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

J. Lodder, MD, PhD, B. Krijne-Kubat, MD, and P.J.M. van der Lugt, MD, PhD

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%-3 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.8 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 thrombotest 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 when 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.\textsuperscript{2,11} Although the question of what subgroup of cardioembolic stroke patients would benefit from anticoagulant treatment is not settled,\textsuperscript{12-16} such treatment is often considered in an attempt to lower the recurrence rate, especially in the early phase following stroke onset.\textsuperscript{17} Hemorrhagic transformation during anticoagulant treatment is likely to worsen the eventual clinical outcome.\textsuperscript{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 findings 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.\textsuperscript{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, hemor-
rhagic 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 consid-
ered in a patient with a presumed cardioembolic
stroke, it may be judicious to postpone such treat-
ment 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 How-
ever, in some patients hemorrhagic transformation
is delayed substantially longer.18

Acknowledgments

The authors want to thank neurologists, radiolo-
gists, and pathologists of the following hospitals for
their kind cooperation: Academisch Ziekenhuis Maa-
stricht; Catharina Ziekenhuis, Eindhoven; De Wever
Ziekenhuis, Heerlen; Dijkzigt Ziekenhuis, Rotter-
dam; Radboud Ziekenhuis, Nijmegen; Westeinde
Ziekenhuis, Den Haag.

References

17:586–589
3. Lodder J, Krijne-Kubat B, Broekman J: Cerebral hemor-
rhagic infarction at autopsy: Cardiac embolic cause and
the relationship to the cause of death. Stroke 1986;17:626–629
4. Ott BR, Zanami A, Kleeheil J, Funkenstein HH: The
clinical spectrum of hemorrhagic infarction. Stroke 1986;
17:630–637
infarction on CT in cardioembolic stroke. Clin Neurol Neuro-
surg 1987;89:103–105
6. Hakim AM, Ryder-Cooke A, Melanson D: Sequential com-
puterized tomographic appearance of stroke. Stroke 1983;
14:891–897
ischemia and atrial fibrillation: Prospective study. Neuro-
logy 1984;34:1285–1291
8. Cerebral Embolism Study Group: Timing of hemorrhagic
transformation of cardioembolic stroke, in Stober T, Shim-
righ K, Gan ten D, Sherman DG (eds): Central Nervous
System Control of the Heart. Boston, Martinus Nijhoff
10. Lodder J, van der Lugt PJM: Evaluation of the risk of
immediate anticoagulant treatment in patients with embolic
stroke of cardiac origin. Stroke 1983;14:42–46
11. Lodder J: CT-detected hemorrhagic infarction; relation with
the size of the infarct and the presence of midline shift. Acta
Neurol Scand 1984;70:329–335
12. Starkey I, Warlow CH: The secondary prevention of stroke
13. Sherman DG, Hart RG, Easton JD: The secondary preven-
tion of stroke in patients with atrial fibrillation. Arch Neurol
1986;43:68–70
14. Lodder J, Dennis MS, Van Raak L, Jones LN, Warlow CP:
Co-operative study on the value of long-term anticoagula-
tion in stroke patients with non-rheumatic atrial fibrillation.
15. Hart RG: Prevention and treatment of cardioembolic stroke,
in Furlan AJ (ed): The Heart and Stroke. New York,
16. Yatsu FM, Hart RG, Mohr JP, Grotta JC: Anticoagulation of
embolic strokes of cardiac origin: An update. Neurology
1988;38:314–316
17. Cerebral Embolism Study Group: Immediate anticoagula-
tion of embolic stroke: Brain hemorrhage and management
18. Laureno R, Shields RW, Narayan T: The diagnosis and
management of cerebral embolism and haemorrhagic infarc-
tion with sequential computerized cranial tomography. Brain
1987;110:93–105

KEY WORDS • cardiovascular diseases • cerebral hemorrhage
• cerebral infarction • embolism
Timing of autopsy-confirmed hemorrhagic infarction with reference to cardioembolic stroke.

J Lodder, B Krijne-Kubat and P J van der Lugt

Stroke. 1988;19:1482-1484
doi: 10.1161/01.STR.19.12.1482

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/19/12/1482

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/