Original Contributions

Stroke Location and Association With Fatal Cardiac Outcomes
Northern Manhattan Study (NOMAS)

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Background and Purpose—Cardiac mortality after stroke is common, and small studies have suggested an association of short-term cardiac mortality with insular location of cerebral infarction. Few population-based studies with long-term follow-up have evaluated the effect of stroke location on the long-term risk of cardiac death or myocardial infarction (MI) after first ischemic stroke. We sought to determine the association between stroke location and cardiac death or MI in a multiethnic community-based cohort.

Methods—The Northern Manhattan Study is a population-based study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic urban population. First ischemic stroke patients age 40 or older were prospectively followed up for cardiac death defined as fatal MI, fatal congestive heart failure, or sudden death/arrhythmia and for nonfatal MI. Primary brain anatomic site was determined by consensus of research neurologists. Hazard ratios (HRs) and 95% CIs were calculated by Cox proportional-hazards models and adjusted for vascular risk factors (age, sex, history of coronary disease, hypertension, diabetes, cholesterol, and smoking), stroke severity, infarct size, and stroke etiology.

Results—The study population consisted of 655 patients whose mean age was 69.7±12.7 years; 44.6% were men and 51.3% were Hispanic. During a median follow-up of 4.0 years, 44 patients (6.7%) had fatal cardiac events. Of these, fatal MI occurred in 38.6%, fatal congestive heart failure in 18.2%, and sudden death in 43.2%. In multivariate models, clinical diagnosis of left parietal lobe infarction was associated with cardiac death (adjusted HR=4.45; 95% CI, 1.83 to 10.83) and cardiac death or MI (adjusted HR=3.30; 95% CI, 1.45 to 7.51). When analysis of anatomic location was restricted to neuroimaging (computed tomography, magnetic resonance imaging, or both [n=447]), left parietal lobe infarction was associated with cardiac death (adjusted HR=3.37; 95% CI, 1.26 to 8.97), and both left (adjusted HR=3.49; 95% CI, 1.38 to 8.80) and right (adjusted HR=3.13; 95% CI, 1.04 to 9.45) parietal lobe infarctions were associated with cardiac death or MI. We did not find an association between frontal, temporal, or insular stroke and fatal cardiac events, although the number of purely insular strokes was small.

Conclusions—Parietal lobe infarction is an independent predictor of long-term cardiac death or MI in this population. Further studies are needed to confirm whether parietal lobe infarction is an independent predictor of cardiac events and death. Surveillance for cardiac disease and implementation of cardioprotective therapies may reduce cardiac mortality in patients with parietal stroke. (Stroke. 2008;39:2425-2431.)

Key Words: acute stroke ▪ cardiac arrhythmia ▪ epidemiology ▪ sudden death

Based on animal models1–4 and clinical studies,5–7 it is well known that cerebrovascular disease can alter cardiovascular and autonomic function. Stroke has been associated with changes in autonomic cardiac dynamics,7–10 cardiac arrhythmias,10–13 myocardial damage,14 increased plasma catecholamines,15 and increased susceptibility to sudden death.16 Although cardiac death after stroke is common,17 its incidence may not be entirely explained by concomitant coronary artery disease (CAD),18 and as previous studies have demonstrated, brain injury alone may contribute directly to the generation of cardiac dysfunction.7,8,11,19 The involvement of the insular cortex (or “cardunculus”20) after stroke, both
The association of insular infarction with adverse cardiac events is usually explained on the basis of its extensive autonomic and limbic connections.22 The right insula has generally been regarded as the center for sympathetic autonomic control, whereas the left serves as the center for parasympathetic control.5 Similarly, there is evidence to support cortical lateralization in the regulation of cardiovascular functions, indicating that left hemispheric stroke with18 and without23 insular involvement has an adverse effect on cardiac outcomes and that stroke-related cardiac events in the long term likely arise from a shift of autonomic function toward an augmented cardiac sympathetic tone.9,24 However, clinical studies have been unable to isolate an independent effect of insular stroke or any other particular stroke location on cardiac outcomes, as insular infarctions are often accompanied by lesions in adjacent areas of the brain.10,12,14,18,23

To date, few long-term, population-based studies have provided data on the risk of cardiac death or myocardial infarction (MI) after incident ischemic stroke, and the majority of reports have concentrated only on short-term outcomes. The purpose of this study was to determine the association between stroke location and long-term risk of cardiac death or MI in a multiethnic cohort.

Subjects and Methods

The Northern Manhattan Study includes a population-based incidence and case follow-up study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic urban population. Northern Manhattan consists of a well-defined area of New York City.23 The race-ethnic mixture consists of 63% Hispanic, 20% non-Hispanic black, and 15% non-Hispanic white residents.

Selection of Subjects

Details of the study have been previously published.26,27 In brief, stroke patients were enrolled if they (1) were diagnosed with first stroke (as defined by the National Institute of Neurological Disorders and Stroke classification of cerebrovascular diseases III28) between 1993 and 1997; (2) were >40 years old; and (3) resided in Northern Manhattan for ≥3 months in a household with a telephone. For the purpose of this analysis, only ischemic stroke cases were included. More than 80% of patients with stroke in northern Manhattan are hospitalized at Columbia University Medical Center (CUMC). Subjects hospitalized at other local hospitals were identified through active surveillance of admissions and through local physicians. Approximately 5% of incident ischemic stroke patients in northern Manhattan are not hospitalized.28 Evaluation of patients was performed at the hospital, and those subjects who were not hospitalized at CUMC were evaluated in the research clinic. The study was approved by the CUMC institutional review board, and all subjects gave consent directly or through a surrogate when indicated.

Index Evaluation

Data were collected through interviews by trained research assistants, and physical and neurologic examinations were conducted by study neurologists. When possible, data were obtained directly from the subjects. When subjects were unable to provide answers, proxies were interviewed (29.1%). Assessments were conducted in the participant’s primary language. Race-ethnicity was based on self-identification through a series of questions modeled after the US census and conforming to standard definitions outlined by directive 15.29 Standardized questions were adapted from the Behavioral Risk Factor Surveillance System by the Centers for Disease Control and Prevention regarding the following conditions: hypertension, diabetes mellitus, hypercholesterolemia, peripheral vascular disease, transient ischemic attack, cigarette smoking, and cardiac conditions (MI, CAD, angina, congestive heart failure [CHF], atrial fibrillation, other arrhythmias, and valvular heart disease). Definitions of risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, CAD, and smoking have been previously published.26,27

Stroke location was determined on the basis of neurologic syndromes and imaging findings in a consensus conference of stroke neurologists. Computed tomography (CT) scanning was performed at least once in 96.7% of patients, magnetic resonance imaging (MRI) in 43.6%, and both CT and MRI in 41.3%. Fewer than 1% of patients had neither a CT scan nor an MRI available for review. Assessment of stroke subtype according to the modified Stroke Data Bank criteria30 was also determined by consensus of stroke neurologists who used available information, as previously described.23 Stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS)31 score derived from a standardized neurologic examination and was categorized into mild (NIHSS ≤5), moderate (NIHSS 6 to 13), and severe (NIHSS ≥14) and based on a previous analysis of stroke severity in relation to stroke outcome from our population.32 Size of the infarction was also determined according to a modified National Institute of Neurological Disorders and Stroke Data Bank scheme and categorized into small (<1), medium (1 to 3), and large (>3 lobe).

Follow-Up and Definition of Outcomes

Follow-up was conducted at 6 months by telephone and then in person annually for 5 years. Information on vital and functional status, intercurrent symptoms, illness, or hospitalizations was collected. Annual in-person follow-up visits were conducted at the medical center and included an interview, vital signs, and physical and neurologic examinations. Patients unable to come to the clinic were visited by a research assistant. Ongoing surveillance of admissions to CUMC and local hospitals, as described previously,28 was used to identify patients who experienced recurrent stroke, MI, hospitalization, or death. All outcome events were reviewed by a specially trained research assistant, and when available, medical records were reviewed for all outcome events, including death. Deaths were also classified as vascular or nonvascular and validated by a study physician. The vascular causes of death included stroke, MI, CHF, pulmonary embolus, cardiac arrhythmia (sudden death), and other vascular deaths. Nonvascular causes of death included accidents, cancer, pulmonary causes (ie, pneumonia, chronic obstructive pulmonary disease), and other miscellaneous causes.

For the purpose of this analysis, cardiac death was considered a primary outcome, and the composite of cardiac death or nonfatal MI was considered a secondary outcome. MI was defined by criteria adapted from the Lipid Research Clinics Coronary Primary Prevention Trial14 and required at least 2 of the 3 following criteria: (1) ischemic cardiac pain, (2) cardiac enzyme abnormalities (creatinine kinase-MB, troponin), and (3) diagnostic ECG abnormalities. The diagnosis of MI was validated by review by 1 of the study cardiologists (S.H., M.R.D.T.). Cardiac deaths were defined as follows: fatal MI was defined by clear documentation of an MI from the death certificate or hospitalization records or by death occurring within 30 days of the event; fatal CHF was determined by clear documentation in cases where the patient died at home with previously diagnosed CHF/dilated cardiomyopathy or was hospitalized with symptoms, radiographic or echocardiographic findings, or clinical signs of heart failure; and death from arrhythmia or sudden death was ascribed in cases of a documented arrest in a medical setting when the death did not meet the aforementioned criteria and in cases of sudden, unexpected, or unwitnessed death. In those cases in which it was difficult to make a determination, consensus was reached after discussion among the investigators from the best available information.

Statistical Analysis

Descriptive statistics were calculated for the population as a whole and for those who had and did not have an outcome event. Comparisons between the 2 groups were made with t tests for
continuous variables and χ² tests for categorical variables. In addition, univariate Cox proportional-hazards models were constructed to estimate hazard ratios (HRs) and 95% CIs for predictors of primary and secondary outcomes. Historical vascular risk factors (age, sex, history of CAD, hypertension, diabetes mellitus, hypercholesterolemia, and smoking), as well as stroke etiologic subtype, stroke severity, and infarct size and side, were included in the models. Multivariate models were then constructed with those variables significant in univariate models at P < 0.10. All models satisfied proportionality assumptions.

Scores were calculated to describe the degree of correlation between stroke diagnosis and anatomic diagnosis (neuroimaging). Statistical analyses were conducted with SAS version 8.2 (SAS Institute, Cary, NC), and significance was set at P < 0.05.

Results

In total, 655 first ischemic stroke patients were included. Baseline characteristics of the study population are presented in Table 1. Mean ± SD age of the total group was 69.7 ± 12.7 years and 44.6% were men. Participants were 51.3% Hispanic, 27.6% black, and 18.9% white. The prevalence of vascular risk factors was high and included a previous history of MI (16.2%), CAD (33.4%), CHF (13.8%), and peripheral vascular disease (21.6%).

The median follow-up for survivors was 4.0 years. Loss to follow-up was 15 patients (2.3%). The 30-day mortality was 5.3% and 5-year total mortality was 37.3%. Among causes of death during the entire follow-up, there were 44 fatal cardiac events: 17 fatal MIs (19.3%), 8 fatal CHF events (9.1%), and 19 sudden deaths (21.6%). Other causes of death included 39 fatal strokes (44.32%) and 5 other vascular causes (5.7%). Nonfatal MIs occurred in 19 patients.

Of the total population, left hemispheric infarctions occurred in 44.3%, right-sided infarctions in 51.4%, and bilateral infarctions in 4.3% of patients. The correlation between brain site of infarction based on consensus clinical diagnosis and radiographic diagnosis was excellent for all infarct locations: for frontal lobe, κ = 0.9228 (P = 0.0196), parietal lobe κ = 0.8943 (P = 0.0237), and temporal lobe κ = 0.7883 (P = 0.0387).

In the univariate Cox models, the following brain infarct locations were predictors of both cardiac death and the composite outcome of cardiac death or MI: frontal lobe, parietal lobe, temporal lobe, and insula. Other significant predictors were age, male sex, NIHSS score, and history of CAD (Table 2).
Table 3. Multivariate Model of Predictors of 5-Year Risk of Cardiac Death or MI Within 5 Years of First Ischemic Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical Death</th>
<th>Neuroimaging Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI Limits</td>
</tr>
<tr>
<td>FrONTAL location</td>
<td>4.19</td>
<td>1.45 to 12.07</td>
</tr>
<tr>
<td>TEMPORAL location</td>
<td>2.39</td>
<td>1.29 to 4.46</td>
</tr>
<tr>
<td>PARIETAL location</td>
<td>2.35</td>
<td>1.13 to 4.87</td>
</tr>
<tr>
<td>INSULAR location</td>
<td>2.72</td>
<td>1.32 to 5.62</td>
</tr>
<tr>
<td>Age</td>
<td>1.07</td>
<td>1.03 to 1.12</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.65</td>
<td>0.96 to 2.84</td>
</tr>
<tr>
<td>CAD</td>
<td>2.33</td>
<td>1.35 to 4.01</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>2.58</td>
<td>1.72 to 3.86</td>
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</tbody>
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In the multivariate models, the consensus clinical diagnosis of left parietal lobe infarction was associated with cardiac death (adjusted HR = 4.45; 95% CI, 1.83 to 10.83) and cardiac death or MI (adjusted HR = 3.30; 95% CI, 1.45 to 7.51; Tables 3 and 4). There was a significant trend in the risk for cardiac death of left parietal lobe infarction being higher than that of right parietal lobe infarction (adjusted HR = 4.45 vs 1.22, P = 0.0737). However, this difference was attenuated when the size of infarction was adjusted for in the model.

When analysis of anatomic location was restricted to those patients with positive findings on neuroimaging alone (n = 447), left parietal lobe infarction was also associated with cardiac death (adjusted HR = 3.37; 95% CI, 1.26 to 8.97; Table 3). Both left (adjusted HR = 3.49; 95% CI, 1.38 to 8.80) and right (adjusted HR = 3.13; 95% CI, 1.04 to 9.45) parietal lobe infarctions were associated with the combined end point of cardiac death or MI. This effect for right parietal stroke was present neither when consensus clinical diagnosis was used nor for the primary outcome of cardiac death (Tables 3 and 4).

In total, 15% of patients (n = 100 patients) had recurrent nonfatal strokes and 1% (6 patients) reached the primary outcome. When the analysis was restricted to patients without recurrent strokes, left parietal infarction remained positively associated with cardiac death (adjusted HR = 5.13; 95% CI, 2.04 to 12.88) and the combined end point of cardiac death or MI (adjusted HR = 3.71; 95% CI, 1.64 to 8.41). Similarly, there was no significant change in the size or direction of the effect of left parietal lobe stroke location on the measured outcomes when administration of cardioprotective medications, such as aspirin, β-blockers, or angiotensin-converting enzyme inhibitors, was accounted for in the multivariate model. In addition, to evaluate for the effect modification due to a history of CAD, MI, or CHF, an interaction term between left parietal lobe and history of CAD, MI, or CHF was included in the final multivariate analysis, but no significant effect modification from a history of CAD, MI, or CHF was observed.

We did not find an association of frontal, temporal, or insular stroke with either cardiac death or cardiac death or MI. The number of purely insular strokes was small, however. In a subgroup analysis of 30-day fatalities, no association was found with stroke location, although the sample size was small.
Discussion

In this study, patients with a left parietal lobe infarction compared with those with infarctions in other brain locations were at higher risk of cardiac death and nonfatal MI. The effect of left parietal stroke was independent of other cardiovascular risk factors, and the magnitude of the effect of parietal stroke was similar or even greater than that of CAD (Tables 3 and 4). In addition, the effect of parietal stroke location was independent of stroke size or mechanism. Similarly, the effect of parietal stroke location was present when localization was determined by consensus of stroke neurologists or by neuroimaging alone (Tables 3 and 4). There was a small but significant effect of right parietal lobe infarction, determined by neuroimaging alone, on the composite secondary outcome of cardiac death or MI (Table 4). This effect was present neither when consensus clinical diagnosis was used nor for the primary outcome of cardiac death (Tables 3 and 4).

The link between parietal lobe infarction and adverse cardiac outcomes is currently unknown. Based on animal models, there is evidence to support the presence of an anterior-posterior insular gradient and that the anterior insular centers have extensive connections with limbic structures. It is possible that infarction of the posterior insula and parietal lobe would spare the insular cardiosympathetic center while disrupting its connections, in effect releasing it from a tonic source of inhibition. Therefore, it is possible to induce autonomic imbalance from infarctions in the posterior regions of the insula or inferior parietal lobule, and this imbalance may result from disruptions of cortical networks in the vicinity of the insular region and disinhibition of the anterior insular centers. In 1 study among 50 patients with ischemic stroke, the right inferior parietal lobule, as well as the right posterior, superior, and medial insulae, was associated with stunned myocardium as defined by elevations in cardiac troponin T. Although that study found a novel association between parietal lobe infarction and stunned myocardium, the outcomes were measured in the acute setting and did not include clinical end points. The authors hypothesized that the parietal lobe lesion was a “bystander” of the insular lesion, as both regions are supplied by a single artery from the inferior division of the middle cerebral artery. Our results support the notion that left parietal lobe stroke may not be just a “bystander” of insular infarction but a potential predictor of adverse cardiac outcomes. Moreover, in a study of 25 patients undergoing preoperative evaluation for epilepsy surgery, left holohemispheric inactivation by intracarotid amobarbital injection was associated with heart rate elevations that decreased after right hemisphere inactivation. The results were consistent with differential left and right cerebral hemispheric effects on autonomic function and appear to be related to functional and anatomic asymmetries in the central nervous system. This observation may help to explain our differential results on the association between left and right parietal lobe stroke location and adverse cardiac outcomes, as enhanced sympathetic activation has been associated with an independent risk of long-term cardiovascular and cerebrovascular events.

Interestingly, when our analysis of adverse cardiac outcomes was limited to the initial 30 days of follow-up, no significant association was found between stroke location and cardiac events. Insular infarction has been associated with adverse cardiac events in other, generally shorter-term, studies, an effect explained by its anatomic connections with important autonomic centers. However, we did not find an independent association between insular stroke location and either primary or secondary outcomes. Several animal and human studies have shown that the insula is a site for the integration of sensory, autonomic, and limbic functions through its reciprocal connections with principal sensory and paralimbic areas with the hypothalamus and the orbital, temporopolar, and cingular cortices. In addition, there appears to be a hemispheric gradient for cardiac autonomic responses. Sympathetic responses in the heart can be elicited by stimulation of both right and left and anterior and posterior insulae, but to different degrees. Oppenheimer et al demonstrated functional laterality in humans, such that stimulation of the left insular cortex tends to cause parasympathetic responses and that right anterior insular cortex stimulation tends to cause sympathetic responses. Furthermore, there is an indication that left insular stroke may be accompanied by decreased parasympathetic tone, increased cardiac sympathetic tone, and decreased heart rate variability. These experimental observations in animal and human models find support in the clinical realm. In a recent report among 116 patients, a risk ratio of 1.75 (95% CI, 1.02 to 3.00) for fatal and nonfatal cardiac events (MI, angina, CHF, or sudden death) was found in patients with left insular stroke versus noninsular stroke, particularly evident in the absence of CAD. The authors, however, defined insular stroke as any stroke that included involvement of the insular region and did not control for size or additional stroke locations. The inability to isolate the insular region from other areas of the brain potentially confounds the association between insular stroke and adverse cardiac events. It is possible that the effect of the infarction in adjacent areas of the brain, such as the parietal or temporal lobe, is actually responsible for the association.

Other studies, like ours, have also found no association between insular infarction and adverse cardiac outcomes. In a secondary analysis of the North American Symptomatic Carotid Endarterectomy Trial database, Algra et al demonstrated that in the long term, left-sided and not right-sided brain infarction is associated with increased risk of sudden death and that insular stroke location was not associated with adverse cardiac events. When adjusting for cardiac disease (previous history of MI) and in comparison with patients without stroke, the HR for sudden death with left-sided cerebral infarction was 1.45 (95% CI, 1.0 to 2.10), right-sided cerebral infarction 0.96 (95% CI, 0.62 to 1.47), and bilateral cerebral infarction 1.40 (95% CI, 0.98 to 2.0). Although that study did not specifically differentiate between cerebral lobes, it was the first long-term analysis to find an association between stroke location and cardiac outcomes. Left-sided infarction was significantly associated with adverse cardiac events, moreover, supporting our findings in NOMAS. Of

Discussion

In this study, patients with a left parietal lobe infarction compared with those with infarctions in other brain locations were at higher risk of cardiac death and nonfatal MI. The effect of left parietal stroke was independent of other cardiovascular risk factors, and the magnitude of the effect of parietal stroke was similar or even greater than that of CAD (Tables 3 and 4). In addition, the effect of parietal stroke location was independent of stroke size or mechanism. Similarly, the effect of parietal stroke location was present when localization was determined by consensus of stroke neurologists or by neuroimaging alone (Tables 3 and 4). There was a small but significant effect of right parietal lobe infarction, determined by neuroimaging alone, on the composite secondary outcome of cardiac death or MI (Table 4). This effect was present neither when consensus clinical diagnosis was used nor for the primary outcome of cardiac death (Tables 3 and 4).

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note, in our univariate analysis, insular infarction was associated with adverse cardiac events, but this effect was attenuated once cardiovascular risk factors and other stroke locations were factored into the multivariable models. In accordance with previous studies, we found that age, stroke severity, male sex, and history of CAD also have a major impact on outcome after stroke.

Several explanations for the differences between the results of studies dealing with short-term and long-term outcomes after stroke are plausible. The effects of acute stroke may be different from those of a chronic state, possibly due to reorganization of neuronal circuitry and balancing between parasympathetic and sympathetic nervous system activity. There is evidence supporting long-term activation of the autonomic nervous system after stroke with increased levels of norepinephrine and pathologic nighttime blood pressure increases, a combination that represents an independent risk for future cardiovascular and cerebrovascular events. Our study has limitations. This was a secondary analysis of the Northern Manhattan Study, and distinguishing insular stroke from other stroke locations was not a primary goal of the study. Neuroimaging was performed for clinical purposes by both CT and MRI, as deemed clinically appropriate, and not according to a standardized research protocol. Only 40% of patients underwent MRI scanning, which is likely not according to a standardized research protocol. Only >40% of patients underwent MRI scanning, which is likely to be more sensitive for anatomic localization, particularly of the insula. It is therefore possible that misclassification of insular or other stroke locations may have occurred. Finally, we did not measure autonomic nervous system function, so our conclusions are not mechanistic but based on the epidemiologic associations seen in our cohort.

In summary, we found that in the long term, left-sided parietal lobe infarction was associated with a higher risk of cardiac death or MI. Further studies are needed to confirm these findings and to better delineate the relation between insular and parietal structures. These findings may have clinical implications, as patients with left parietal lobe infarction may require more intensive monitoring or prophylactic medical treatment to prevent adverse cardiac outcomes.

Disclosures
None.

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