Nonvalvular Atrial Fibrillation as a Cause of Fatal Massive Cerebral Infarction in the Elderly

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By studying 3,408 consecutive autopsied elderly patients, we found that two thirds of the 132 massive cerebral infarctions (86) were embolic, of cardiac origin. Embolic infarction associated with nonvalvular atrial fibrillation was seen in 48 cases (36%), half due to the first stroke. Embolic infarction associated with heart diseases other than nonvalvular atrial fibrillation was seen in 23 cases (17%), and that from nonbacterial thrombotic endocarditis was seen in 15 cases (11%). Thrombotic infarction or infarction of nonembolic cardiac origin was found in only 39 cases (30%). Of 56 patients with fatal massive cerebral infarction who died ≤2 weeks after their stroke, 25 (45%) had embolic strokes associated with nonvalvular atrial fibrillation. Our study shows that nonvalvular atrial fibrillation is a very important cause of fatal massive cerebral infarction in the elderly. (Stroke 1989;20:1653-1656)

The incidence of atrial fibrillation (AF) increases with age.1-2 Kuramoto et al1 reported that approximately 17% of all autopsied elderly patients had AF, and 20% of these had large cerebral infarcts at autopsy. Although nonvalvular atrial fibrillation (NVAF) is emphasized as a cause of embolic stroke,3-7 there is little information about the incidence of NVAF in fatal massive cerebral infarction. We report from our autopsy series the importance of NVAF as a cause of massive cerebral infarction, especially of fatal cerebral infarction in the elderly.

Subjects and Methods

Among 3,408 consecutive autopsies of patients >60 years of age during the 13 years from 1975 to May 1988, supratentorial massive cerebral infarcts were found in 132. Cerebral infarction was defined as massive when half or more of the volume of a cerebral hemisphere was involved. We excluded cases with basilar artery occlusion. The age and sex distribution of the patients autopsied are listed in Table 1.

We classified the massive cerebral infarction as one of the following types according to the onset of neurologic symptoms and pathologic findings: 1) embolic infarction of cardiac origin associated with NVAF, 2) embolic infarction with valvular or other heart diseases, 3) embolic infarction with nonbacterial thrombotic endocarditis (NBTE) or disseminated intravascular coagulation syndrome (DIC), 4) thrombotic infarction or nonembolic infarction of cardiac origin, 5) infarction of another unusual cause, and 6) infarction of an undetermined cause.

Cerebral infarction was diagnosed as embolic of cardiac origin when the onset of focal neurologic symptoms was abrupt in patients with heart diseases such as AF, valvular disease, or NBTE and in patients with DIC. Cerebral infarction was diagnosed as thrombotic or as nonembolic of cardiac origin in patients without AF or other heart disease and/or in patients in whom intracardiac thrombus was absent at autopsy. Even when AF or heart disease existed, stroke with the gradual onset of neurologic symptoms was considered to be thrombotic or nonembolic of cardiac origin.

In patients who died ≤2 weeks after their stroke, the cause of death was judged to be cerebral in principle when death had resulted from severe brain swelling or brain herniation and as noncerebral when death had resulted from pneumonia, infectious disease, myocardial infarction, renal failure, or other complications. Recent cerebral infarction was classified as either ischemic necrosis or hemorrhagic infarction (HI) by macroscopic criteria. The extent
TABLE 1. Age and Sex Distribution of Autopsied Elderly Patients With Massive Cerebral Infarction

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-69</td>
<td>10</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>70-79</td>
<td>22</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>80-89</td>
<td>17</td>
<td>38</td>
<td>55</td>
</tr>
<tr>
<td>≥90</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>54</td>
<td>78</td>
<td>132</td>
</tr>
</tbody>
</table>

of hemorrhage in the infarcted area was judged to be small HI when one or a few small areas of petechial hemorrhage were present and to be large HI when confluent hemorrhages were observed. Statistical analysis was performed by χ² test.

Results

Among 132 cases of massive cerebral infarction confirmed at autopsy, 48 (36%) were embolic stroke associated with NVAF, 38 (29%) were embolic stroke associated with organic heart diseases or NBTE, and 39 (30%) were thrombotic infarction or nonembolic infarction of cardiac origin. The other seven cases were infarction of another or an undetermined cause.

The incidence of embolic cerebral infarction associated with NVAF was high among patients who died within 2 weeks but low among those who survived longer (Table 2); 43 (77%) of the 56 patients who died within 2 weeks did so from direct cerebral causes. Among those who died ≤2 weeks after their stroke, the incidences of cerebral death, brain herniation, secondary brainstem hemorrhage, or HI did not differ significantly among infarction types (Table 3).

Of the 48 patients with NVAF, 23 (48%) had a history of ischemic stroke prior to the final massive infarction. Fourteen of the 23 were considered to be embolic strokes of cardiac origin in which many of the old infarcts were cortical in the contralateral middle cerebral artery (MCA) territories. The remaining nine previous strokes were of undetermined type due to insufficient clinical records or the lack of confirmation of AF at that time; the old infarcts were seen in the white matter, the basal ganglia, or the cerebral cortices. Ischemic strokes prior to the massive infarction were also seen in 12 (52%) of the 23 patients with valvular or other heart disease. Ten of the 12 were considered clinically to be embolic stroke, in which many of the old infarcts were found in the cerebral cortices, especially in the territories of the contralateral MCA. Previous strokes were also observed in 12 (31%) of the 39 patients with thrombotic infarction. In these 12 cases, old infarcts were found in the deep white matter, the basal ganglia, the thalamus, or the cerebral cortices; one case showed an old putaminal hemorrhage.

Hypertension or history of hypertension was seen in 69% of the patients with NVAF, in 61% of those with valvular or other heart disease, in 53% of those with NBTE, and in 87% of those with thrombotic infarction.
TABLE 3. Cause of Death, Pathologic Findings of Brain, and Incidence of Hemorrhagic Infarction by Type of Infarction in Autopsied Elderly Patients Who Died ≤2 Weeks After Massive Cerebral Infarction

<table>
<thead>
<tr>
<th>Type of Infarction</th>
<th>Embolic</th>
<th>Other Heart Diseases</th>
<th>NBTE</th>
<th>Thrombotic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>NVAF (n=25)</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Cause of Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral</td>
<td>N=56</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>43</td>
<td>19</td>
<td>77</td>
<td>7</td>
</tr>
<tr>
<td>Brain Pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain herniation</td>
<td></td>
<td></td>
<td>38</td>
<td>68</td>
<td>17</td>
</tr>
<tr>
<td>Secondary brainstem hemorrhage</td>
<td>17</td>
<td>30</td>
<td>32</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Hemorrhagic Infarction</td>
<td></td>
<td>Large</td>
<td>15</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Small</td>
<td>23</td>
<td>41</td>
<td>11</td>
<td>44</td>
</tr>
</tbody>
</table>

NVAF, nonvalvular atrial fibrillation; NBTE, nonbacterial thrombotic endocarditis.

At autopsy, intracardiac thrombi in the left heart were confirmed in 27% of the NVAF patients and in half of those with valvular or other heart disease. Severe atherosclerotic changes of the cerebral or carotid arteries were observed significantly less frequently in cases of embolic infarction with NVAF or other heart disease than in those with thrombotic infarction (Table 4).

Discussion

Approximately 35% of patients with AF will experience an ischemic stroke during their lifetime.8-10 Åberg11 reported that among 504 autopsied AF patients without valvular or congenital heart diseases, systemic embolism was evident in 42%, half of which were brain embolism. NVAF is the most common cardiac source of embolism, accounting for approximately 45% of all embolic strokes.3-7 Although the risk of early death is not high in cerebral infarction,12-16 it is greater with embolic stroke than with thrombotic infarction.12-13,16,17

In our study, three fourths of the patients with massive cerebral infarction who died within 2 weeks showed embolic stroke of cardiac origin, and 45% of the cases of early death were associated with NVAF. On the other hand, among patients who

TABLE 4. Pathologic Findings of Heart, Extracranial Arteries, and Intracranial Arteries in Autopsied Elderly Patients After Massive Cerebral Infarction

<table>
<thead>
<tr>
<th>Type of Infarction</th>
<th>Embolic</th>
<th>Other than NVAF</th>
<th>NBTE</th>
<th>Thrombotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finding</td>
<td>NVAF (n=48)</td>
<td>Heart disease</td>
<td>NBTE (n=15)</td>
<td>Thrombotic (n=39)</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Intracardiac thrombi in left heart</td>
<td>13*</td>
<td>27.0</td>
<td>12</td>
<td>52.2</td>
</tr>
<tr>
<td>Cerebral arterial occlusion‡</td>
<td>19</td>
<td>39.6</td>
<td>9</td>
<td>39.1</td>
</tr>
<tr>
<td>Severe atherosclerosis of cerebral arteries in affected site</td>
<td>16</td>
<td>33.3</td>
<td>7</td>
<td>30.4</td>
</tr>
<tr>
<td>Severe atherosclerotic change of carotid artery</td>
<td>6</td>
<td>12.5</td>
<td>3</td>
<td>13.0</td>
</tr>
<tr>
<td>Occlusion of carotid artery</td>
<td>6</td>
<td>12.5</td>
<td>6</td>
<td>26.1</td>
</tr>
<tr>
<td>Occlusion in other systemic arteries</td>
<td>14</td>
<td>29.2</td>
<td>10</td>
<td>43.5</td>
</tr>
</tbody>
</table>

NVAF, nonvalvular atrial fibrillation; NBTE, nonbacterial thrombotic endocarditis; Severe atherosclerosis of cerebral arteries, ≥50% narrowing of lumen; Other systemic arteries: subclavian, mesenteric, renal, iliac, or femoral.

*All in left atrium.
†All at mitral or aortic valve.
‡Many at stem of middle cerebral artery or intracranial internal carotid artery.
§p<0.01, 0.05, respectively, greater than NVAF and Heart disease other than NVAF by χ² test.
∥Many at femoral artery.
survived ≥6 months, half had thrombotic infarction or nonembolic infarction of cardiac origin. Jørgensen and Torvik\(^8\) also indicated a better prognosis for nonembolic than for embolic stroke, finding that only 19% of old infarcts but half of recent infarcts were embolic. The most frequent cause of early death in massive cerebral infarction is transtentorial herniation associated with acute brain swelling.\(^9,20\)

HI is related to cause of death and to brain herniation but not always to embolic infarction of cardiac origin.\(^21,22\) Our study also shows that many patients with massive cerebral infarction resulting in early death had had brain herniation and HI regardless of embolic or nonembolic stroke (Table 3).

Atherosclerosis in the carotid or cerebral arteries was less severe in cases of embolic infarction with NVAF than in cases of thrombotic infarction, but there was no difference in incidence of occlusions in these arteries (Table 4). Many of the occlusive thrombi in NVAF patients could have originated from the left atrium, although only one fourth of the cases with NVAF showed left atrial thrombi at autopsy. Many of the thrombi formed in the left atrium could have already been carried away to the systemic arteries.

Half of the embolic stroke cases with NVAF or other heart disease had ischemic strokes prior to the final massive infarction, but the other half had no previous stroke. Many of the earlier strokes were considered to be embolic clinically. The recurrence rate of embolic stroke is high not only in AF associated with rheumatic heart disease\(^23-26\) but also in NVAF.\(^7,8,10,25,27\) Our study shows that half of the fatal massive infarctions associated with NVAF were first strokes and suggests that primary prophylaxis,\(^28,29\) as well as secondary prevention,\(^30\) should be considered to prevent fatal massive infarction in elderly NVAF patients.

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