Side of Brain Infarction and Long-Term Risk of Sudden Death in Patients With Symptomatic Carotid Disease

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Background and Purpose—Current publications suggest increased risk of sudden death in experimental animals with acute right insular lesions and in patients with recent right-sided brain infarction, particularly if the insula is involved.

Methods—Using 3 different time definitions, we related long-term risk of sudden death to presence and side of brain infarction on the baseline brain scan and handedness in 2885 patients with symptomatic carotid disease.

Results—In 1295 patients without brain infarction, 5-year risk of sudden death was 5.3% (24-hour definition); in those with left-sided infarction (n=471), 8.8%; in those with right-sided infarction (n=477), 6.0%; and in those with bilateral infarction (n=535), 9.7%. After accounting for differences of other risk factors (eg, previous myocardial infarction) in Cox regression, adjusted hazard ratios (HRs) compared with no infarction were as follows: left-sided HR, 1.45 (95% confidence interval [CI], 1.00 to 2.10); right-sided HR, 0.96 (95% CI, 0.62 to 1.47); and bilateral HR, 1.40 (95% CI, 0.98 to 2.00). Insular infarction occurred in 41 patients; none died suddenly. Left-handed or ambidextrous patients had a lower risk of sudden death than right-handers; the adjusted HR for left-handed or ambidextrous patients was 0.24 (95% CI, 0.07 to 0.70). These results were essentially the same for the 10- and 60-minute definitions of sudden death.

Conclusions—In the long-term, left-sided, not right-sided, brain infarction is associated with increased risk of sudden death. Left-handed or ambidextrous patients have a lower risk of sudden death than right-handed patients, suggesting a role for the brain. (Stroke. 2003;34:2871-2875.)

Key Words: autonomic nervous system ▪ carotid arteries ▪ cerebral infarction ▪ death, sudden

Sudden death is not rare in stroke patients. In 3 major trials on secondary prevention in transient ischemic attack (TIA) or minor ischemic stroke patients, a total of 186 died suddenly during 19 462 years of patient observation, with an annual incidence of 1.0% (95% confidence interval [CI], 0.8 to 1.1).1–3 This result indicates the relevance of sudden death in these patients and the opportunity to study determinants of sudden death in stroke trials.

A strong positive relationship exists between decreased heart rate variability and sudden death. In patients with cardiac disease, decreases in both short- and long-term variation of the RR interval on 24-hour ECG were associated with a 4-fold increase in risk of sudden death.4–5 Brain infarction is implicated to cause diminished heart rate variability.6–8 Patients with acute right-sided hemispheric lesions have lower levels of heart rate variability than those with infarction on the left; lesions of right insula were most likely to be associated with decreases in heart rate variability.8

The aim of this study was to assess implications of the presence, side, and insular site of brain infarction for long-term risk of sudden death in patients presenting with symptomatic carotid disease entered in the North American Symptomatic Carotid Endarterectomy Trial (NASCET).9

Methods
From December 1987 to December 1996, 2885 patients with a TIA or minor ischemic stroke and carotid disease were randomized into NASCET. This trial addressed the efficacy of carotid endarterectomy in addition to best medical treatment. Details of the design and outcome of the trial have been described.9 In brief, patients were eligible after ischemic symptoms, retinal or hemispheric, maximally 180 days before randomization, with cardiac embolism not likely to be the cause of the ischemia. Patient follow-up was a mean of 5.0 years.

Received March 27, 2003; final revision received June 29, 2003; accepted August 1, 2003.
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This article was edited by Associate Editor Graeme Hankey.
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© 2003 American Heart Association, Inc.
Stroke is available at http://www.strokeaha.org
DOI: 10.1161/01.STR.0000099964.34430.2D

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Baseline brain CT or MRI was required for all patients to exclude causes other than ischemia and to establish a baseline for subsequent events. Hard-copy film was sent to the central NASCET office and evaluated by an experienced neuroradiologist blinded to clinical details. Location and size of brain infarctions were recorded. All infarctions that included the insula were classified as insular. Initial patient evaluation included standardized history, examination, and investigations. Data on important risk factors of sudden death were recorded.

Information on all strokes and deaths was collected prospectively. Deaths initially classified as vascular were reviewed again by 2 authors (P.C.G., A.A.) to verify that death was sudden. For this purpose, a time definition rather than a definition based on the cause of death was used.1,11 We distinguished 3 categories of sudden death: (1) death within 10 minutes of symptom onset (witnessed and with reliable information), (2) death within 1 hour of onset (also witnessed and reliable), and (3) death within 24 hours of onset (witnessed without reliable data on timing, or the patient was found dead unexpectedly). Thus, categories with longer time definitions include those with shorter interval definitions. Death within 24 hours was used for primary analyses.

The relationship of presence and side of brain infarction to sudden death was determined with the Cox proportional-hazards model and expressed as hazard ratio (HR). Crude HRs were adjusted for other risk factors for sudden death in multivariate analyses. Kaplan-Meier event-free survival curves were used for graphical data inspection and calculation of sudden death risk. Similar analyses were used for handedness and sudden death.

**Results**

Among 2885 NASCET patients, 663 deaths occurred; of the 410 people who died of vascular causes, 217 (53%) died within 24 hours of symptom onset. Ninety-one deaths were classified as occurring within 1 hour of onset and 65 as within 10 minutes. Annual risk of death within 24 hours was 1.5% (95% CI, 1.3 to 1.7).

**Side of Brain Infarction**

Of the 2885 NASCET patients, 2778 (96.3%) had a baseline CT or MRI available. At least 1 area of brain infarction was present in 1483 patients (53.4%); 471 (17.0%) had ≥1 left-sided lesions, 477 (17.2%) had ≥1 right-sided lesions, and 535 (19.3%) showed evidence of bilateral infarction. Patients with bilateral lesions more often had large infarcts (Table 1). Patients with brain infarctions were slightly older than those without; their qualifying event more often was stroke (as opposed to TIA) or in a hemisphere more than in retina; and they more frequently had a history of diabetes mellitus and hypertension or old myocardial infarction on 12-lead ECG (Table 1). Risk factors for sudden death were most prevalent in patients who had bilateral brain infarction.

Kaplan-Meier event-free survival curves (the Figure) show graphically the outcome event of death within 24 hours after symptom onset. The 5-year risks were higher in patients with infarction on the left, with or without accompanying infarction on the right (see also Table 1, available online at http://stroke.ahajournals.org).

The crude HR of left-sided brain infarction versus no infarction for death within 24 hours was 1.67 (95% CI, 1.16 to 2.41; Table 2) and for bilateral brain infarction was 1.91 (95% CI, 1.35 to 2.71). If differences between patients with and without brain infarction regarding the prevalence of 6 risk factors for sudden death were taken into account, these HRs decreased to 1.45 (95% CI, 1.00 to 2.10) and 1.40 (95% CI, 0.98 to 2.00), respectively. Adjustment for other patient characteristics in Table 1 did not further influence the HRs; neither did adjustment for use of angiotensin-converting enzyme inhibitors, calcium antagonists, statins, and a group of antihypertensives. The crude HR of right-sided brain infarction was virtually unity and remained essentially the same after multivariable adjustment (Table 2). For death within 1 hour and death within 10 minutes, similar observations were made; however, HRs of left-sided brain infarction were higher for stricter outcome definitions.

In a direct comparison of patients with left-sided brain infarction only and those with right-sided infarction only, the adjusted HR for death within 24 hours was 1.47 (95% CI, 0.91 to 2.38; Table 2). Because of similar risks of left-sided only and bilateral infarction (adjusted HRs, 1.45 and 1.40, respectively) and of right-sided only infarction and no infarction (adjusted HR, 0.96), we decided a posteriori to perform a comparison between these paired groups. Death within 24 hours was 1.44 times more frequent in patients with any left-sided lesion than in those without left-sided lesion (95% CI, 1.09 to 1.90).

Insular infarction occurred in 41 patients; none died suddenly.

**Handedness**

During assessment of factors confounding the relationship between side of brain infarction and sudden death, a strong association between handedness and sudden death was observed. On entry into NASCET, study neurologists classified 145 of 2885 patients (5.0%) as left-handed and 38 (1.3%) as ambidextrous. The 183 left-handed or ambidextrous patients did not differ importantly from the right-handed patients (n = 2702) (Table II, available online at http://stroke.ahajournals.org). The unadjusted HR for death within 24 hours for left-handed or ambidextrous versus right-handed patients was 0.21 (95% CI, 0.07 to 0.66), a value that hardly changed after adjustment for the 6 variables listed in the footnote of Table 2 or for side of brain infarction. Similar results were obtained with stricter outcome definitions: adjusted HR for death within 1 hour was 0.18 (95% CI, 0.03 to 1.32) and for death within 10 minutes was 0.25 (95% CI, 0.03 to 1.78).

**Discussion**

**Side of Brain Infarction**

This study demonstrated an increased long-term risk of sudden death for patients with left-sided brain infarction, regardless of the presence of concurrent right-sided brain infarction, compared with the absence of brain infarction or right-sided brain infarction only in patients with symptomatic carotid disease who participated in NASCET. Depending on outcome definition and infarct comparison used, the risk was 1.5- to 2-fold higher, an increase consistent over 3 different definitions of sudden death. This finding is at odds with previous acute-phase studies in animals and humans.

There are several possible explanations for the differences between the current and earlier studies. First, virtually all previous observations addressed the hyperacute (hours) or acute (days) phase of stroke, whereas this study dealt with the long-term effects of brain infarction. It is conceivable that acute effects of brain lesions differ from chronic...
effects. During weeks or months after brain infarction, a new balance between parasympathetic and sympathetic nervous system activity may develop, as well as between the left and right sides of the sympathetic nervous system.

A second, partly related, explanation may be patient selection in NASCET. Slightly more patients with left-sided carotid disease (52.5%) than right-sided disease were included, probably because patients were more aware of dominant-hemisphere injury. In keeping with this hypothesis, we found that infarctions on the left were somewhat smaller than on the right. The smaller size of left-sided infarctions, however, can hardly explain the higher risk of sudden death in these patients. Alternatively, if right-sided infarction is indeed associated with a higher rate of sudden death in the acute phase, only patients with right-sided infarction surviving this stage would have entered NASCET. The same argument might be made for insular strokes.

Third, preexisting cardiac disease might explain our data. However, we consider this unlikely for 2 reasons: our findings persisted after adjustment for known cardiac risk factors of sudden death, and analysis restricted to patients without known cardiac disease yielded the same results (data not shown).

Fourth, the findings may be ascribed to the definition of sudden death used. This is unlikely, however, because the study results were consistent over 3 different definitions of sudden death.
Finally, the results may be a chance finding. Although the adjusted HR of left-sided infarction with or without concomitant right-sided lesion versus no infarction for death within 24 hours remained statistically significant (HR, 1.44; 95% CI, 1.09 to 1.90) after adjustment for known confounding factors, one cannot rule out the possibility that the adjusted HR would have dropped further after additional adjustment for unknown confounding factors.

Handedness
The proportion of patients who were left-handed or ambidextrous in NASCET was 6.3%. This percentage was similar to that in the Framingham Heart Study, in which 8.3% (95% CI, 6.3 to 10.8) of participants were reported to be left-handed. Thus, it is not likely that selection of handedness into NASCET will explain away the finding that left-handed and ambidextrous persons have only a quarter of the risk of sudden death of right-handers. This finding is all the more remarkable because previous reports suggested that left-handers had a shorter life expectancy.

The number of left-handed or ambidextrous patients was limited, as was the number who died suddenly. Thus, this observation may be a chance finding, even though the upper limit of the 95% CI was 0.70. However, it more likely reflects different organization of neuronetworks in the brain of left-handed and ambidextrous individuals. Left-handers may have a more distributed autonomic network in the brain, rendering them less vulnerable to sympathetic/parasympathetic imbalance, a common prelude to sudden death.

Study Population
This large population of 2885 patients was used as a basis because they had already experienced cerebral ischemic events, were studied at the outset with CT scans, and had an average of 5 years of follow-up, and all deaths were recorded in adequate detail. Patients with contraindications for surgery, including cardiac disease, were excluded from NASCET, possibly lowering the incidence of sudden death. We consider it unlikely, however, that this would affect the strength of its relationship with side of brain lesion and handedness.

Similar studies could feasibly be conducted in a community population, but doing so would be a huge undertaking, and answers would be long in coming. Databases may already exist with the essential data on lateralization of brain infarction, handedness, and sudden death. Their analysis could

TABLE 2. Crude and Adjusted HRs (95% CIs) of Side of Brain Infarction for Risk of Sudden Death

<table>
<thead>
<tr>
<th>Outcome and Adjustments</th>
<th>Left Side Only vs None</th>
<th>Right Side Only vs None</th>
<th>Both Sides vs None</th>
<th>Left Side Only vs Right Side Only</th>
<th>Any Left Side vs Right Side or None*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death within 24 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.67 (1.16–2.41)</td>
<td>1.06 (0.69–1.63)</td>
<td>1.91 (1.35–2.71)</td>
<td>1.58 (0.99–2.54)</td>
<td>1.77 (1.34–2.32)</td>
</tr>
<tr>
<td>6-Variable adjustment†</td>
<td>1.45 (1.00–2.10)</td>
<td>0.96 (0.62–1.47)</td>
<td>1.40 (0.98–2.00)</td>
<td>1.47 (0.91–2.38)</td>
<td>1.44 (1.09–1.90)</td>
</tr>
<tr>
<td>Death within 1 h</td>
<td></td>
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</tr>
<tr>
<td>None</td>
<td>2.12 (1.18–3.79)</td>
<td>1.55 (0.82–2.95)</td>
<td>2.75 (1.60–4.72)</td>
<td>1.37 (0.67–2.72)</td>
<td>2.14 (1.40–3.27)</td>
</tr>
<tr>
<td>6-Variable adjustment†</td>
<td>1.86 (1.03–3.36)</td>
<td>1.36 (0.71–2.58)</td>
<td>1.98 (1.14–3.43)</td>
<td>1.29 (0.63–2.62)</td>
<td>1.76 (1.14–2.70)</td>
</tr>
<tr>
<td>Death within 10 min</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.88 (0.92–3.84)</td>
<td>1.25 (0.55–2.83)</td>
<td>3.10 (1.66–5.77)</td>
<td>1.51 (0.62–3.69)</td>
<td>2.35 (1.41–3.90)</td>
</tr>
<tr>
<td>6-Variable adjustment†</td>
<td>1.69 (0.82–3.48)</td>
<td>1.06 (0.46–2.41)</td>
<td>2.17 (1.15–4.10)</td>
<td>1.55 (0.62–3.90)</td>
<td>1.93 (1.15–3.29)</td>
</tr>
</tbody>
</table>

*Left-sided brain infarction with or without right-sided brain infarction vs right-sided or no brain infarction.
†Adjustment for age, history of angina, diabetes mellitus, or hypertension and ECG signs of previous myocardial infarction or left ventricular hypertrophy; adjustment for other risk factors of sudden death did not influence the HRs.
contribute further data on the generalizability of the observations and on other issues raised by our findings.

In summary, we found that left-sided brain infarction was associated with a higher risk of sudden death, whereas left-handed patients had a distinctly lower risk of sudden death. Our findings may have clinical implications, eg, the use of β-blocking drugs in patients with left-sided brain infarction, and need to be corroborated in other clinical studies.

Acknowledgments

This study was supported by a grant (RO1-NS-24456) from the National Institute of Neurological Disorders and Stroke. We acknowledge the support of all participants in NASCET and Smith-Kline Beechman for providing Ecotrin for all NASCET patients. We thank Dr M. Eliasziw for help in accessing and analyzing the NASCET database. Drs S. Alamowitch and L.J. Kappelle contributed through their stimulating discussion at the analysis phase. Dr J. van Gijn commented on one of the last versions of the manuscript.

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Stroke. 2003;34:2871-2875; originally published online November 20, 2003;
doi: 10.1161/01.STR.0000099964.34430.2D

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