**Short Communication**

Hemorrhagic Transformation in Cardioembolic Cerebral Infarction

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**Background and Purpose:** Because the frequency of hemorrhagic transformation of cerebral infarcts is still a matter of controversy, we performed a prospective magnetic resonance imaging study in a series of consecutive patients with cardioembolic stroke.

**Summary of Review:** Among 200 consecutive patients with transient ischemic attack or ischemic stroke, 41 were identified with a computed tomographically proven supratentorial infarct due to cardioembolic embolism. Magnetic resonance imaging (T1-weighted) was performed 3 weeks after the stroke in 35 of these 41 patients. Eight patients received anticoagulants. Magnetic resonance images showed hemorrhagic transformation in 68.6% (24) of the 35 infarcts, always without clinical deterioration. In a stepwise forward logistic regression analysis only the volume of infarction edema on the initial computed tomogram was linked significantly with the risk of hemorrhagic transformation (p=0.037). Hemorrhages were a regular finding on magnetic resonance images of infarcts exceeding a volume of 10 cm³ (94.4%, 17 of 18).

**Conclusions:** Hemorrhagic transformation is a regular finding in medium-sized and large cardioembolic infarcts. Thus, in therapeutic and preventive studies of acute stroke the severity, not the frequency, of hemorrhages into brain infarcts should be the matter of interest. (Stroke 1993;24:465–468)

**KEY WORDS** • cardioembolic stroke • cerebral hemorrhage • cerebral infarction • embolism

Hemorrhagic transformation of ischemic cerebral infarcts is still a matter of controversy, particularly concerning immediate anticoagulation in cardioembolic stroke. This is not surprising because even the true incidence of hemorrhagic transformation is not known yet. Frequency of hemorrhagic transformation varies widely in different types of studies. It is lowest in retrospective computed tomography (CT) studies and highest in autopsy series of acute embolic stroke. Serial CT examinations reveal an incidence of about 40%. Most hemorrhages become visible within the first 2 weeks after a stroke. Actually, hemorrhagic transformation may be even more frequent. Small amounts of blood may be invisible by CT. Magnetic resonance imaging (MRI) is more sensitive, and blood degradation products are detectable for several months after the bleeding. We therefore prospectively studied consecutive patients with supratentorial infarcts due to cardioembolic embolism by MRI 3 weeks after the stroke.

**Subjects and Methods**

Two hundred consecutive patients up to the age of 75 years with a transient ischemic attack (TIA) or ischemic stroke within the last 48 hours underwent a routine diagnostic protocol that included CT, extracranial and transcranial Doppler ultrasonography, color-coded duplex sonography, and examination by a cardiologist with Holter electrocardiography and transesophageal echocardiography. Among these 200 patients 41 (20.5%) could be identified with a CT-proven supratentorial infarct due to embolism from the heart. Criteria for the diagnosis of cardiogenic brain embolism were an embolic heart disease and the absence of ipsilateral common or internal carotid artery stenosis of >50%. Patients with a history of hypertension or diabetes mellitus and more than two lacunes being the only CT abnormality were never categorized as having cardioembolic stroke. All patients had a nonenhanced CT examination within 72 hours after the stroke. The CT scans were evaluated with regard to 1) the vascular territory affected, 2) the volume of infarction edema calculated as maximum length×maximum width×number of 1-cm slices; 3) the mass effect, and 4) the presence of hemorrhagic infarction. Color-coded duplex sonography of the carotid arteries was performed during hospitalization, and results were categorized as indicating no atherosclerosis, atherosclerosis without significant stenosis, or atherosclerosis with stenosis of >50% of the common or internal carotid artery. All 36 patients with a middle cerebral artery infarct underwent transcranial Doppler ultrasonography within 72 hours after the stroke.

Three weeks after the stroke 35 of the 38 patients with cardioembolic stroke who survived had an MRI examination (T1-weighted images; spin/echo sequence: resonance time, 510 msec, echo time, 15 msec; Magnetom SP 63, Siemens, Erlangen, FRG; 1.5-T supercon-
TABLE 1. Source of Embolism in 41 Patients With Cardiogenic Stroke

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial thrombus</td>
<td>10</td>
</tr>
<tr>
<td>Nonvalvular atrial fibrillation without thrombus formation</td>
<td>7</td>
</tr>
<tr>
<td>Noninfective mitral valve disease</td>
<td>6</td>
</tr>
<tr>
<td>Atrial fibrillation with mitral valve insufficiency or prolapse</td>
<td>5</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>3</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
</tbody>
</table>

Other sources were myocarditis, noninfectious thrombotic endocarditis, atrial myxoma, acute myocardial infarction, aortic valve prolapse, patent foramen ovale, prosthetic heart valve, and coronary surgery (intraoperative) (one patient each).

ducting unit). MRI could not be performed in three cases because of claustrophobia or pacemaker. The MRI scans were evaluated concerning hemorrhagic transformation of the infarct and its pattern.

Eight of the 41 patients with cardioembolic stroke received heparin in therapeutic dosage (maximum prolongation of the partial thromboplastin time, 2.5 times). Heparin treatment was started 3–11 days after the stroke except in one patient with a prosthetic heart valve, who received anticoagulant therapy immediately. Volume of the infarct on CT in the seven patients who received anticoagulants within the first week after the stroke was <20 cm$^3$ in every case. A further 25 patients were treated with low-dose heparin for prophylaxis of venous thrombosis. During the first 3 weeks after the stroke 34 patients at some time received acetylsalicylic acid (ASA), five until anticoagulant therapy with heparin was started.

**Results**

Mean±SEM age of the 41 patients with cardioembolic stroke was 61.4±13.6 (range 23–75) years. Twenty patients (48.8%) were male, 18 (43.9%) were hypertensive, and 23 (56.1%) suffered from diabetes mellitus. Due to the stroke 12 patients (29.3%) developed a disturbance of consciousness. Concerning functional outcome, 15 patients (36.6%) had a minor stroke, 23 (56.1%) a disabling event, and three (7.3%) died during the first 3 weeks.

The most frequent source of embolism in the 41 patients was a thrombus in the left atrium, followed by nonvalvular atrial fibrillation without thrombus formation (Table 1).

Concomitant atherosclerosis of the carotid arteries was detectable by duplex sonography in 20 patients (48.8%), affecting the symptomatic artery in 13 (31.7%). Evaluation of the middle cerebral artery by transcranial Doppler ultrasonography was technically sufficient in 29 of the 36 patients with infarcts in the middle cerebral artery territory. Seven patients had evidence of recanalization (increased blood flow velocity, in four cases with signal loss before) within 4 days after the stroke, and none had evidence of persistent occlusion of the stem of the middle cerebral artery.

Most infarcts (18 patients) involved the territory of one or two pial branches of the middle cerebral artery. Ischemia was restricted to subcortical structures in 13 cases and included nearly the whole territory of the middle cerebral artery in the other five. Five infarcts were located in the area of the posterior cerebral artery. Calculated volume of the hypodensity on CT scans was ≤10 cm$^3$ in 18 cases, 11–50 cm$^3$ in 12, and >100 cm$^3$ in eight. Sixteen patients had compression of a lateral ventricle due to ischemic edema, and another two had a midline shift. Only one patient already had minor hemorrhages on the initial CT scan taken on the second day after the stroke.

MRI 3 weeks after the stroke showed hemorrhages in 24 of 35 infarcts (68.6%) (Figures 1 and 2). Most of the patients (17) had petechial hemorrhages along the gyri; five also had disseminated petechial hemorrhages within the basal ganglia. The latter occurred exclusively in three further cases. Four MRI scans showed confluent areas of bleeding, resembling small hematomas, in the subcortical structures; two also showed a gyral hemorrhage. Larger confluent areas of bleeding with a mass effect were observed in two patients. Both suffered from mild arterial hypertension with diastolic blood pressure always <110 mm Hg and received ASA, but not anticoagulants.

Several parameters (age, concomitant atherosclerosis on duplex sonography, arterial hypertension, diabetes mellitus, localization of ischemia, volume of infarction edema on the initial CT scan, evidence of recanalization of the middle cerebral artery on transcranial Doppler sonography, medication with ASA, and anticoagulation with heparin in therapeutic dosage) were tested in a stepwise forward logistic regression analysis for their influence on hemorrhagic transformation of a cerebral infarct. The volume of infarction edema on the initial CT scan was the only parameter independently linked with the occurrence of bleeding into the infarct [exp(β) = 1.22; 95% confidence interval, 1.01–1.48; p = 0.037]. Of 18 infarcts with a volume exceeding 10 cm$^3$ (79.4%) became hemorrhagic compared with only seven of 17 (41.2%) small infarcts up to 10 cm$^3$ in volume (odds ratio, 24.3; 95% confidence interval, 2.6–227.4; p = 0.0052).

**Discussion**

The frequency of hemorrhagic transformation of cerebral infarcts and its clinical significance is still a matter of controversy. Autopsy studies reveal an incidence of bleeding into embolic infarcts of up to 70%,5–7 serial CT examinations of up to >40%. The discrepancy might be explained by differences in the severity of stroke or by insufficiency of CT to detect small hemorrhages. Therefore, the true incidence of hemorrhagic transformation in embolic stroke is still not known. MRI proves to be the appropriate tool to solve this question. MRI has a high sensitivity to detect even small amounts of blood, and blood degradation products are visible for a long time, which makes repeated examinations unnecessary. We performed MRI 3 weeks after the stroke because most hemorrhages occur during this time, as former CT studies have shown. To avoid a selection bias, the patients were consecutive victims of acute TIA or ischemic stroke who underwent a standardized diagnostic routine. All patients of this series with a CT-proven supratentorial ischemic infarct due to cardiogenic embolism were included.
The incidence of hemorrhagic transformation was about 69% on MRI due to enhanced sensitivity and was thus much higher than in studies with sequential CT examinations. It might be surprising that the bleeding rate was as high as or even higher than in autopsy studies, in which large infarcts with greater risk of hemorrhagic transformation should predominate. On the other hand, some patients might not survive until the second or third week after their stroke, by which time some hemorrhagic transformation might just occur.
The patterns of bleeding on MRI and their frequencies resemble those found in CT studies. Most patients had petechial hemorrhages in the cortex and/or basal ganglia as indicated by a disseminated, partly confluent area of increased signal intensity on T1-weighted MRI. The question might arise whether it is actually blood that underlies these lesions or the accumulation of fat-laden macrophages during tissue reaction after ischemic necrosis. Because the cortical pattern of hemorrhage on CT resembles very closely the picture found on MRI, we believe that blood is imaged. As in a former CT study of cardioembolic stroke, about 16% of the hemorrhages were confluent and formed small hematomas. Larger hematomas accounted for about 8% of all hemorrhages in this series, compared with about 11% in two serial CT studies. No patient of this study with hemorrhagic transformation deteriorated clinically, although clinical worsening may occur due to extensive bleeding.

The only factor independently linked with the risk of hemorrhagic transformation of cardioembolic infarcts in this study was the volume of infarction edema on the initial CT scan. The probability of bleeding was about 95% if the volume of infarction edema exceeded 10 cm³. Other parameters did not have any predictive value in this series, but the rather small number of patients has to be taken into account. Besides the size of the infarct, age and arterial hypertension have been discussed as further risk factors but could not be identified as such in different studies consistently. Recently, areas of hypodensity on early (≤4 hours after stroke) CT scans have been discussed as a further predictor of hemorrhagic transformation. In our series such early CT examinations were not performed. Whether anticoagulant therapy increases the risk or the severity of bleeding into infarcted tissue could not be answered from this study because no patient with a large infarct received heparin immediately.

Hemorrhagic transformation of cerebral infarcts due to cardiogenic embolism seems to be a regular finding in medium-sized and large infarcts even without anticoagulation. Thus, concerning therapeutic or preventive studies in cardioembolic stroke, the question should not be whether a certain regimen increases the risk of bleeding into the infarcted tissue. Rather, the matter of interest is whether more severe hemorrhages occur with clinical consequences.

References
Hemorrhagic transformation in cardioembolic cerebral infarction.
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