Insular Cortex Infarction in Acute Middle Cerebral Artery Territory Stroke

Predictor of Stroke Severity and Vascular Lesion

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Background: Insula infarction is an early computed tomographic sign of middle cerebral artery (MCA) territory stroke and may affect cardiovascular autonomic function.

Objective: To determine insula involvement in MCA territory infarction and its relationship with infarcts in the remainder of the MCA territory, stroke severity, and clinically relevant cardiovascular conditions.

Design: Case series (August 1, 1997, to June 30, 2000).

Setting: Academic stroke center.

Patients: A total of 150 consecutive patients with non-lacunar MCA territory stroke who underwent magnetic resonance imaging within 48 hours of stroke onset.

Main Outcome Measures: Association of insula infarction with the National Institutes of Health Stroke Scale (NIHSS) score, location of vascular occlusion, and cardiovascular events.

Results: Insular lesions were present in 72 patients (48%); 34 (23%) had major insular lesions and 38 (25%) had minor lesions. Insula infarction was associated with lenticulostriate territory infarction (46% vs 14%; $P<.001$), more than one third of MCA territory infarction (35% vs 3%; $P<.001$), higher NIHSS score (13.5 vs 6; $P<.001$), and proximal vascular occlusion detected on magnetic resonance angiography. These associations were strongest for patients with major insular lesions. Clinically significant new arrhythmia was present in 15 of 72 with insula infarction (13 atrial fibrillations) and 4 of 78 without ($P=.06$). Insula infarction was associated with lower diastolic blood pressure at admission but was not associated with pulse rate, QTc interval, myocardial infarction, or sudden death.

Conclusions: The insular cortex is involved in almost half of patients with nonlacunar ischemic MCA territory strokes. Major insula involvement is associated with large MCA territory infarcts, proximal MCA occlusions, and greater stroke severity. Insula infarction was not a predictor of clinically significant acute cardiovascular events during hospital stay in our patients.

Arch Neurol. 2005;62:1081-1085

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THE INSULA IS AN "ISLAND" OF cortex that lies at the base of the sylvian fissure, overlying the extreme capsule and claustrum. Insular stroke is associated with poor functional outcome[1] and neurologic abnormalities, including somatosensory, gustatory, neuropsychological, language, auditory processing, vestibular, and swallowing disorders.[2] The role of the insula in cardiovascular autonomic functions is supported by strong experimental evidence,[3-5] and a role of insula infarction in causing cerebrogenic arrhythmia and sudden cardiac death has been suggested.[6-9] Insula infarction has also been recognized as an important early sign of cerebral infarction on computed tomographic (CT) brain images and is predictive of the arterial occlusion site.[10-12]

However, insula infarction is rarely seen without involvement of other adjacent structures supplied by the middle cerebral artery (MCA). The frequency and extent of insula involvement in MCA territory infarction and its relationship with stroke severity and clinically relevant cardiovascular disorders are not well established. Magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI), is more sensitive than CT for early indication of brain infarction and allows detailed analysis of infarct topography. We report an analysis of a consecutive series of patients with MCA territory stroke who underwent imaging with DWI whom we assessed for insula involvement, infarct topography, stroke severity, and cardiovascular outcomes.

METHODS

Patients who presented to the stroke service at Beth Israel Deaconess Medical Center between August 1, 1997, and June 30, 2000, with acute MCA territory ischemic stroke were identified from a prospective stroke database. Patients who had undergone MRI, including DWI, within 48 hours of stroke onset were included in the study. Patients with lacunar stroke, defined by imaging criteria as a solitary DWI lesion smaller than 1.5 cm in diameter within the lenticulostriate arterial field,[13] were excluded.

IMAGING PROTOCOL

The MRI studies were performed on a Siemens Vision 1.5-T echo-planar imaging system (Siemens Medical Solutions Inc, Malvern, Pa). Imaging parameters were published previously.[14] During the study period, this MRI protocol was the primary brain imaging modality for all patients with acute stroke unless contraindicated. Computed tomography was performed in a few patients.

IMAGE ANALYSIS

We assessed and graded DWI studies using previously described anatomical templates.[15] Insular lesions were defined as *major* if more than two thirds of the length of the insula was involved on any imaging section or more than half the length was involved on 2 or more slices. Smaller insular lesions were termed *minor*. Infarcts that involved only the anterior or posterior insula were recorded. Magnetic resonance angiograms of patients who underwent imaging within 6 hours of stroke onset were analyzed. Vascular occlusions of the extracranial internal carotid artery (ECICA), intracranial internal carotid artery (ICICA), or proximal M1 segment MCA were termed *proximal*; those beyond the bifurcation or trifurcation of the M1 segment of the MCA were termed *distal*. The CT scans of patients who underwent both CT and MRI within 6 hours were analyzed by 2 independent readers (J.N.F. and W.C.F.) for the presence of the CT "insular ribbon" sign.[10]

CLINICAL DATA

Clinical data including age, National Institutes of Health Stroke Scale (NIHSS) score at admission, stroke etiology, and risk factors were available from the prospective stroke register. The patients' clinical records were examined for data such as neurologic signs, electrocardiographic and blood pressure recordings, cardiovascular complications, and drug treatments.

STATISTICAL ANALYSIS

Primary comparisons were made between patients with and without insular cortex infarction. Patients with insula infarct were subdivided into major and minor lesion groups for subgroup analyses. The *t* test was used for parametric data, the Wilcoxon rank sum test for nonparametric data, and the Fisher exact or χ^2 test for proportional comparisons. Cardiovascular parameters were analyzed in a multivariate model. The primary analyses explored the univariate relationships between the cardiovascular parameters (systolic blood pressure, diastolic blood pressure, pulse rate, QTc interval, and creatine kinase level) and the clinical and imaging variables (age, smoking status, history of ischemic heart disease and diabetes, NIHSS score, insula involvement, lesion side, lenticulostriate involvement, and stroke size). These analyses were performed using 1-way analysis of variance and correlation coefficients as appropriate. Clinical and imaging variables that showed some association ($P<.10$) with the individual cardiovascular variables were entered into a multiple linear regression model to determine their independent associations. Statistical analyses were performed using SPSS statistical software, version 10 (SPSS Inc, Chicago, Ill).

RESULTS

One hundred fifty patients were included in the study. Mean age at stroke onset was 71 years (age range, 24-94 years). Insula DWI lesions were present in 72 patients (48%); 34 (23%) had major insula lesions and 38 (25%) had minor. Right MCA territory infarction was present in 72 patients, of whom 38 (53%) had insula infarction, whereas 34 (44%) of 77 patients with left MCA infarction had insula involvement ($P=.29$). Both the anterior and posterior insula were involved in 36 (50%) of 72 patients with insula infarction. The anterior insula alone was involved in 8 patients (11%), 7 associated with infarction in the territory of the MCA superior division. The posterior insula alone was involved in 28 patients (39%), 25 in association with inferior division infarcts. Forty-four patients had lenticulostriate territory infarction, 33 (75%) with insula infarction (25 major, 2 minor anterior, and 6 minor posterior).

Truly isolated infarction of the insular cortex without involvement of other MCA territories was not seen. In 1 patient, complete left insula infarction was associated with minor involvement of some adjacent structures, such as the temporal operculum and putamen (**Figure 1**). This patient presented mute and with right facial weakness but with no other focal neurologic deficits. The cause of this isolated insula infarction was considered to have been cardiogenic embolism to the MCA due to atrial fibrillation, with probable early spontaneous recanalization.

Insula infarction was associated with lenticulostriate territory infarction, larger MCA territory strokes, and more severe clinical deficits (**Table, Figure 2**). These associations remained when only patients who underwent imaging within 6 hours of stroke onset were considered, and they were strongest for patients with major insula lesions. Large infarcts (more than one third of the MCA territory) were seen in 20 patients (59%) with major insula infarction, compared with 5 patients (13%) with minor insula infarction ($P=.002$). All 5 patients with large infarcts and minor insula lesions had minor infarction of the posterior insula in association with complete inferior division MCA infarction, without lenticulostriate territory involvement (**Figure 3**). No patient had an infarction larger than one third of the MCA territory without insula involvement.

VASCULAR OCCLUSION

Sixty-two patients underwent MRI within 6 hours of stroke onset, 57 with analyzable magnetic resonance angiograms. Proximal vascular occlusions were found in 16 (84%) of 19 patients with major insula infarction (3 ECICA, 1 ICICA, and 12 M1 MCA) compared with 5 (42%) of 12 patients with minor insula infarction (all M1 MCA; $P=.02$) and 6 (35%) of 26 patients with no insula infarction (3 ECICA and 3 M1 MCA; $P<.001$). Isolated distal MCA occlusions were identified in 12 patients: none
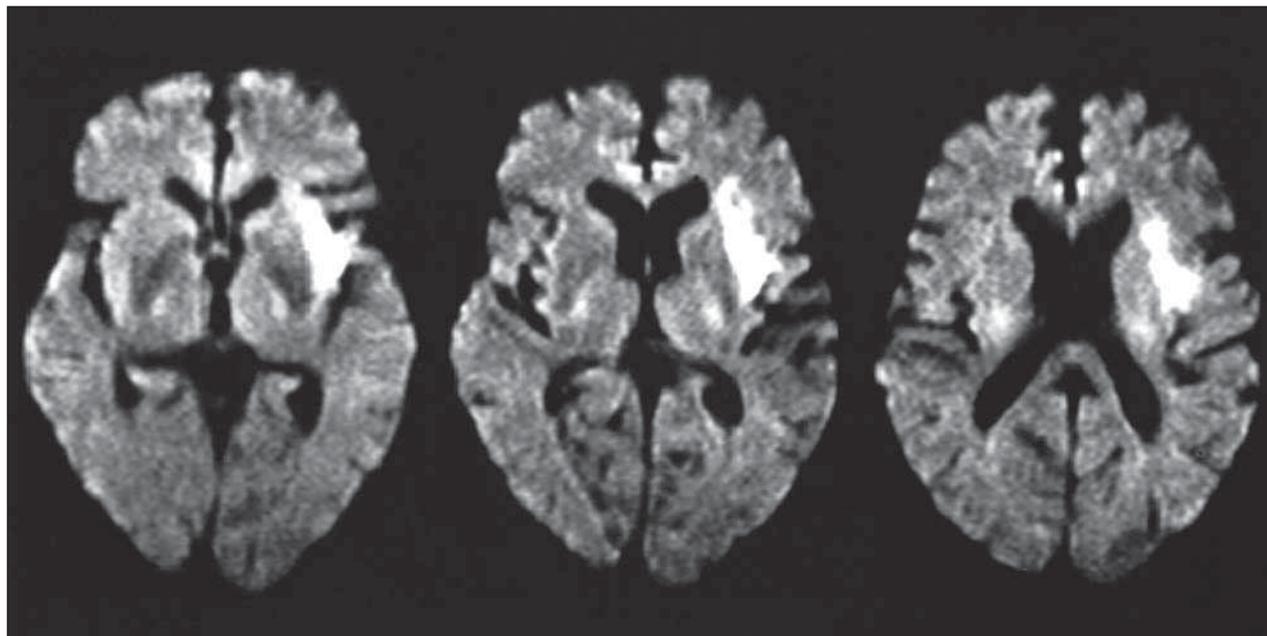
Figure 1. Isolated insula infarction. Diffusion-weighted image at the level of the insula from a single patient.

Table. Insula Involvement vs No Insula Involvement

Variable	Insula (n = 72)	No Insula (n = 78)	P Value
Lenticulostriate involvement, No. (%)	33 (46)	11 (14)	<.001
More than one third of MCA territory infarction, No. (%)	25 (35)	2 (3)	<.001
Median NIHSS score	13.5	6	<.001
TOAST mechanism, No. of patients			.08
Cardiac source	40	29	
Large artery*	24	36	
Unknown or other	8	13	

Abbreviations: MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.[16]
*χ^2 = 5.11.

had major insula infarction, 5 had minor, and 7 had no insula infarction.

CORRELATION OF MRI AND CT

Eleven patients underwent both MRI and CT within 6 hours. Mean time to first image was 2.8 hours from stroke onset (MRI first in 4); mean time between studies was 2.5 hours. All 6 patients with the CT insular ribbon sign had major insula infarction on DWI. All 5 patients with negative CT scan results had either no or minor insula infarction on DWI.

CARDIOVASCULAR EFFECTS OF INSULA INFARCTION

Four patients received antihypertensive treatment within the first 48 hours of stroke onset in addition to any usual long-term antihypertensive medications; none had insula infarction (P=.15). Minor electrocardiographic changes, predominantly nonspecific ST/T-wave abnor-
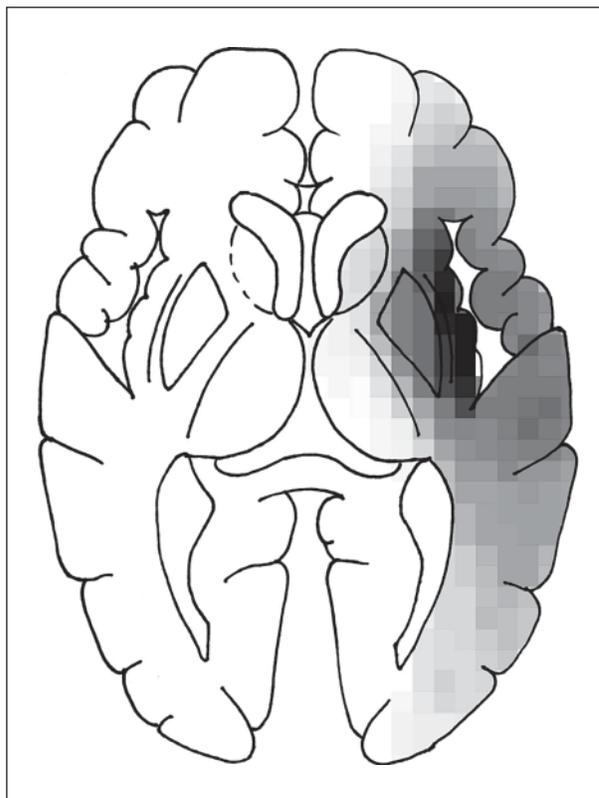
Figure 2. Composite image at the level of the insula that demonstrates the topography of middle cerebral artery infarctions with major insula involvement. Degree of shading is proportional to frequency of involvement of 5 x 5-mm brain regions.

malities, were present in 29 patients with insula infarction and 23 patients with no insula infarction (P=.16) but were more common with left hemisphere infarction (34 vs 18; P=.01). There was no difference in QTc interval between patients with or without insula infarction of either
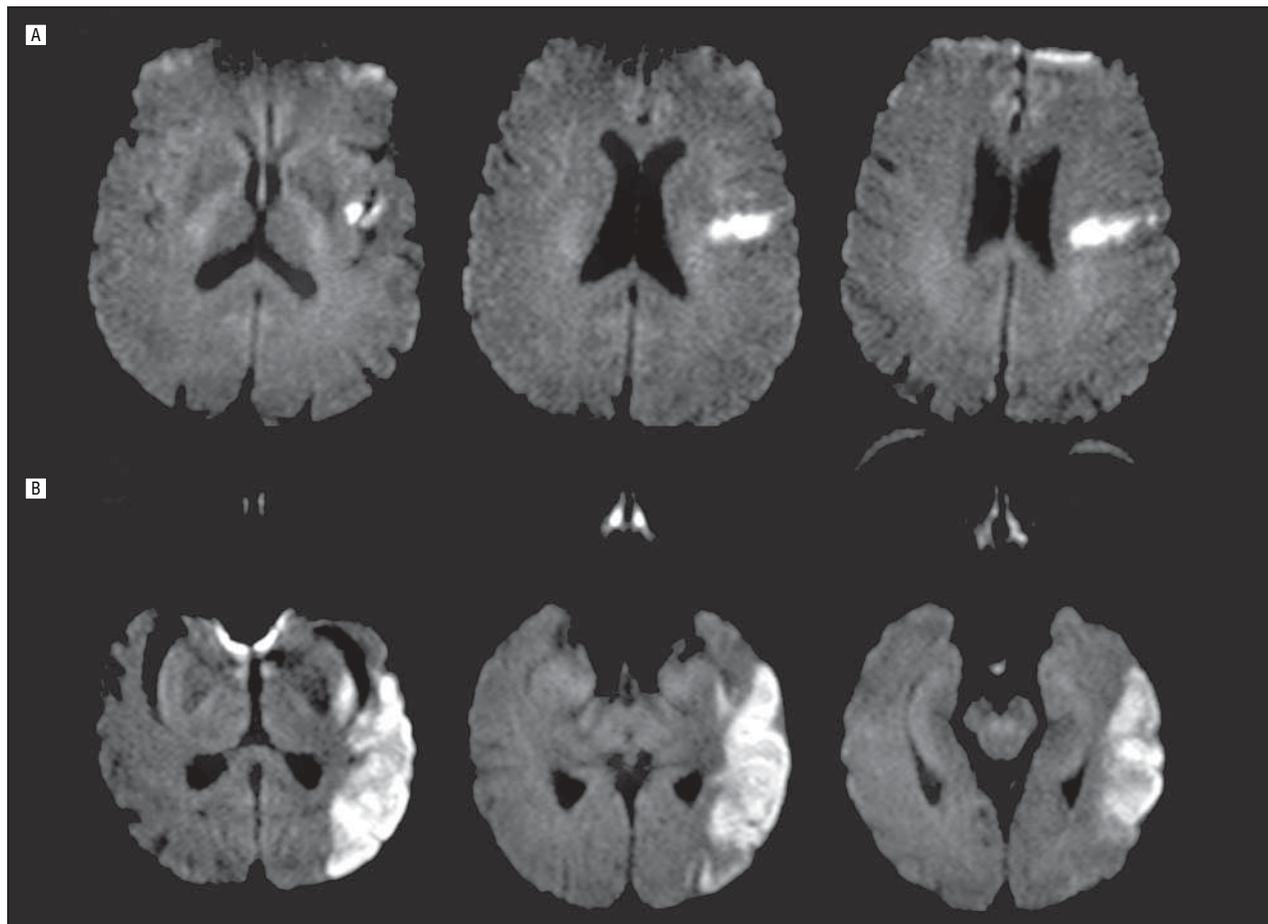
Figure 3. Minor insula infarction. Diffusion-weighted images from 2 patients. A, Minor insula infarction associated with infarction in the territory of an M2 middle cerebral artery (MCA) branch. B, Minor posterior insula infarction associated with large inferior division MCA infarction.

side. Clinically significant new arrhythmia was detected in 15 patients (atrial fibrillation in 13), 11 with insula infarction and 4 without ($P=.06$). No patient was diagnosed as having myocardial infarction during the hospital stay. Congestive heart failure was recorded in 1 patient. Two unexpected sudden deaths occurred, one from presumed pulmonary embolism (no insula infarction) and the other in a patient with post–coronary artery bypass surgery stroke (minor left posterior insula infarction).

Multivariate analysis found a significant independent association of insula infarction with diastolic blood pressure (insula involved: mean diastolic blood pressure, 76 mm Hg; insula not involved: 81 mm Hg; $P=.02$); the side of the lesion was not a significant factor. Insula involvement was not significantly associated with any other cardiovascular parameter. Lenticulostriate involvement but not insula involvement was independently associated with reduced pulse rate (68 vs 75/min; $P=.01$). Age and history of ischemic heart disease were independently and positively associated with QTc interval.

COMMENT

We found that infarction of the insular cortex occurs frequently in nonlacunar MCA territory stroke, with major insula infarction seen in nearly one quarter and any in-

sula infarction in almost half of patients. Major insula infarction was significantly associated with proximal vascular occlusions, larger infarct size, lenticulostriate territory infarction, and more severe clinical deficits than minor or no insula infarction. Previous studies that combined CT and angiography showed similar associations.[11,12] For the limited number of patients in our series with both early MRI and CT studies, we found excellent correlation of the CT insular ribbon sign[10] and major insula DWI lesions.

The associations found with major insula infarction are understandable from knowledge of the vascular supply to the insular cortex.[17-19] The insula lies at the heart of the pial territory of the MCA. Its arterial supply is exclusively from branches of the MCA, predominantly the M2 segment, with a small contribution from insular branches of the M1 segment in some individuals.[19] The superior MCA division gives rise to branches that supply the anterior insula, whereas the inferior division supplies the posterior insula. Involvement of the lenticulostriate territory with major insular infarction or involvement of both the anterior and posterior portions of the insula indicates that a temporary or permanent proximal M1 occlusion must have been present. We found that isolated anterior insula infarcts were often accompanied by other infarcts in the superior MCA division territory, whereas posterior insula infarcts were accompanied by inferior division infarction.

This pattern suggests an embolic occlusion of an M2 MCA division or its branches (Figure 3).

The insula is vulnerable to ischemia due to thromboembolic vascular occlusion of the M1 MCA segment and the superior and inferior MCA trunks because no possibility exists of pial collateral supply from the anterior or posterior cerebral arteries. However, the proximal origin of vascular supply protects the insula from ischemia due to hemodynamic factors in the absence of thromboembolic occlusion.

We found little evidence of clinically significant effects of insula infarction on cardiovascular parameters during the initial period of hospitalization following acute stroke. Electrocardiographic changes were associated with left hemisphere stroke but seen equally among those with and without insula infarction. New diagnosis of atrial fibrillation was somewhat more common among patients with insula infarction, but association of atrial fibrillation with larger embolic strokes and proximal MCA occlusion is a likely explanation for the association. However, parietoinsular stroke was associated more strongly with new-onset atrial fibrillation than with cardiogenic stroke in general in a previous series.[7] Sudden unexpected death was rare in our series, and no association with insula infarction was evident. Analysis of long-term risk of sudden death from the North American Symptomatic Carotid Endarterectomy Trial cohort has shown some association between left-sided infarction and sudden death but no association with insula infarction.[20]

Insula infarction was associated with lower diastolic blood pressure recording but with no other cardiovascular parameter measured. The clinical significance of this finding is uncertain. Evidence of decreased cardiac autonomic tone has previously been found following acute ischemic stroke,[6,21-23] with reduced heart rate variability being most prominent after stroke that involves the right hemisphere,[21,23] particularly the right insula.[6] Our conclusions are limited by the retrospective nature of our cardiovascular data. We analyzed only routinely collected electrocardiographic, blood pressure, and pulse rate recordings, data that are insensitive to abnormalities of cardiac autonomic tone that can be detected with measures such as 24-hour electrocardiographic and blood pressure monitoring.

Our series represents a relatively large cohort of patients with nonlacunar MCA territory stroke investigated with MRI, including DWI. Major insula infarction was present in approximately one quarter of patients and represents the early ischemic core of proximal MCA occlusion. Our study helps to confirm the prognostic importance of major insula infarction or the insular ribbon sign.[10] However, the clinical effects of insula infarction itself are generally overwhelmed by the involvement of adjacent brain regions. Despite the experimental and clinical evidence that links insula infarction to autonomic dysfunction, our findings suggest that insula infarction is unlikely to be an important predictor of clinically significant cardiovascular events for most patients during the initial hospitalization period following acute stroke.

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