Middle Cerebral Artery Infarcts Encompassing the Insula Are More Prone to Growth

Hakan Ay, MD; E. Murat Arsava, MD; Walter J. Koroshetz, MD; A. Gregory Sorensen, MD

Background and Purpose—Based on previous observations that infarcts encompassing the insula were linked to unfavorable clinical outcome, we hypothesized that insular damage was directly associated with worsened infarction in ischemic but potentially viable neighboring brain tissue.

Methods—Using acute diffusion- and perfusion-weighted MRI within the first 12 hours of symptom onset and a follow-up MRI on day 5 or later, we calculated the percentage of mismatch lost (PML) in 61 consecutive patients with ischemic stroke within the middle cerebral artery territory. PML denoted the percentage of mismatch tissue between diffusion-weighted imaging and mean transit time maps that eventually underwent infarction. We explored the relationship between PML and insular location using a regression model.

Results—The median PML was 17.7% (interquartile range, 3.5% to 54.2%) in insular and 2.5% (0.0% to 12.7%) in noninsular infarcts (P<0.01). The PML correlated with the volume of abnormal regions on diffusion-weighted imaging (P<0.01), mean transit time (P<0.01), cerebral blood flow maps (P<0.01), and cerebral blood volume maps (P<0.01). A linear regression model with PML as response and with acute MRI volumes, age, and the site of vascular occlusion as covariates showed that insular involvement was an independent predictor of PML (P=0.01). The regression model predicted an approximately 3.2-fold increase in PML with insular involvement.

Conclusions—Infarction of the insula is associated with increased conversion of ischemic but potentially viable neighboring tissues into infarction. The unfavorable tissue outcome in insular infarcts may not be a mere bystander effect from proximal middle cerebral artery occlusions. (Stroke. 2008;39:373-378.)

Key Words: cerebral infarct ■ diffusion-weighted imaging ■ heart–brain relationships ■ insula ■ MRI ■ neurocardiology ■ sympathetic nervous system

The insula, or the island of Reil, is an invaginated portion of the cortex that is completely enclosed within the sylvian fissure. Although the first description of the insula dates back 200 years ago,1 insular infarcts and their clinic–anatomic features have not been studied in depth. This is partly because insular infarcts are only occasionally exclusively limited to the insula2–3; more frequently, they occur as a part of large middle cerebral artery (MCA) territory infarcts.3

Despite the infrequency of solitary insular infarction, infarcts that encompass the insula are associated with higher stroke severity and poorer clinical outcome compared with infarcts sparing the insula.3–6 The exact means by which insular infarcts are associated with unfavorable outcome is not known. At first glance, the large size of infarcts due to proximal MCA occlusions that accompany insular infarcts may be a reason for unfavorable outcome. However, alternative approaches may also be worthy of consideration. The insula is a functional integration site for autonomic responses and therefore, unlike most other brain regions, it has a unique ability to provoke systemic responses.7 Autonomic responses such as alterations in blood glucose, blood pressure, myocardial contractility, and body temperature can in turn contribute to adverse tissue outcome in cerebral ischemia.4,8–10 In the current study, we sought to test the hypothesis that insular damage is a risk factor for increased conversion of ischemic but potentially viable neighboring tissues into infarction in patients with MCA stroke.

Study Population
The current study was a retrospective analysis of a prospective, ongoing, National Institutes of Health-funded study evaluating the use of diffusion-weighted imaging (DWI) and perfusion-weighted imaging in predicting tissue risk of infarction in acute stroke. The study enrolled consecutive patients who were admitted within the first 12 hours of symptom onset and who did not receive thrombolytic treatment or investigational drugs. Each patient had 2 MRI studies, one obtained within 12 hours of symptom onset and the

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From the Department of Neurology (H.A.) and A.A. Martins Center for Biomedical Imaging, Department of Radiology (H.A., E.M.A., A.G.S.), Massachusetts General Hospital, Harvard Medical School, Boston, Mass; and the National Institute of Neurological Disorders and Stroke, National Institutes of Health (W.J.K.), Bethesda, Md.
Correspondence to Hakan Ay, MD, A.A. Martins Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, 149 13th Street, Room 2301, Charlestown MA 02129, E-mail hay@partners.org
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second on day 5 or later. In the first MRI, T2-weighted images, apparent diffusion coefficient maps, DWI, and mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV) maps were obtained. The purpose of the second MRI was to evaluate the final infarction and included only T2- or fluid-attenuated inversion recovery (FLAIR)-weighted sequences. The current study was conducted in a subgroup of patients with MCA territory infarcts who were admitted between 2000 and 2005. A part of the study population has been previously published within the context of another study. To depict the effect of insular location on lesion growth, only patients with DWI/MTT mismatch that was greater than 20% of the DWI volume were studied. Hence, none of the included patients had complete spontaneous reperfusion at the time of initial imaging. Age, gender, stroke risk factors, site of vascular occlusion, time from symptom onset to MRI, and etiologic stroke subtype per SSS-TOAST criteria were recorded in each patient. The SSS-TOAST subtypes included large artery atherosclerosis, cardioembolic embolism, small artery occlusion, other causes, and undetermined causes. The site of vascular occlusion was determined using MR angiography and CT angiography. Because these tests had limited sensitivity for clots in distal MCA branches, the anatomic distribution of infarct(s) on DWI and the lesion topography on MTT maps were also used in circumstances where angiographic demonstration of arterial clot was not successful. The site of occlusion was categorized as previously described in 5 major arterial segments from M1 to M5. The study was conducted at a single academic center and the study protocol was approved by the local Institutional Review Board.

**Image Acquisition**

MRI was performed on 1.5-T whole body scanners (GE Signa; GE Medical Systems or Siemens Sonata; Siemens Medical Solutions). DWI was obtained using echo planar imaging with a repetition time of 6000 ms to 10000 ms, an echo time of 78 ms to 101 ms, a field of view of 22×22 cm, image matrix of 128×128, slice thickness 5 mm to 6 mm with a 1-mm gap, and b values of 0 s/mm² and 1000 s/mm². DWIs were corrected for motion and eddy-current distortions using FMIRB’s Linear Image Registration Tool (FLIRT 5.0; Oxford Centre for Functional Magnetic Resonance Imaging of the Brain). Average DWI maps as well as apparent diffusion coefficient maps were computed from these images. Perfusion-weighted images were acquired using dynamic susceptibility contrast echo planar imaging. Imaging parameters were repetition time 1500 to 1517 ms and echo time 50 to 75 ms with the same spatial resolution as for DWI. Mean transit time and CBF maps were calculated using methods described previously. Fast spin-echo T2-weighted images were acquired with repetition time of 4000 ms to 6500 ms, echo time of 85 ms to 110 ms, field of view of 22×22 cm or 24×24 cm, acquisition matrix of 256×192 pixels or 320×256 pixels, and slice thickness of 5 mm to 6 mm with a 1-mm gap. FLAIR images were acquired with repetition time = 10002 ms, echo time = 126 ms, field of view of 22 cm×22 cm, acquisition matrix of 256×256 pixels, and slice thickness 5 mm with a 1-mm gap.

**Image Analysis**

The insula was identified as the portion of cerebral cortex beneath the sylvian fissure encircled by frontal, temporal, and parietal opercula laterally and extreme capsule and claustrum medially. For volumetric analyses, all images were coregistered to a T2 template using FMIRB’s Linear Image Registration Tool. The lesion on DWI, MTT maps, and final T2 or FLAIR-weighted images were manually outlined using a commercial image display and analysis program (ALICE; Hayden Image Processing Solutions) and lesion volumes were computed. In patients with multiple infarcts, we calculated the sum of all infarcts within the MCA territory. The relationship between insular infarct and infarct progression was evaluated by calculating “percentage mismatch lost or PML.”

![Figure 1. Schematic representation of the PML. The figure shows acute DWI (gray), acute MTT (gray, red, and yellow), and follow-up T2/FLAIR lesions (gray and red) coregistered into the DWI. Areas marked in red and yellow designate the region of diffusion–MTT mismatch, whereas regions in red alone correspond to the area of infarct growth from acute to chronic time points (follow-up T2/FLAIR–acute DWI). The PML indicates the proportion of DWI/MTT mismatch region that has eventually undergone infarction (the volume of red/red + yellow).](image)

**Statistics**

Statistical analyses explored relationships among insular infarct, PML, and clinical and imaging predictors of infarct growth (Table 1). Univariate relationships were tested using Spearman correlation analysis, Student t test, or Mann-Whitney U test and Fisher exact test for situations in which the covariates were both continuous, one continuous and one categorical, and both categorical, respectively. Due to the small number of patients in each category, the site of vascular occlusion was dichotomized as large (internal carotid artery, M1, M2, or M3) and small artery occlusion (M4 or M5).

To test the a priori hypothesis that insular damage was associated with adverse tissue outcome irrespective of tissue perfusion and the site of vascular occlusion, a linear regression model with PML as response and imaging determinants of the PML (volume of regions abnormal on acute DWI, MTT, CBF, and CBV maps), the site of vascular occlusion, insular involvement, and age as covariates was developed. Infarct volumes and age were assessed as continuous variables, whereas the site of vascular occlusion and insular involvement were introduced into the model as categorical variables. Because PML did not conform to normal distribution, it was log-transformed before being introduced to the model. Standard regression diagnostics were used to assess linear regression assumptions. There was no evidence of collinearity between the covariates.

\[
PML = 100 \times \frac{\text{follow-up T2 or FLAIR volume}}{\text{initial DWI volume} + \text{initial MTT volume}} - \text{initial DWI volume}
\]
or nonlinearity between the dependent variable and independent variables. After the final model was developed, all possible dual interactions between the covariates were introduced into the model one at a time and the presence of interaction was excluded. All numerical variables were expressed as mean ± SD or median and interquartile range (IQR). A level of \( P < 0.05 \) was considered statistically significant. All statistical analyses were performed using SPSS 11.5.

### Results

A total of 99 patients were prospectively enrolled during the study period. Twenty-three patients had infarcts outside the MCA territory and were therefore excluded. Fifteen of the remaining 76 patients were further excluded because their DWI/MTT mismatch volume was \(<20\%\) of the DWI volume. The remaining 61 patients comprised the study population. There were 44 male and 17 female patients. The mean age was 66.7 ± 15.1 years. The mean time to initial MRI was 6.5 ± 2.8 hours. The median time between initial and follow-up MRI was 7.0 (IQR, 4.5 to 52.5) days. The stroke mechanism per the SSS-TOAST classification system was cardioaortic embolism in 23, large artery atherosclerosis in 21, other causes in 9 (4 with dissection, 2 after cardiac catheterization, one after carotid endarterectomy, one after internal carotid artery balloon occlusion during endovascular

### Table 1. Baseline Patient Characteristics With Respect to Insular Involvement

<table>
<thead>
<tr>
<th></th>
<th>Insula Involvement (−) (n=16)</th>
<th>Insula Involvement (+) (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female/male</td>
<td>5/11</td>
<td>12/33</td>
</tr>
<tr>
<td>Age, mean ± SD*</td>
<td>74.3 ± 11.4 years</td>
<td>64.0 ± 15.4 years</td>
</tr>
<tr>
<td>Time from symptom onset to acute MRI, mean ± SD</td>
<td>7.2 ± 2.9 hours</td>
<td>6.3 ± 2.7 hours</td>
</tr>
<tr>
<td>Time from initial to follow-up MRI, median (IQR)</td>
<td>11.0 (5.0–67) days</td>
<td>7.0 (4.0–33) days</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 patients (69%)</td>
<td>30 patients (67%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 patients (13%)</td>
<td>9 patients (20%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 patients (19%)</td>
<td>18 patients (40%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 patients (25%)</td>
<td>13 patients (29%)</td>
</tr>
<tr>
<td>SSS-TOAST stroke subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>4 patients (25%)</td>
<td>17 patients (38%)</td>
</tr>
<tr>
<td>Cardioaortic embolism</td>
<td>6 patients (38%)</td>
<td>17 patients (38%)</td>
</tr>
<tr>
<td>Small vessel occlusion</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Other causes</td>
<td>3 patients (19%)</td>
<td>6 patients (13%)</td>
</tr>
<tr>
<td>Undetermined—cryptogenic embolism</td>
<td>...</td>
<td>2 patients (4%)</td>
</tr>
<tr>
<td>Undetermined—other cryptogenic</td>
<td>3 patients (19%)</td>
<td>2 patients (4%)</td>
</tr>
<tr>
<td>Undetermined—unclassified</td>
<td>...</td>
<td>1 patient (2%)</td>
</tr>
<tr>
<td>Undetermined—incomplete evaluation</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Infarct territory*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery/M1/M2/M3</td>
<td>11 patients (69%)</td>
<td>41 patients (91%)</td>
</tr>
<tr>
<td>M4/M5</td>
<td>5 patients (31%)</td>
<td>4 patients (9%)</td>
</tr>
<tr>
<td>Acute DWI lesion volume, median (IQR)*</td>
<td>14.6 (5.8–31.7) mL</td>
<td>40.6 (15.3–79.1) mL</td>
</tr>
<tr>
<td>Acute MTT lesion volume, median (IQR)*</td>
<td>51.7 (22.4–193.5) mL</td>
<td>179.0 (84.7–298.9) mL</td>
</tr>
<tr>
<td>Acute CBF lesion volume, median (IQR)*</td>
<td>28.0 (0.8–99.7) mL</td>
<td>122.1 (45.1–226.9) mL</td>
</tr>
<tr>
<td>Acute CBV lesion volume, median (IQR)*</td>
<td>4.4 (0.0–29.0) mL</td>
<td>42.3 (15.1–71.6) mL</td>
</tr>
<tr>
<td>Follow-up T2 lesion volume, median (IQR)*</td>
<td>15.1 (7.1–49.4) mL</td>
<td>79.5 (20.3–121.0) mL</td>
</tr>
<tr>
<td>PML, median (IQR)*</td>
<td>2.5 (0.0–12.7) %</td>
<td>17.7 (3.5–54.2) %</td>
</tr>
<tr>
<td>Acute stroke treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>11 patients (69%)</td>
<td>37 patients (82%)</td>
</tr>
<tr>
<td>Antiplalet treatment</td>
<td>10 patients (63%)</td>
<td>21 patients (47%)</td>
</tr>
<tr>
<td>Admission mean blood pressure, mean ± SD</td>
<td>106.0 (± 18.7) mm Hg</td>
<td>106.5 (± 14.5) mm Hg</td>
</tr>
<tr>
<td>Admission body temperature, mean ± SD</td>
<td>36.4 (± 0.4) °C</td>
<td>36.4 (± 0.5) °C</td>
</tr>
<tr>
<td>Admission plasma glucose level, median (IQR)</td>
<td>111.5 (98.5–122.0) mg/dL</td>
<td>117.0 (105.5–140.0) mg/dL</td>
</tr>
<tr>
<td>Preadmission angiotensin-converting enzyme inhibitor therapy</td>
<td>3 patients (19%)</td>
<td>9 patients (20%)</td>
</tr>
<tr>
<td>Preadmission statin therapy</td>
<td>7 patients (44%)</td>
<td>12 patients (27%)</td>
</tr>
<tr>
<td>Preadmission antiplalet therapy</td>
<td>7 patients (44%)</td>
<td>14 patients (31%)</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \).
and follow-up MRI, SSS-TOAST subtypes, in-hospital stroke treatment (antiplatelet treatment or anticoagulation), admission body temperature, and admission blood pressure.

The linear regression model with PML as response showed that the association between PML and insular infarct was statistically significant ($P=0.01$). The F ratio for the overall model was statistically significant ($P<0.01$). The model predicted an approximately 3.2 times increase in PML with insular involvement. In addition to insular location, age ($P<0.01$) and CBV volume ($P<0.01$) were also significant in this model.

**Discussion**

The current study demonstrates that the amount of initially ischemic tissue that eventually turns into infarction is greater in MCA infarcts encompassing the insula compared with those sparing the insula; the amount of adjusted PML was approximately 3.2 times more with insular infarcts. Our findings also show that insular infarcts are more often associated with proximal MCA occlusions, larger region of ischemia, and greater extent of severe perfusion failure.

The insula mainly receives its blood supply from the M2 segment of MCA. Occasionally, branches from the M1 segment (in 50%) and from the M3 segment (in 25%) contribute to the supply of the insula. In each hemisphere, there are on average 96 insular arteries. Insular arteries are very small caliber vessels; according to one study, the average diameter of insular arteries is 0.23 mm (range, 0.1 to 0.8 mm). Due to their multiplicity and small caliber, insular infarcts often do not occur as a result of occlusion of individual insular branches. A more common mechanism for insular infarcts is M1 or M2 occlusion. Therefore, it is plausible to consider that the higher rate of growth in infarcts encompassing the insula might be a mere bystander effect of proximal MCA occlusions. However, our findings suggest that this is not the case because insular involvement was still a predictor of growth when adjusted for the volume of ischemic tissue as well as the site of vascular occlusion in the current study. Therefore, it may be valuable to consider what additional factors may play a role in the link between insular location and worsened tissue outcome.

Another explanation that is also directly linked to the vasculature is that growth in insular infarcts might simply be a proxy for poor collaterals. An infarct due to proximal MCA occlusion that spares the insula but involves the subcortical gray and white matter might be indicative of good pial collateral circulation, whereas an MCA occlusion with infarct including the insula can be a harbinger of insufficient cortical collaterals and thus infarct growth. The extent of perfusion failure across the ischemic region is not uniform in every proximal MCA occlusion. Perfusion-weighted MRI identifies at least 3 different perfusion zones within the region of compromised perfusion. MTT maps outline the outer border of perfusion abnormality. CBF maps delineate a smaller region with more severely compromised tissue perfusion within the MTT defect. CBV maps designate even a smaller region than the CBF defect with very severely impaired perfusion secondary to the failure of compensatory vasodilation in the leptomeningeal vessels. Although col-
latterals certainly play an important role in determining infarct size, our findings indicate, within the limits of the measurement technique, that insular infarcts are associated with worsened tissue outcome even when adjusted for the volume of each perfusion zone. This suggests that there may be perfusion-independent mechanisms that contribute to insula-related infarct growth.

The insula represents a transition point between the surrounding cerebral neocortex and the limbic system. It has reciprocal connections with the amygdala, cingulate gyrus, thalamus, entorhinal cortex, and with certain regions in the frontal, parietal, and temporal lobes. The insula is supposed to be involved in pain processing, volitional swallowing, vestibular and gustatory functions, some aspects of speech and language, and in the cortical modulation of the autonomic nervous system activity. This latter point is particularly relevant because clinical and experimental investigations indicate that there is increased sympathetic nervous system activity, activity, including increased plasma catecholamine levels, indicate that there is increased sympathetic nervous system activity. This latter point is particularly relevant because clinical and experimental investigations indicate that there is increased sympathetic nervous system activity. This latter point is particularly relevant because clinical and experimental investigations indicate that there is increased sympathetic nervous system activity.

Perfusion-independent mechanisms that contribute to insula-related infarct growth.

Table 2. Systemic Effects of Pathologic Sympathetic Nervous System Activation

<table>
<thead>
<tr>
<th>Effect</th>
</tr>
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<tbody>
<tr>
<td>Cardiac tachyarrhythmia</td>
</tr>
<tr>
<td>Left ventricular stunning (low cardiac output)</td>
</tr>
<tr>
<td>Leukocytosis</td>
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<tr>
<td>Prolinflammatory cytokine production</td>
</tr>
<tr>
<td>Immunodepression and infection</td>
</tr>
<tr>
<td>Polycythemia</td>
</tr>
<tr>
<td>Acute stress hyperglycemia</td>
</tr>
<tr>
<td>Hyperthermia</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Cerebral vasoconstriction</td>
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<tr>
<td>Increased blood brain barrier permeability</td>
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<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Peripheral vasoconstriction</td>
</tr>
<tr>
<td>Others (piloerection, hyperhidrosis, bronchodilation, decreased gastrointestinal motility, urinary retention, and so on)</td>
</tr>
</tbody>
</table>

Although the autonomic system conveys a survival advantage against internal and external threats, its activation can lead to a number of undesirable effects, some of which could even be life-threatening. Some sequelae of sympathetic nervous system activation are listed in Table 2. Many of these alterations are associated with adverse clinical or tissue outcome in stroke. For instance, elevated norepinephrine concentration after stroke is a predictor of insular involvement and poor neurological outcome. Likewise, poststroke hyperglycemia occurs more often with insular infarcts and is associated with larger infarct size and poor neurological outcome. Similarly, infarcts in the right posterior insula are associated with elevated serum troponin-T levels indicative of acute myocardial injury. Cardiac troponin elevations are, in turn, independent risk factors for poor clinical outcome after ischemic stroke. Other signs and symptoms of sympathetic nervous system activation are also factors that can boost the ischemic brain injury—factors such as fever, leukocytosis, polycythemia, inflammation, and increased blood–brain barrier permeability. Even hypertension might be included in this list based on data that high blood pressure during acute ischemic stroke is associated with poor outcome in the general stroke population. In summary, it might be possible that the insula, which when infarcted triggers a series of mechanisms, which might also be thought of as “neurovascular kindling of infarction,” might ultimately lead to worsened infarction in ischemic but potentially viable neighboring brain tissue.

The current study is subject to a number of limitations. Although the published evidence in humans is contradictory that both right and left insular infarcts have been linked to cardiac and/or systemic alterations indicative of sympathetic nervous system activation, the true effect of hemispheric lateralization on the PML might have been missed in the current study because of the small sample size. Small sample size also limits the ability of this study to explore relationships with other covariates that can potentially affect infarct progression such as hyperglycemia, fever, hemodynamic instability, and medications after stroke. Although there was a trend toward higher blood glucose level and white blood cell count in patients with insular infarcts, the sample size was too small to establish any cause-and-effect relationship.

The current study is, to our knowledge, the first to show that insular infarcts are associated with unfavorable tissue outcome in ischemic stroke. This finding adds on the prior clinical work that increased conversion of ischemic but potentially viable neighboring brain tissue into infarction can be a potential mechanism for unfavorable clinical outcome observed with infarcts that encompass the insula. Further research in larger data sets with simultaneous assessment of insular involvement, collateral circulation, markers of sympathetic nervous system activation, and infarct progression is required to elucidate the mechanism of unfavorable tissue outcome in infarcts encompassing the insula. If confirmed, our findings could open new avenues to strategies to halt the progression of ischemic injury and improve neurological outcome.

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Disclosures

None.

References


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