Cerebral Hemorrhagic Infarction at Autopsy: Cardiac Embolic Cause and the Relationship to the Cause of Death

J. Lodder, M.D.,* B. Krüne-Kubat, M.D.,* and J. Broekman, M.D.†

SUMMARY In 48 patients dying within 15 days following a supra-tentorial cerebral infarct, the presence of hemorrhagic infarction at autopsy was related to a cardiac embolic cause of the infarct, and to the cause of death. Hemorrhagic infarcts were more common among patients dying from brain herniation than among those dying from a non-cerebral cause. Cardiac embolic strokes were more often hemorrhagic at autopsy than strokes without such cause; this could be explained by a significant higher rate of brain herniation and death after embolic stroke. On the other hand infarcts with extended hemorrhages more often tended to have a cardiac than a non-cardiac cause. These data, together with earlier clinical findings suggest that autopsy studies are biased in relating hemorrhagic infarction almost exclusively to a cardiac embolic cause of stroke, although cardiac emboli may produce more extended hemorrhages.

RECENT STUDIES show that early anticoagulation can safely be used in cardiac embolic strokes.14 The timing of such treatment, however, remains controversial.54 Incidental clinical reports on cerebral complications of anticoagulant therapy2-11 and autopsy studies support the fear for such complications because a high rate of hemorrhagic infarcts was related to embolic stroke.12-14 On CT, however, hemorrhagic infarction is rarely seen15-18 even in embolic stroke.11 Furthermore, hemorrhagic infarction is most prevalent in large infarcts with mass effect.19 Embolic strokes relatively often result in large infarcts with bad outcome.14,20-24 Therefore, autopsy findings are probably biased in establishing a high rate of embolic cause in cases with hemorrhagic infarction. The finding of many more embolic strokes in autopsy studies12,13,20,25 than in clinical and epidemiological studies22,26,27 also suggest such bias. Alternatively, the incidence of clinical emboli might be underestimated because of the difference between autopsy and clinical criteria for cardioembolic infarction. Moreover, CT might miss minor hemorrhagic infarction. On the other hand a substantial number of patients with clinically diagnosed cardioembolic stroke have concomitant carotid artery disease as a possible cause of their stroke.25 Clinically the number of cardioembolic strokes might well be overestimated. If the presence of hemorrhages in an infarct is primarily a function of the size of the infarct, one ought to find hemorrhagic infarction more often in cases dying from the direct consequence of large infarction which is brain herniation, regardless of the cause of the infarct. Therefore, in a consecutive autopsy series of ischemic stroke, we studied the incidence of hemorrhagic infarction in patients with and without brain herniation.

Methods

Clinical data and autopsy findings of patients who died between 01-01-1979 and 01-01-1985 within 15 days following a supra-tentorial, non-lacunar, focal cerebral ischemia were evaluated. On pathological examination the cerebral infarct compatible with the recent stroke was listed as either ischemic necrosis (IN), or as hemorrhagic infarction (HI) when on macroscopic examination a (partial) hemorrhagic infarct was present and confirmed by microscopic examination.20 The extent of hemorrhage was judged as 'small', if one or some small areas of petechial hemorrhages were present, or as 'large' when areas of confluent hemorrhages were observed. Examples of both categories are represented in figures 1 and 2. The cause of death was judged to be either 'cerebral' when death had resulted directly from brain herniation, or 'non-cerebral' when death had resulted from an other cause such as: pneumonia, myocardial infarction, pulmonary embolus, etc.

Although the study was partially done on retrospect, apart from two cases these data could be gathered without exception since they were systematically mentioned in the pathologist's report. Patient records were reviewed for the following features: patient's age and sex; number of days between stroke and death; cardiac

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embolic cause of the infarct on clinical grounds such as: rheumatic heart disease, paroxysmal or chronic atrial fibrillation, aortic or mitral valve stenosis or prosthesis, myocardial infarction in the preceding two weeks, and myocarditis; whether the cause of death was ‘cerebral’ when the patient had died from central, or uncinate herniation, or ‘non-cerebral’. On the basis of clinical and pathology data the definite cause of death was established, and if doubt existed the most probable cause was chosen. We considered the question when anticoagulation should be started in patients with cardiac embolic stroke as most relevant. Therefore, we made the diagnosis ‘cardiac embolic stroke’ on clinical grounds. No attempt was made to separate embolic strokes caused otherwise since it would not effect the clinical decision about anticoagulation.

**Results**

Data are expressed as median with range. There were 25 males and 23 females aged 73 (39-90) year. Interval from stroke till death was 6 (0-15) days for all cases, 4 (0-14) days for patients dying from brain herniation, and 8 (0-15) days for patients dying from non-cerebral causes (p < 0.01; two-tailed RIDE test). Non-cerebral causes were: pneumonia: 8, myocardial infarction: 6, pulmonary embolus: 2, sepsis/shock: 3, hepatic coma: 1, diabetic coma: 1. The number of cases with cerebral or non-cerebral cause of death, and the corresponding numbers of either HI or IN are shown in table 1. Almost all patients with HI at autopsy had died from brain herniation (15/16, = 94%). Fifteen of 27 patients (56%) dying from brain herniation had HI at autopsy against one of 21 patients (5%) who died from a non-cerebral cause (p < 0.001; X²-test). Table 2 gives the data on the cause of death, and the aspect of the infarct at autopsy separately for patients with a cardiac embolic cause of stroke and patients without such a cause. Of the 16 cases with HI 10 had a cardiac embolic cause (63%). Ten of 19 (53%) with a cardiac embolic stroke had HI at autopsy against only six of 29 cases (21%) in the remaining group (p < 0.05; X²-test). However, 14 of 19 patients (74%) with a cardiac embolic stroke died from brain herniation against 13 of 29 (45%) with non-cardiac cause. Since we expected the difference in this direction, one-tailed testing sufficed to establish the difference to be significant below the five percent level (X²-test). In patients dying from brain herniation HI was equally present in

![Figure 1](image1.png)

**Figure 1.** Large confluent hemorrhages in a left-sided infarct that was caused by a cardiac embolus in a 63-year-old female.

![Figure 2](image2.png)

**Figure 2.** Small areas of petechial hemorrhages in a large, left-sided infarct that resulted from internal carotid artery thrombosis in a 68-year-old female.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Autopsy Findings in Patients Dying from Brain Herniation or from a Non-cerebral Cause, within 15 Days following a Supra-tentorial Brain Infarct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain herniation:</td>
<td>27</td>
</tr>
<tr>
<td>Non-cerebral death:</td>
<td>21</td>
</tr>
<tr>
<td>HI: 15</td>
<td>IN: 12</td>
</tr>
<tr>
<td>Brain infarct:</td>
<td>4K</td>
</tr>
<tr>
<td>HI: 1</td>
<td>IN: 20</td>
</tr>
</tbody>
</table>

HI = hemorrhagic infarction; IN = ischemic necrosis.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Autopsy Findings in Patients with, and without a Cardiac Embolic Caused Stroke who Died within 15 Days following the Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain herniation:</td>
<td>14</td>
</tr>
<tr>
<td>Non-cerebral death:</td>
<td>5</td>
</tr>
<tr>
<td>HI: 9</td>
<td>IN: 5</td>
</tr>
<tr>
<td>Cardiac embolic stroke:</td>
<td>19</td>
</tr>
<tr>
<td>HI: 1</td>
<td>IN: 4</td>
</tr>
<tr>
<td>Non-cardiac caused stroke:</td>
<td>29</td>
</tr>
<tr>
<td>HI: 0</td>
<td>IN: 16</td>
</tr>
</tbody>
</table>

HI = hemorrhagic infarction; IN = ischemic necrosis.
the group of cases with a cardiac cause of stroke (9/14, 
= 64%), and those without such cause of stroke (6/13, 
= 46%).

However, in these patients 6 of 9 (= 67%) with a cardioembolic stroke had large confluent hemorrhages, and only 2 of 6 (= 36%) patients with a non-cardiac cause of stroke.

Discussion

Recently, discussion on the timing of anticoagulant treatment in cardiac embolic stroke has been revived. One of the arguments to oppose early anticoagulant comes from autopsy findings: the close relationship of hemorrhagic infarction with cardiac embolic stroke leads to the fear of cerebral bleeding should anticoagulants be started. The concept of hemorrhagic infarction indicating an embolic cause was introduced by Fisher and Adams. In an autopsy series they found that 63 hemorrhagic infarcts (95%) had an embolic cause, and 66 of 132 embolic strokes (54%) were hemorrhagic infarcts. The authors neither mentioned the interval from stroke till death nor wether patients died from brain herniation. They did not define 'embolic stroke', but most probably they referred to cardiac embolic strokes. Because Fisher and Adams found no obstruction in the feeding vessel to the infarcted area in ten cases, they proposed a pathophysiological mechanism of hemorrhagic infarction that was further validated by autopsy and angiography studies. At autopsy Adams and Van der Eecken found hemorrhagic infarcts in 26 of 57 cases (65%) after a cardiac embolic stroke. They also did not mention the interval between stroke and death, nor the direct cause of death. Jørgensen and Torvik found a cardiac embolic cause in 42 of 54 (78%) hemorrhagic infarcts, and hemorrhagic infarcts in 42 of 59 (71%) cardiac embolic strokes. Aggregated data of the three above-mentioned studies indicate that 134 of 239 (56%) embolic infarcts were hemorrhagic, and 105 of 120 (88%) hemorrhagic infarcts had a cardiac embolic cause. If more than half of all clinically diagnosed cardiac embolic strokes would consist of hemorrhagic infarcts, the more the authors neither mentioned the interval from stroke till death nor wether patients died from brain herniation. Patients with a cardiac embolic cause...
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