Occurrence of Hemispheric and Retinal Ischemia in Atrial Fibrillation Compared With Carotid Stenosis

D.C. Anderson, MD; L.J. Kappelle, MD; M. Eliasziw, PhD; V.L. Babikian, MD; L.A. Pearce, MS; H.J.M. Barnett, MD

Background and Purpose—The goal of this study was to examine the hypotheses that retinal ischemia is caused more often by carotid atherosclerosis than by atrial fibrillation and that the odds of retinal events compared with hemispheric events increase with worsening carotid stenosis.

Methods—We used data from the Stroke Prevention in Atrial Fibrillation (SPAF) I through III trials and North American Symptomatic Carotid Endarterectomy Trial (NASCET), calculating hemispheric:retinal (H:R) odds for the territory of ischemic events during follow-up in patients with atrial fibrillation and medically treated 50% to 99% carotid stenosis or occlusion in the respective trials.

Results—The H:R odds were 25:1 in the SPAF aspirin-assigned patients and 2:1 for NASCET vessels. In NASCET patients, the H:R odds of recurrent ischemic events were 1:4 for vessels randomized initially for retinal symptoms compared with 6:1 for those randomized for hemispheric events (significant difference; P < 0.001). Moreover, the H:R odds of first events in the territory of the contralateral asymptomatic artery were 1:1 if the randomized vessel had retinal symptoms compared with 4:1 if the randomized vessel had hemispheric symptoms (significant difference; P < 0.01). Increasing carotid stenosis in the 50% to 99% range had no effect on H:R odds (P = 0.8).

Conclusions—These findings confirm that retinal symptoms are more typical of carotid stenosis. Hemodynamic effects do not appear to be more important in the pathogenesis of retinal events than hemispheric ones in carotid stenosis. The retinal versus hemispheric location of initial symptoms is strongly predictive of the location of subsequent events in patients with carotid stenosis, even when new symptoms are contralateral to the original ones. (Stroke. 2002;33:1963-1968.)

Key Words: atrial fibrillation ■ carotid stenosis ■ cerebrovascular disorders

Retinal ischemia is believed to be more characteristic of carotid stenosis than of atrial fibrillation. The study reported here tests this construct through prospectively collected data from 2 relevant stroke prevention projects, the Stroke Prevention in Atrial Fibrillation (SPAF) I through III trials and the North American Symptomatic Carotid Endarterectomy Trial (NASCET). The hypothesis that retinal ischemia caused by carotid disease is promoted by more severe stenosis is also tested.

Subjects and Methods

Study Subjects

Characteristics of study participants, trial designs,1–4 and primary results of the SPAF trials5–8 and NASCET9,10 have been reported previously. In brief, the SPAF I through III trials examined the effects of antithrombotic agents in preventing stroke in patients with nonvalvular atrial fibrillation. The 2012 patients in these analyses include 1722 SPAF I through III patients assigned aspirin (325 mg/d) alone and the 290 patients in SPAF III given aspirin plus ineffica-

Outcome Events and Follow-Up

Outcome events were defined as the first occurrence of transient monocular blindness, retinal infarction, transient ischemic attack...
(TIA), or ischemic stroke after randomization. Hemispheric events were defined as ischemic events that occurred in the supply area of the ICA, whereas vertebrobasilar events occurred in the territory of the posterior circulation. In the SPAF trials and NASCET, clinical events were detected, characterized, and validated in several steps. Characterization of events included severity of deficit, territory of involvement, and presumed mechanism of ischemia. For SPAF events, the local neurologist-investigator made the initial assessment, and a blinded events committee made a final determination. In NASCET, the local neurologist-investigator and members of the trial outcomes committee independently assessed each event, with a final determination made by blinded external adjudicators. In the present study, patient follow-up for both the SPAF and NASCET patients was censored at the time of a retinal event, brain TIA, ischemic stroke, death, end of study, or 5 years, whichever occurred first. Follow-up of NASCET vessels was also censored at the time of ipsilateral carotid endarterectomy.

Statistical Analysis
Odds of hemispheric:retinal (H:R) and brain:retinal (B:R) ischemic events were computed, excluding ischemic events that occurred in multiple or unknown vascular territories. Retinal and hemispheric events occurring ipsilateral to the relevant stenosis were considered in both H:R and B:R event odds. Verteobasilar events were included in the B:R but not the H:R event odds. Retinal and hemispheric events occurring in 1 carotid system were assumed to be independent of events occurring in the contralateral system within the same NASCET patient. H:R event odds were compared between groups with an exact test for the odds ratio. All tests were 2 sided, and statistical significance was accepted at $P < 0.05$.

Results
The SPAF aspirin-assigned patients and the NASCET patients included in these analyses were of similar age and sex (Table 1). Clinical atherosclerotic risk factors were more prevalent in the NASCET groups.

Among the 2012 aspirin-assigned SPAF patients, retinal events ($n=5$) were infrequent compared with brain events ($n=160$; Table 2). Relative to hemispheric events ($n=127$), retinal events occurred about 1/25th as often (H:R odds, 25:1). This was not statistically different ($P=0.07$) from the H:R odds of 7:1 (40 hemispheric events, 6 retinal events) observed in the SPAF I placebo patients. Confirming our first hypothesis, retinal events were more frequent in the NASCET study groups, occurring about half as often as hemispheric events in both the symptomatic and asymptomatic groups (H:R odds, 2:1; Table 2 and Figure 2).

In symptomatic NASCET vessels, the location of the index event was a strong predictor of site of a recurrent event (Table 3); ie, retinal events usually preceded retinal events (H:R odds, 1:4), and hemispheric events preceded hemispheric events (H:R odds, 6:1; $P<0.001$). The index event corresponding to the symptomatic artery also predicted the site of the first event in the contralateral vessel that was asymptomatic at study entry (Table 4; $P<0.01$).

Increasing stenosis did not significantly affect the H:R odds for outcome events in the territory of the symptomatic NASCET vessels, regardless of location of index event (Table 3; $P=1.0$ retinal index event; $P=0.3$ hemispheric index event). Similarly, there was no significant difference in the odds by stenosis severity in the asymptomatic systems ($P=0.3$). In the separate group of 86 asymptomatic occluded ICAs, the H:R odds were 4:1. When the 3 vascular groups

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>SPAF, Aspirin Treated (n=2012)</th>
<th>NASCET, 50% to 99% Symptomatic ICA (n=759)</th>
<th>NASCET, 50% to 99% Asymptomatic ICA (n=324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean follow-up, y</td>
<td>1.9</td>
<td>1.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>69</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Men, %</td>
<td>72</td>
<td>71</td>
<td>68</td>
</tr>
<tr>
<td>History of, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>52</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>MI or angina</td>
<td>16</td>
<td>40</td>
<td>44</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>7</td>
<td>15</td>
<td>18</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction.
(symptomatic-retinal index event, symptomatic-hemispheric index event, asymptomatic) were considered together (test for common odds ratio, \( P = 0.2 \)), the H:R odds were not significantly different by degree of stenosis (\( P = 0.8 \)).

A minority of subjects followed up in SPAF and NASCET had or developed both atrial fibrillation and carotid stenosis, potentially confusing assignment of blame for subsequent ischemic events. In an SPAF substudy, carotid stenosis \( \geq 50\% \) was documented ultrasonographically in 12% of enrollees at entry, and a remote history of stress-related (eg, during acute pulmonic infection or alcohol intoxication) atrial fibrillation was elicited in 13 NASCET subjects (1.7%) at entry. Investigations at the time of events discovered both atrial fibrillation and relevant carotid stenosis in 11 SPAF events and 10 NASCET events. The events in which the mechanism was ambiguous are indicated in Table 2.

**Discussion**

As hypothesized, retinal ischemia makes up a smaller proportion of events during prospective observation of patients with atrial fibrillation than with carotid stenosis. The hypothesis that more severe stenosis favors the subsequent occurrence of retinal versus hemispheric ischemia is not supported in vessels with \( \geq 50\% \) ICA stenosis.

It might be reasoned that the relative paucity of retinal events compared with brain events in patients with atrial fibrillation results because a particle from the heart may potentially travel to the territories supplied by the vertebro-basilar system, whereas one originating from a carotid bifurcation is restricted to the ipsilateral ophthalmic or hemispheric cerebral vessels. The observed H:R odds, however, are quite similar to the B:R odds for both SPAF and NASCET.

**TABLE 2. Number of Outcome Events by Territory, Type, and Odds of Occurrence**

<table>
<thead>
<tr>
<th></th>
<th>SPAF, Aspirin Treated (n=2012)</th>
<th>NASCET, 50% to 99% Symptomatic ICA (n=759)</th>
<th>NASCET, 50% to 99% Asymptomatic ICA (n=324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemispheric, n</td>
<td>127</td>
<td>253</td>
<td>48</td>
</tr>
<tr>
<td>Vertebrobasilar, n</td>
<td>33</td>
<td>37</td>
<td>22</td>
</tr>
<tr>
<td>TIA[†]</td>
<td>11</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>Stroke[†]</td>
<td>22</td>
<td>10 [1]</td>
<td>7</td>
</tr>
<tr>
<td>Retinal, n</td>
<td>5</td>
<td>124</td>
<td>22</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>H:R odds</td>
<td>25:1</td>
<td>2:1</td>
<td>2:1</td>
</tr>
<tr>
<td>B:R odds</td>
<td>32:1</td>
<td>2:1</td>
<td>3:1</td>
</tr>
</tbody>
</table>

*The following additional events occurred in multiple/unknown territories: SPAF patients, 4 TIA; and 7 strokes; NASCET patients, 0.
[†]Events with both atrial fibrillation and relevant carotid stenosis.

**TABLE 3. Number of Outcome Events in NASCET by Territory, Index Event, Degree of ICA Stenosis, and Odds of Occurrence**

<table>
<thead>
<tr>
<th>Territory of Index Event</th>
<th>Hemispheric ICA</th>
<th>Retinal ICA</th>
<th>Asymptomatic ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>50%–69% ICA stenosis</td>
<td>n=331</td>
<td>n=97</td>
<td>n=198</td>
</tr>
<tr>
<td>Hemispheric event, n</td>
<td>130</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>Retinal event, n</td>
<td>17</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>H:R odds</td>
<td>8:1</td>
<td>1:4</td>
<td>2:1</td>
</tr>
<tr>
<td>70%–99% ICA stenosis</td>
<td>n=219</td>
<td>n=112</td>
<td>n=126</td>
</tr>
<tr>
<td>Hemispheric event, n</td>
<td>101</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Retinal event, n</td>
<td>20</td>
<td>54</td>
<td>5</td>
</tr>
<tr>
<td>H:R odds</td>
<td>5:1*</td>
<td>1:4†</td>
<td>3:1‡</td>
</tr>
<tr>
<td>Occluded ICA</td>
<td>n=86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemispheric event, n</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal event, n</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H:R odds</td>
<td>4:1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*H:R odds in 36 patients with a near-occlusion ICA was 4:1.
†H:R odds in 21 patients with a near-occlusion ICA was 1:3.
‡H:R odds in 29 patients with a near-occlusion ICA was 5:1.
patients, arguing that a more limited potential destination for atherothromboembolism does not explain this difference in likelihood of retinal versus hemispheric symptoms between the 2 groups.

A hypothesis suggested to explain this observation is that retinal symptoms may occur with embolism of smaller particles, characteristic of artery-to-artery embolism, in contrast to brain symptoms, which require larger particles, perhaps more typical of clots from a cardiac source. Implied in this explanation is that smaller particles may frequently be launched from the carotid bifurcation to the retina and brain, causing symptoms in the former because of greater sensitivity while being mostly silent in the latter. Hence, the embolism of small particles to the brain would be underascertained, driving down the B:R odds. According to this explanation, larger particles from the heart, presumably distributed according to relative flow, are less frequent but equally likely to cause symptoms in either location. The same reasoning has been used to explain the greater likelihood of long-duration TIAs and completed strokes among those with a cardiac source of embolism such as atrial fibrillation and shorter attacks in those with carotid disease.13–16

Supporting the idea of a particle size differential is the relative frequency of TIAs compared with strokes observed in this study: 1:2 in SPAF patients and 3:1 in NASCET. More proximal obstruction resulting from embolism by larger particles may also be a factor in explaining why cardioembolic strokes are more severe than those caused by other mechanisms.18–20

That tighter stenosis in patients with carotid disease favors retinal as opposed to brain ischemia has been previously reported.21–25 In fact, considering the degree of stenosis as it relates to the distribution of the index events supports these reports. Table 3 shows H:R odds of index or qualifying events in symptomatic vessels of 3:1 (331:97) versus 2:1 (219:112) for 50% to 69% and 70% to 99% stenosis, respectively (P=0.001). The outcome data, however, show no such relationship in any vascular group (ie, symptomatic vessels regardless of site of index event or initially asymptomatic vessels). It is unclear why a relationship is seen for the index events but not for outcome events. These findings suggest that in carotid stenosis, hemodynamic factors are probably not more important in retinal than in brain symptoms.

In NASCET patients, the location (retinal versus hemispheric) of the ischemic event for which the patient was randomized strongly influenced where subsequent events occurred; recurrent events tended to recapitulate the initial event with respect to location, a trend that has been noted previously.13,25,26 If only the randomized vessel had been considered in this analysis, it would have been impossible to separate this recapitulation effect from that of the atherothrombotic mechanism under study. That is, the apparent greater propensity for retinal ischemia in NASCET patients might have been due to initial enrollment of a larger proportion of retinal than hemisphere patients. The fate of the nonrandomized, asymptomatic stenotic vessels, however, shows that lower H:R odds are characteristic of carotid stenosis itself. Further evidence is provided by data from the medical arm of a trial of carotid endarterectomy in asymptomatic patients. In the Veterans Affairs Study Group Trial, 11 episodes of transient monocular blindness, 15 TIAs, and 22 strokes occurred in the distribution of the randomized vessel during an average of 48 months of follow-up in the 233 medical patients, an H:R outcome events odds of 3:1.27

The explanation for the recapitulation effect in symptomatic carotid vessels is speculative. Flow is laminated in the large arteries, and various laminae are directed to different distal vascular beds.28–32 It is postulated that particulate matter of uniform size consistently deposited into one lamina from a mural plaque or ulcer will be swept into the same distal bed, a streaming effect. This model emphasizes the importance of artery-to-artery embolism in atherothrombotic stroke. The finding that the recapitulation effect crosses carotid systems within a patient, however suggests alternative explanations. That is, when the qualifying event was retinal, there was an increased likelihood that a new contralateral atherothrombotic event would also be retinal, and similarly with hemispheric events. This suggests that factors inherent to the individual may affect the H:R odds in patients with carotid stenosis. Idiosyncratic characteristics that might vary between individuals include susceptibility of retinal or cerebral tissues, plaque makeup, hemostatic or other factors influencing particle size or composition, and angles of vascular bifurcations.33,34 It is also possible that there is enhanced sensitivity for a symptom when there has been previous experience with it. Whatever its basis, the tendency of retinal events to presage retinal recurrence is in keeping with the lower rate of subsequent stroke reported in patients with transient monocular blindness compared with TIAs.25,26,35,36

This study had several strengths. Because patients were characterized ahead of time, the factors under study could be examined as predictors rather than associations. The endpoint data were collected without knowledge of the hypotheses of this study, thus avoiding bias. Ongoing surveillance and uniform procedures for event detection and characterization in both the SPAF trials and NASCET optimized endpoint ascertainment. On the other hand, differences in trial goals and conduct represent potential limitations. We cannot exclude the possibility that clinical bias about the mecha-
nisms under study in the trials affected ascertainment of events. For example, more emphasis may have been devoted to ascertaining retinal symptoms in NASCET. Also, the 2 populations were different with respect to symptom status at the time of trial entry. A minority of SPAF enrollees (8%) had had previous thromboembolic events, whereas all NASCET patients had. We were unable to examine whether the recapitulation effect, which influenced the retinal versus hemispheric location of recurrent events in NASCET patients, also affects the site of recurrent cardioembolic strokes. Because almost all patients received antithrombotic therapy, the results cannot be construed as natural history. Finally, both cohorts were selected to be free of trial exclusions. In that sense, they differed from the total spectrum of patients with the risk factors of interest. Despite these limitations, a dramatic difference in the relative occurrence of retinal events according to ischemic mechanism has been unequivocally shown.

Acknowledgments

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References

Editorial Comment

Amaurosis in Carotid Stenosis Versus Atrial Fibrillation: Prediction or Observation?

The observation by Anderson et al that amaurosis fugax is more common in patients with carotid disease than in those with atrial fibrillation is interesting and potentially useful. Some patients with amaurosis fugax will have atrial fibrillation in addition to significant carotid stenosis, and endarterectomy should be considered if carotid disease is the culprit.

As interesting and potentially useful as this observation is, it remains just an observation, and the authors overstate the strength of their evidence. They state “because patients were characterized ahead of time, the factors under study could be examined as predictors rather than associations.” Nothing could be further from the truth.

To be a predictor, an association must be specified before the results are known. That the patients were described in advance, in whatever detail, does not render an association predictive.

This study was preceded by the impression of a low incidence of retinal ischemia in the SPAF-II study (D.C. Anderson, MD, et al, personal communication, 2002), and the study compared NASCET with SPAF-I, -II, and -III. The hypothesis that “there will be few retinal events in the SPAF trials” is virtually certain to be confirmed by counting them once one has noticed that there were not many. A probability value calculation just reflects the size of the trials. The data on which a hypothesis is generated cannot be used to confirm it (common practice notwithstanding).

The test is, could you have made money on it? Although lots of us noticed the meteoric rise of the “dot.com” stocks, only those who “got their money down” made a profit. The essence of prediction is that you must “get the money down” in advance of the observation.

A second issue is the extent to which the experience of the SPAF trials is representative of other trials of atrial fibrillation. That the hemispheric-retinal ratio was 3:1 in the VA trial is reassuring, but there have now been at least 11 trials of warfarin in atrial fibrillation, and it would be useful to know whether these contain sufficient data to put the hypothesis to the test.

Recapitulation effect, the tendency of patients randomized for retinal index events to experience retinal rather than hemispheric outcome events, is unlikely to have accounted for the result. Patients randomized to NASCET for hemispheric events had 5 times the ratio of retinal to hemispheric events as the patients in the SPAF trials.

Ascertainment bias, the probability that a retinal event will be noticed and recorded more often in one trial than another, is more difficult to exclude. This is a general risk of comparisons of different treatments in different trials. The most reassuring confirmation of the present hypothesis would be direct prospective observation (a randomized trial is not necessary) of retinal and hemispheric events in patients with carotid disease and patients with atrial fibrillation, by the same observers, using a common protocol.

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