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Insular Cortex Hypoperfusion and Acute Phase Blood Glucose After Stroke

A CT Perfusion Study

Fiona C. Moreton, BSc; Michael McCormick, MRCP; Keith W Muir, MD, FRCP

Background and Purpose—Insular cortex ischemia is proposed to mediate a sympathetic stimulus that leads to acute hyperglycemia after stroke.

Methods—We retrospectively analyzed insular perfusion on perfusion CT (median 180 minutes after onset) in 35 patients.

Results—We found no association of hypoperfusion (relative cerebral blood flow <0.51) with early (<6 hours) or delayed (<72 hours) hyperglycemia, or hemispheric lateralization.

Conclusions—Insular cortex hypoperfusion <6 hours after stroke onset was not associated with hyperglycemia. (***Stroke***. 2007;38:407-410.)

Key Words: blood glucose ■ cerebral blood flow ■ hyperglycemia ■ insula ■ perfusion CT

Poststroke hyperglycemia (PSH) affects 40% to 60% of patients and independently predicts poor outcome.[1] Multiple adverse pathophysiological consequences of hyperglycemia may impair penumbral survival.[2,3] It is proposed that insular cortex ischemia may specifically mediate PSH by releasing tonic inhibition of sympathetic centers,[4] and that this effect differs between hemispheres.[5] However, anatomical infarct location is inconsistently associated with PSH in clinical studies.[6,7]

We sought associations of hyperglycemia and insular cortex hypoperfusion on perfusion CT in acute stroke patients. We hypothesized that insular hypoperfusion was associated with PSH, and that the association differed between hemispheres.

Methods

Clinical and imaging studies of all acute ischemic stroke patients undergoing perfusion CT routinely over 42 months were reviewed. The Local Research Ethics Committee approved data analysis without requiring individual consent.

Exclusion criteria were blood glucose not recorded within 6 hours of onset or perfusion CT scans uninterpretable, eg, because of motion, established insular infarction, or omission of a slice through the basal ganglia.

Clinical findings reviewed included whole blood and capillary glucose concentrations, National Institutes of Health Stroke Scale (NIHSS) scores, demographics, and Oxfordshire Community Stroke Project classification. Hyperglycemia was defined as blood glucose ≥ 7.0 mmol/L. Both admission glucose concentration ($[Glu]_{Ad}$) and maximal documented blood glucose within 72 hours ($[Glu]_{max}$) were recorded.

Dynamic perfusion CT was performed on a Philips MX8000 scanner using a previously described protocol[8] and analyzed using MxView software (Philips Medical Systems), which calculates perfusion parameters by the maximum slope method.

Regions of interest were drawn manually to define anterior and posterior insular cortex gray matter of each hemisphere by a single investigator blind to glucose results. The average of 3 readings from each region of interest was taken. Cerebral blood flow, time to peak, and cerebral blood volume were expressed relative to the contralateral regions of interest. Hypoperfusion was primarily defined as relative cerebral blood flow ≤ 0.50. For exploratory analyses, time to peak delay >6 seconds or relative cerebral blood volume <0.6 were used.

For blood glucose as a continuous variable, independent t test, analysis of variance, and general linear modeling were used. For blood glucose as a categorical variable, Fisher's exact test and multivariate logistic regression analyses were used. For NIHSS scores, the Mann Whitney U test was used. Values are quoted as mean ($\pm$SD) unless otherwise stated. Significance was taken at $P<0.05$ (2-tailed).

Results

Thirty-five subjects fulfilled study criteria (Table). Subjects were divided into groups with normal or hypoperfusion of the insula (anterior or posterior portions) by relative cerebral blood flow criteria.

$[Glu]_{max}$ was significantly higher than $[Glu]_{Ad}$ (7.73 versus 6.49 mmol/L, $P=0.001$, paired t test). Glucose increase from admission was documented in 18/35 subjects (11/16 normal perfusion, 7/19 hypoperfusion; $P=0.092$; Fisher's exact test).

Insular hypoperfusion was associated with nonsignificantly higher $[Glu]_{Ad}$ and $[Glu]_{max}$. Admission hyperglycemia was present in 9 of 23 subjects with left and 2 of 12 subjects with right hemisphere hypoperfusion, and within 72 hours in 12 of 23 subjects with left and 6 of 12 with right hemisphere ischemia.

Anterior insular hypoperfusion was present in 18 subjects, 10 of whom also had posterior insular hypoperfusion. Only one subject had isolated posterior insular hypoperfusion.

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Patient Characteristics

		Insular Cortex	
	All Patients	rCBF>0.50	rCBF<0.51
No.	35	16	19
Age, mean±SD, y	68±13	69±13	67±14
Male, n (%)	17 (49%)	7 (44%)	10 (53%)
Stroke hemisphere, left:right	23:12 (66%:34%)	12:4 (75%:25%)	11:8 (58%:42%)
OCSP classification, n (%)			
TACS	18 (51%)	7 (44%)	11 (58%)
PACS	15 (43%)	7 (44%)	8 (42%)
LACS	2 (6%)	2 (12%)	0 (0%)
Blood glucose, mean±SD, mmol/L			
Admission	6.5±1.3	6.24±1.43	6.71±1.21
Highest documented within 72 hours	7.73±2.38	7.69±2.91	7.76±1.92
Admission NIHSS, median [IQR]	15 [11,19]	13 [10, 20]	16 [12.5, 18.5]
Median time to perfusion CT [IQR], min	170 [150, 210]	167.5 [140, 185]	170 [165, 220]
Median 24 hours NIHSS [IQR]	7 [5, 16.5]	7 [5, 15]	7 [5, 17]
Thrombolytic therapy, n (%)	20 (57%)	11 (69%)	9 (47%)
3-Month modified Rankin scale, n (%)			
0–2	11 (34%)	4 (29%)	7 (39%)
3–5	12 (38%)	5 (36%)	7 (39%)
6	9 (28%)	5 (36%)	4 (22%)
Risk factors, n (%)			
Diabetes	2 (6%)	1 (6%)	1 (5%)
Hypertension	24 (71%)	12 (75%)	12 (67%)
Previous stroke	9 (27%)	7 (44%)	2 (11%)
Ischemic heart disease	10 (29%)	4 (25%)	6 (33%)
Previous TIA	9 (27%)	5 (31%)	4 (22%)
Hypercholesterolemia	11 (32%)	6 (38%)	5 (28%)
Present smoker	8 (24%)	3 (19%)	5 (28%)
Ex-smoker	7 (21%)	4 (25%)	3 (19%)
Admission medication, n (%)			
Insulin	1 (3%)	0 (0)	1 (6%)
Hypoglycemics	1 (3%)	1 (7%)	0 (0%)
Antihypertensives	22 (67%)	11 (73%)	11 (61%)

IQR indicates interquartile range; LACS, lacunar syndrome; OCSP, Oxfordshire Community Stroke Project; PACS, partial anterior circulation syndrome; rCBF, relative cerebral blood flow; SD, standard deviation; TACS, total anterior circulation syndrome; TIA, transient ischemic attack.

Analyzing $[Glu]_{Ad}$ (Figure 1A) and $[Glu]_{max}$ (Figure 1B) by insular hypoperfusion and lateralization by 2-way ANOVA, including thrombolytic therapy as a random factor and NIHSS as a covariate, there was no significant effect of hypoperfusion or lateralization, and no significant interaction between factors.

Binary logistic regression including insular hypoperfusion (anterior or posterior), hypoperfusion of anterior and posterior insular cortices individually, NIHSS, and lateralization found no significant predictors of admission or 72-hour peak hyperglycemia.

Univariate general linear modeling of $[Glu]_{Ad}$ or $[Glu]_{max}$ including the same terms found no significant associations. Exploratory analyses of relative cerebral blood volume or time to peak delay as alternative perfusion indices were also nonsignificant. After adjustment for NIHSS, mean $[Glu]_{Ad}$ was higher with hypoperfusion of left hemisphere lesions involving the anterior insula (Figure 2A, 2B). Findings were similar for $[Glu]_{max}$.

Discussion

In patients imaged a median 3 hours after onset, we found no relationship between insular cortex hypoperfusion and hyperglycemia, either on admission or within the first 72 hours. There was no difference between hemispheres. The absence of significant findings was consistent across several approaches to analysis.

While different cardiovascular effects of right and left brain hypoperfusion are seen in rodents,[9] clinical reports disagree both on lateralization and the nature of any dysrhythmia.[10,11] Left insular stimulation causes bradycardia and hypotension, with opposite effects on the right;[12] however, lesion studies are limited by the rarity of isolated insular infarction.[13]
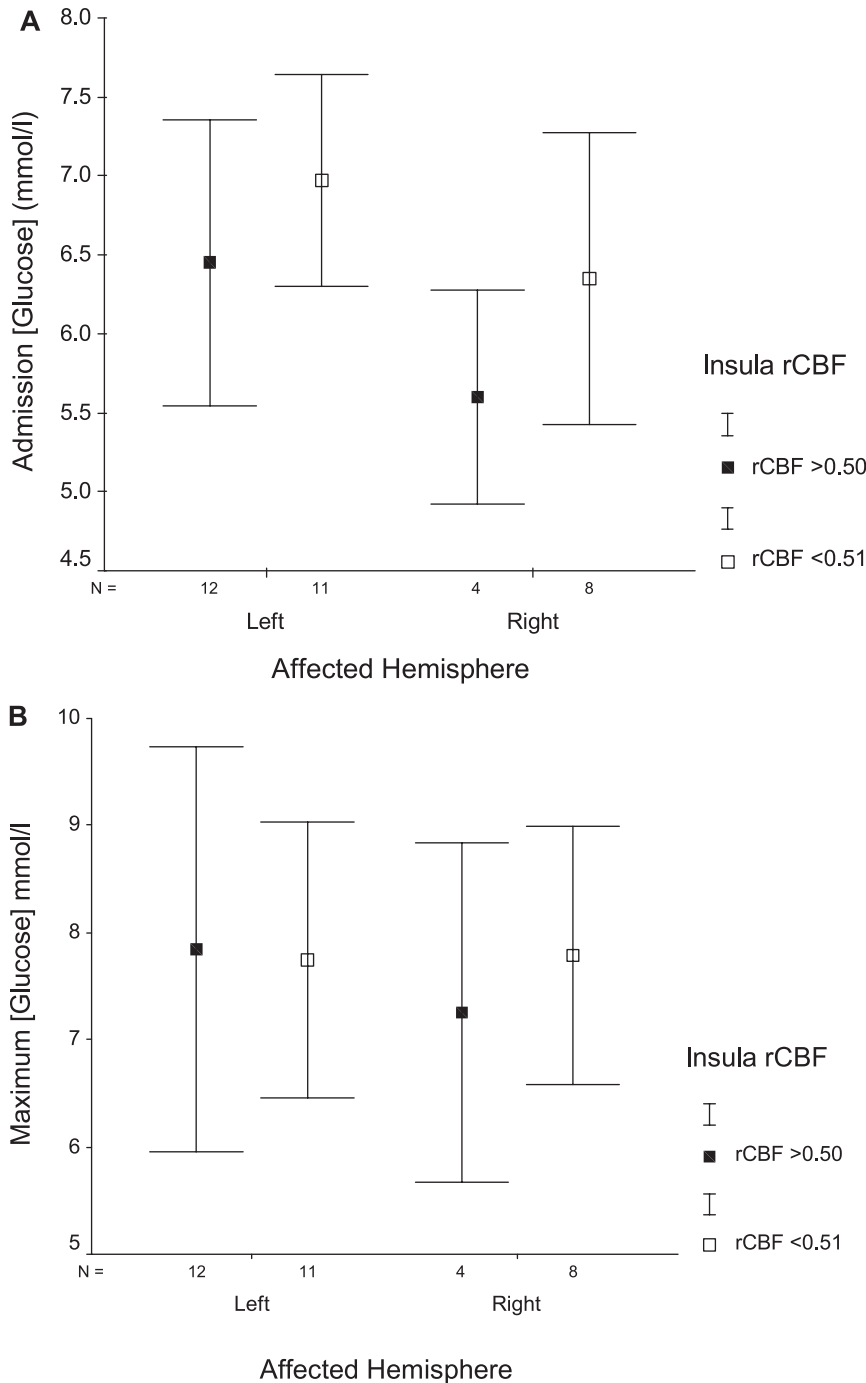
Figure 1. Insular hypoperfusion in right and left hemisphere lesions, (A) [Glu]$_{Ad}$, and (B) [Glu]$_{max}$.

Allport et al reported that insular infarction on diffusion-weighted imaging at median of 13 hours after stroke predicted PSH,[4] independent of lesion volume, NIHSS, glycosylated hemoglobin concentration, and history of diabetes. There are several explanations for our differing findings. First, diffusion-weighted imaging at 13 hours almost certainly indicates infarction, whereas hypoperfusion at 3 hours may be reversible, particularly with a high proportion of our patients receiving thrombolysis. While the severity of ischemia might be less than required to produce definite diffusion-weighted imaging lesions, indices of more severe hypoperfusion (relative cerebral blood volume <0.61 or time to peak delay >6 seconds) were also nonsignificant. Further, Christensen found

no relationship of CT-defined insular infarction with mean blood glucose in 179 patients within 6 hours of onset.[7]

Different autonomic effects of anterior and posterior insular cortical ischemia are proposed. Allport identified few subjects with anterior insular lesions, whereas we found the opposite. However, our exploratory analyses indicated higher admission glucose with left anterior insular hypoperfusion, whereas previous studies suggest exactly the opposite.

Limitations of this study may reduce the chance of finding a relationship. Accurate delineation of the insular cortex is difficult because of its small anatomical size, liability to movement artifact with dynamic perfusion CT, and signal averaging artifacts. To minimize variability, the average value of multiple readings, ob-
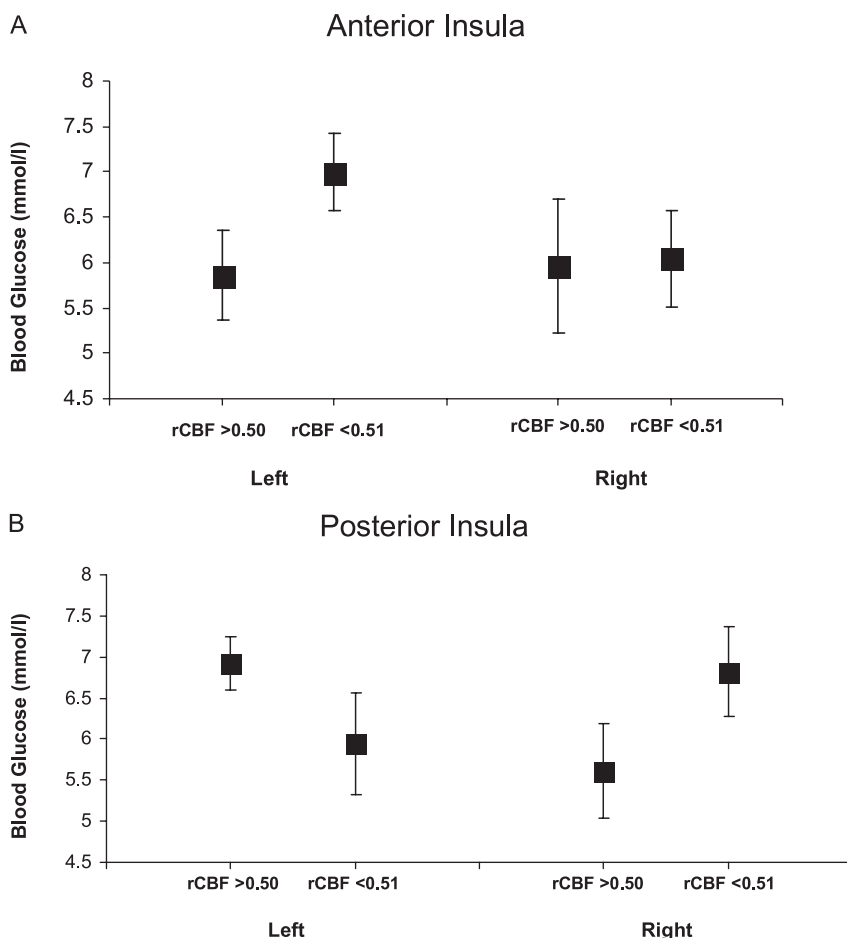
A

Anterior Insula

B

Posterior Insula

Figure 2. Mean±SEM [Glu]$_{ad}$ in right and left hemisphere strokes with and without hypoperfusion of (A) anterior and (B) posterior insular cortex, adjusted for stroke severity.

tained by a single observer at different times, was taken. All regions of interest were defined on the basis of the maximal intensity projection map of the perfusion CT to maximize tissue contrast, and without reference to the perfusion maps.

This study was retrospective, and routinely documented results may underestimate PSH incidence.[3] It is possible that the study size was inadequate; nonetheless, the sample size was greater than for previous studies that have reported an association.

In conclusion, we were unable to confirm an association of insular cortex hypoperfusion with poststroke hyperglycemia.

Disclosures

None.

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