Timing of Autopsy-Confirmed Hemorrhagic Infarction With Reference to Cardioembolic Stroke

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We studied the temporal profile of hemorrhagic transformation in 34 cases with autopsy-confirmed hemorrhagic infarction who died within 15 days following a supratentorial brain infarct, provided they had undergone computed tomography. It appeared that within 4 days, at least 76% (95% confidence interval 39–100%) of 21 cardioembolic strokes had become hemorrhagic. We conclude that if anticoagulation is considered in cardioembolic stroke, such treatment should not be started sooner than at least 4 days after the onset of stroke, provided that computed tomography at that time shows no hemorrhagic infarction. (Stroke 1988; 19:1482-1484)

Recent clinical studies of the value of anticoagulant treatment of patients with cardioembolic stroke has revived interest in the occurrence and mechanism of hemorrhagic infarction (HI).1-4 Anticoagulation during hemorrhagic transformation of an infarct might worsen the eventual clinical outcome. 2 The incidence of HI on computed tomography (CT) performed shortly after a cardioembolic stroke is approximately 5%,2 but serial CT scanning increases this percentage to 25% or even 43%,1 indicating that hemorrhagic transformation is a dynamic process. In respect to early anticoagulation, it is important to consider the timing of hemorrhagic transformation in the early phase following the onset of stroke. There is only one study addressing this issue by means of early CT scanning at different intervals after stroke to detect HI. Therefore, we studied the timing of hemorrhagic transformation in autopsied patients who had undergone CT during life.

Subjects and Methods
We studied the neuropathology reports of patients dying within 15 days after a CT-confirmed supratentorial brain infarct. On pathologic examination HI was diagnosed in the presence of a (partial) hemorrhagic infarct on macroscopic inspection, confirmed by a microscopic examination. Cases with HI were included only when large, confluent hemorrhages that would not have gone undetected by CT were present. Infarct size was classified as large when an infarct involved the area supplied by one of the three main cerebral arteries, as moderate when it was restricted to a major branch division, and as small when it was confined to a smaller branch area. The cause of death was considered cerebral following brain herniation and as noncerebral following other causes. Patient records were reviewed for age, sex, and number of days between stroke, CT, and death. A cardioembolic cause of stroke was diagnosed in the presence of rheumatic heart disease, paroxysmal or persistent atrial fibrillation, myocardial infarction in the preceding 2 weeks, or aortic or mitral valve stenosis or prosthesis. Initial neurologic deficit was categorized according to Pes- sin et al.,9 slightly modified,10 as mild, moderate, or severe. CT was studied with special reference to the presence of HI. Because the number of cases fulfilling all our criteria (i.e., dying within 15 days after a supratentorial brain infarct, CT as well as eventual autopsy performed, significant HI on pathologic examination) was very low in Maastricht Hospital alone, we collected data from five other major Dutch hospitals as well.

Results
Data are expressed as median (range). Thirty-four cases (13 men, 21 women; age 70 [57–86] years) with confluent hemorrhages in an infarcted area were identified. The interval from stroke until death was 5 (1–15) days, from stroke until CT 2 (0–8) days, and from CT until death 2 (1–11) days. Two patients without a cardioembolic cause were receiving anticoagulant treatment at the time of stroke. In one, warfarin treatment with a thrombo-
test percentage within the therapeutic range was antagonized at stroke onset; CT on Day 3 was without HI. Because of suspected pulmonary embolus, the other patient had been receiving heparin treatment without the activated partial thromboplastin time being therapeutically prolonged at the time of stroke, when the treatment was antagonized; CT on Day 2 showed HI. Warfarin treatment with a thrombostest percentage within the therapeutic range in two patients with cardioembolic stroke was immediately discontinued on admission. Because CT on Days 4 and 6, respectively, in these two patients was without HI, we considered the ultimate occurrence of HI not to be caused by the previous anticoagulation. All remaining patients were without anticoagulant treatment.

Initial neurologic deficit was severe in all but one patient, who had a moderate deficit. Considering both clinical and autopsy data, 25 patients died of brain herniation while eight of the other nine died of cardiac causes (three), pneumonia (two), pulmonary embolism (one), septic shock (one), or mesenteric artery thrombosis (one); in one case the exact cause of death could not be identified. Thirty-three cases had large infarcts; one had a moderate-sized infarct at autopsy. All infarcts were located in the middle cerebral artery territory. In eight cases the anterior and/or posterior cerebral artery territory was involved as well, while five had bilateral middle cerebral artery infarcts.

Twenty-one cases had a potential cardioembolic cause of their stroke; seven of the 21 had HI on CT. Figure 1 shows the number of CT scans with HI in relation to the interval from stroke onset to CT for all 34 cases. In the 21 cases with cardiac embolism, Figure 2 shows the interval during which HI developed (from stroke or negative CT until positive CT or autopsy).

**Discussion**

Especially large cerebral infarcts are considered prone to undergo hemorrhagic transformation.2,11

Although the question of what subgroup of cardioembolic stroke patients would benefit from anticoagulant treatment is not settled,12-16 such treatment is often considered in an attempt to lower the recurrence rate, especially in the early phase following stroke onset.17 Hemorrhagic transformation during anticoagulant treatment is likely to worsen the eventual clinical outcome.2 Therefore, it is important to know whether CT can reliably detect HI and how hemorrhagic transformation develops over time.

Ideally, given the dynamic nature of HI, to answer the first question postmortem CT should be compared with autopsy findings, but this option seems hardly feasible. Therefore, although there are no studies available comparing CT and autopsy findings of HI, it was not our primary aim to relate CT and autopsy data in this respect. Related to the second question, the only available study with serial early CTs found HI on 18 of 27 (67%, 95% confidence interval [CI] 36-97%) CT scans performed within 48 hours after stroke onset in 27 nonanticoagulated cardioembolic stroke patients with eventual HI on CT, and 20 of 27 scans (74%, 95% CI 41-100%) showed HI within 4 days.8 All our cases had eventual autopsy-proven HI to such a degree that its presence would not have gone undetected by CT; this allowed us to conclude that in the instance of a negative CT scan there was indeed no significant HI at that time, enabling us to consider both CT and autopsy findings in relation to the timing of HI. We found 6 of 21 (29%, 95% CI 1-51%) within 48 hours and 16 of 21 (76%, 95% CI 39-100%) with HI within 4 days after stroke. Both studies agree that if HI develops, it does so in
approximately 75% of patients within the first 4 days after the onset of a cardioembolic stroke, irrespective of whether the patient lives or dies. When both studies are analyzed together, hemorrhagic transformation by 4 days occurred in 36 of 48 patients (75%, 95% CI 50–100%); the lower limit of the 95% CI indicates that at 4 days at least half of the patients have developed HI.

When anticoagulant treatment is being considered in a patient with a presumed cardioembolic stroke, it may be judicious to postpone such treatment for at least 4 days, after which CT has effectively excluded HI in most patients. This may be particularly important in patients with large infarcts, who appear to be especially at risk.\(^2\) However, in some patients hemorrhagic transformation is delayed substantially longer.\(^18\)

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References


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