest that patients with large infarctions may be at particular risk for this complication. Our recommendation, therefore, is to avoid immediate anticoagulation therapy of cerebral embolism in patients with hemorrhagic infarctions, large infarctions and hypertension. The detection of hemorrhagic infarction by means of CT scan and lumbar puncture may be optimally accomplished if these tests are obtained after a delay of at least 3–4 days from the onset of cerebral embolism.36 If no evidence of bleeding is present and the patient is normotensive, anticoagulant therapy may then be instituted. Great caution however must be taken to avoid excessive anticoagulant activity. In those patients with hemorrhagic infarction or large infarctions, anticoagulant therapy should be avoided in the acute setting.

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