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Infarction Involving the Insula and Risk of Mortality after Stroke

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Key Words
Infarction · Stroke risk factors · Outcome research

Abstract
Background: Cerebral infarction involving the insula has been associated with decreased survival following stroke. We hypothesized that infarct volume may reduce this association. ***Methods:*** The subjects were acute stroke patients who had consented to 2-year follow-up after stroke as part of the Michigan Acute Stroke Care Overview and Treatment Surveillance System registry. One hundred and eleven subjects exhibited areas of acute ischemic infarction on neuroimaging studies, 25 of whom had infarction involving the insula. Cox proportional hazard ratios (HR) were calculated to determine the association between mortality and acute infarction involving the insula, infarct volume, and other factors known to affect survival after stroke. ***Results:*** In unadjusted analysis, subjects with insula infarction had a nonsignificant twofold increase in 1-year mortality (HR = 2.1, 95% CI 0.6–7.0; p = 0.25). When adjusted for infarct volume, however, the HR for insula infarction was reduced to the null value (HR = 1.0, 95% CI 0.2–4.1; p = 1.00), indicating that the effect of insula infarction was entirely confounded by infarct volume. ***Conclusions:*** Insula infarction was associated with a nonsignificant twofold increase in mortality after stroke; however, this association was completely eliminated after adjusting for infarct volume. Infarct volume thus should be considered in future studies of insula infarction and mortality.

Background

Lesions in, or stimulation of, the insula cortex in animals [1, 2] and man [3–5] disturbs various parameters of cardiovascular function. Following these observations, several clinical studies have found an association between ischemic cerebral infarction involving the insula and decreased survival in stroke patients [6–9], although this association has not been uniformly supported [10–12]. Subsequently, dysregulation of the autonomic nervous system in stroke patients with insula infarction has

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been proposed to cause 'neurocardiogenic death' and 'cerebrogenic' sudden cardiac death [13, 14], and prophylactic treatment against such complications has even been considered for patients with infarction involving the insula [15].

Although manipulation of the insula affects cardiovascular function, it may not necessarily follow that infarction of the insula reduces the survival of stroke patients by means of disrupting cardiovascular function, or, for that matter, because of any inherent property of the insula per se. For instance, stroke patients who have insula infarction also tend to have larger overall infarctions [6, 10], and infarct volume itself predicts poor outcome after stroke [16–19] particularly when outcome measures related to neurological injury (e.g. the National Institutes of Health Stroke Scale) are evaluated. Thus, we suspected that infarct volume might confound the reported association between insula infarction and decreased survival.

The primary objective of this study, then, was to assess the independent effect of acute insula infarction on survival at 1 year measured from the time of the index stroke, and to determine the effect of infarct volume as a confounding variable therein. Given the aforementioned focus on death attributable to cardiovascular dysregulation after insula infarction, we examined a population consisting of patients who survived the post-stroke hospitalization period, thereby avoiding mortality caused by complications of the acute infarct itself (e.g. brain herniation) or of hospitalization [20].

Materials and Methods

Subjects

The Michigan Acute Stroke Care Overview and Treatment Surveillance System (MASCOTS) is a statewide, hospital-based, acute stroke registry prototype for the Paul Coverdell National Acute Stroke Registry [20]. The MASCOTS registry was designed to track the quality of acute stroke care in a representative sample of Michigan hospitals [14, 20]. Acute stroke admissions were prospectively identified at each of 15 registry hospitals during a 6-month period in 2002 by trained clinical coordinators. As described elsewhere in detail [21], a subset of subjects from 9 hospitals were consented and enrolled in a follow-up study called the MASCOTS Outcome Study. To be eligible for the MASCOTS Outcome Study, subjects had to be discharged from hospital alive. Study participants were interviewed by telephone 3, 12, and 24 months after their enrollment. For any subject whose death was reported during an interview by an informant, and for subjects who appeared to be lost to follow-up, a death certificate search was conducted by the Division of Vital Statistics of the Michigan Department of Community Health to determine vital status and date of death. We did not attempt to identify the specific cause of death from the death certificates because of the questionable accuracy of this sort of data [7, 22].

Of the original 9 hospitals that participated in the outcome substudy, 6 agreed to participate in this study, which yielded 189 potential subjects. We excluded subjects with incomplete neuroimaging data (n = 31) or evidence of intracranial hemorrhage (n = 9), as well as subjects who did not exhibit any identifiable area of acute infarction on neuroimaging (n = 38). These exclusions left 111 subjects for analysis.

Neuroimaging Studies, and Definitions of Acute and Chronic Infarction

Approval from the institutional review boards at the participating hospitals and from the coordinating site (Michigan State University) was obtained. A fellowship-trained stroke/vascular neurologist (M.B.) reviewed all the neuroimaging studies from each subject that were performed around the time of the index hospitalization. Neuroimaging studies were reviewed in a manner blinded to the subjects' demographic information, medical history, and survival data.

Two types of evaluations provided the neuroimaging data for this study. When available, brain magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) sequence (n = 96 subjects) was used. On MRI, acute ischemic infarction was identified as an area of increased DWI signal. If MRI was unavailable, then multiple head computed tomography (CT) scans demonstrating an interval change were used (n = 15 subjects). A hypodensity appearing on a follow-up CT scan that was not present on the admission CT scan was considered to be an area of acute ischemic infarction.

The MRI studies were conducted on average 2 days after hospitalization (range 0–22 days). When serial CT scans were used, the last CT study was obtained on average 5 days after hospitalization (range 1–22 days).

Cerebral infarctions that apparently predated the index stroke (i.e., chronic infarctions) were also measured and recorded. Chronic infarctions were identified on MRI scans as areas of low T_1 signal without a corresponding increase in DWI signal. Similarly, areas of chronic infarction were identified by head CT if they were present on the admission CT scan and remained unchanged on subsequent studies.

Volumes of acute and chronic infarctions were calculated according to the (A + B + C)/2 method that was initially developed for measuring the volume of intracranial hemorrhage [23] but that has subsequently been applied to ischemic infarction [24, 25]. Regions of the brain were defined prior to data collection according to the atlas of DeArmond et al. [26], and are listed in tables 1 and 2.

Definition of Registry Data Variables

Information on baseline demographic and clinical variables that could affect survival following stroke were collected as part of the MASCOTS registry. Age was recorded as a continuous variable. Sex, smoking status (current vs. other), and prior medical history including history of heart disease (defined as coronary artery disease (CAD) or myocardial infarction (MI)), stroke, atrial fibrillation (including preexisting atrial fibrillation and atrial fibrillation diagnosed during the index hospitalization), congestive heart failure, and diabetes mellitus were defined as dichoto-

Table 1. Association of demographic factors, prior medical history, and neuroimaging data with survival at 1 year

	Total	Survived to 1 year		p[a]
		yes	no	
Total	111 (100.0)	100 (90.1)	11 (9.9)	
Baseline characteristics				
Age, mean ± SEM (range 29–98), years	64.1 ± 1.3	63.5 ± 1.4	69.2 ± 3.3	0.18
Female	62 (55.9)	56 (56.0)	6 (54.6)	0.93
Prior medical history				
Heart disease (MI/CAD)	38 (34.2)	31 (31.0)	7 (63.6)	<0.05[b]
Previous stroke	50 (45.1)	46 (46.0)	4 (36.4)	0.54
Diabetes mellitus	33 (29.7)	29 (29.0)	4 (36.4)	0.73[b]
Smoking	38 (34.2)	34 (34.0)	4 (36.4)	0.99[b]
Hypertension	76 (68.5)	70 (70.0)	6 (54.6)	0.30
Dyslipidemia	45 (40.5)	41 (41.0)	4 (36.4)	0.99[b]
Atrial fibrillation	17 (15.3)	12 (12.0)	5 (45.5)	<0.01
Heart failure	13 (11.7)	12 (12.0)	1 (9.1)	0.99[b]
Stroke outcome				
Modified Rankin Scale at discharge[d]				
0–1	29 (27.1)	27 (27.8)	2 (20.0)	0.84
2–3	45 (42.1)	41 (42.3)	4 (40.0)	
4–5	33 (30.8)	29 (29.9)	4 (40.0)	
Neuroimaging studies				
Number of acute infarcts				
1	86 (77.5)	76 (76.0)	10 (90.9)	0.26[b]
>1	25 (22.5)	24 (24.0)	1 (9.1)	
Side of acute infarction				
Left	49 (44.1)	45 (45.0)	4 (36.4)	0.90[b]
Right	53 (47.8)	47 (47.0)	6 (54.5)	
Bilateral	9 (8.1)	8 (8.0)	1 (9.1)	
Total acute infarct volume[e], mean ± SEM, cm^3	23.1 ± 3.6	19.9 ± 3.4	52.1 ± 16.7	0.05[c]
Quartile 1 (range 0.1–1.0)	27 (24.3)	25 (25.0)	2 (18.2)	
Quartile 2 (range 1.1–7.1)	29 (26.2)	28 (28.0)	1 (9.1)	0.19[b]
Quartile 3 (range 7.9–22.7)	27 (24.3)	25 (25.0)	2 (18.2)	
Quartile 4 (range 23.5–205.7)	28 (25.2)	22 (22.0)	6 (54.5)	
Areas of acute infarction				
Insula	25 (22.5)	21 (21.0)	4 (36.4)	0.25[b]
Peri-insular cortex	22 (19.8)	18 (18.0)	4 (36.4)	0.22[b]
Anterior internal capsule	12 (10.8)	10 (10.0)	2 (18.2)	0.41[b]
Posterior internal capsule	25 (22.5)	22 (22.0)	3 (27.3)	0.71[b]
Thalamus	13 (11.7)	12 (12.0)	1 (9.1)	0.99[b]
Striatum	27 (24.3)	23 (23.0)	4 (14.8)	0.33[b]
Corona radiata	68 (61.3)	60 (60.0)	8 (72.7)	0.52[b]
Frontal cortex	24 (21.6)	21 (21.0)	3 (27.3)	0.70[b]
Temporal cortex	15 (13.5)	13 (13.0)	2 (18.2)	0.64[b]
Parietal cortex	20 (18.0)	19 (19.0)	1 (9.1)	0.69[b]
Occipital cortex	5 (4.5)	5 (5.0)	0 (0)	0.99[b]
Brainstem	12 (10.8)	12 (12.0)	0 (0)	0.61[b]
Cerebellum	15 (13.5)	12 (12.0)	3 (27.3)	0.17[b]
Chronic infarction present	35 (31.5)	33 (33.0)	2 (18.2)	0.50[b]

Unless otherwise stated, figures represent number of subjects. Figures in parentheses are percentages.

[a] p value from χ^2 test, unless otherwise noted; [b] p value from Fisher's exact test; [c] p value from Student t test; [d] Modified Rankin Scale missing for 4 patients (3 who survived 1 year and 1 who did not); [e] Variable log-transformed prior to statistical analysis but untransformed means are presented in the table.

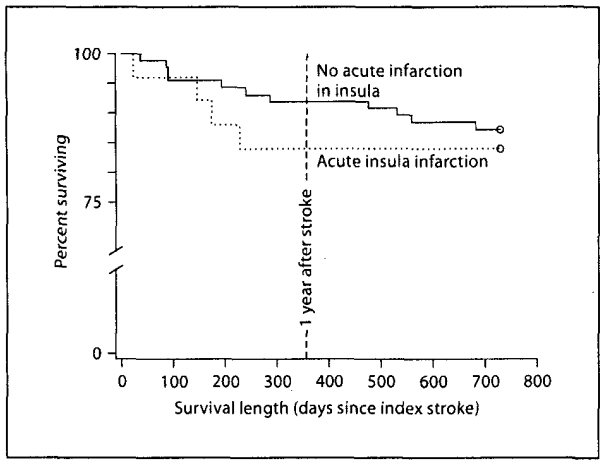

Fig. 1. Kaplan-Meyer curves for survival up to 2 years from the time of the index stroke. Dotted line: subjects with acute insula infarction; black line: subjects without acute infarction involving the insula.

mous variables. Modified Rankin Scale at discharge was recorded in all but 4 patients, and was used in our analysis. Although the MASCOTS registry defined the National Institutes of Health Stroke Scale as a measure of stroke severity, it was not recorded in the medical records for most patients and so was not available for our analysis.

Statistical Analysis

Demographic data, clinical characteristics, and neuroimaging findings were compared between subjects who did or did not die within 1 year of the index stroke, and between subjects who did and did not have infarctions involving the insula. Frequencies were compared using χ^2 tests or, when necessary, by Fisher's exact test. Continuous variables were compared using t tests. Infarct volumes were log-transformed prior to analysis to normalize their distribution; infarct volume was also analyzed as a categorical variable, i.e., in quartiles.

The unadjusted association between acute insula infarction and survival was explored using a Kaplan-Meier plot (fig. 1). The largest separation between the survival curves of subjects with and without acute insula infarction occurred at about 1 year from the time of the index stroke, whereas there was little difference remaining between the two groups after the full 2-year follow-up period. Thus, we chose a 1-year period for all subsequent analyses so as to examine the largest possible effect of acute insula infarction.

The relationship between acute insula infarction and survival controlling for other variables was evaluated using Cox proportional hazards models. Subjects known to be alive after 1 year were regarded as censored at that time. First, unadjusted hazard ratios (HR) and 95% confidence intervals (CI) were generated for key neuroimaging variables, including insula infarction, acute infarct volume (top quartile vs. other), and the presence of chronic infarction. Because of the relatively small sample size and low number of events, a parsimonious modeling strategy was employed. Stroke risk factors can impact survival independently of the index stroke and so could be confounders of any apparent association between neuroimaging measures and mortality; thus, adjustment for these factors would be appropriate. However, neuroimaging data are also likely to be in the causal pathway between stroke risk factors and survival, so adjusting for stroke risk factors could alternatively be inappropriate in assessing the relation between neuroimaging data and mortality. Therefore, we assessed the contributions of upstream stroke risk factors and neuroimaging data in two separate models ('Model 1' and 'Model 2'). Model 1 considered age, sex, smoking, heart disease (i.e., MI or CAD), prior stroke, atrial fibrillation, and heart failure. Model 1 was developed using a backward selection method with $p < 0.5$ to enter and $p < 0.2$ to stay in the model, and then acute insula infarction was added in to create a final model. Model 2 considered only neuroimaging variables (using backward selection methods as described for Model 1) and then it added in acute insula infarction. For all variables in Model 1 and Model 2, the proportional hazards assumption was tested using an interaction between each variable and log survival time using a significance level of $p < 0.05$ [27]. The proportional hazards assumption was not violated for any of these variables.

SAS version 9.1.3 (Statistical Analysis Software, Cary, N.C., USA) was used for all statistical tests.

Results

Descriptive Analysis

At the 1-year follow-up, 4 subjects with acute insula infarction (16.0%) and 7 subjects without acute insula infarction (8.1%) had died ($p = 0.26$). In comparison, at the 2-year follow-up, 4 subjects with insula infarction (16.0%) and 12 subjects without insula infarction (13.9%) had died ($p = 0.75$). Unadjusted associations between demographic, medical history, and neuroimaging measures are presented in table 1. Eleven of the 111 study subjects (9.9%) died within the 1-year follow-up period. Subjects who died were significantly more likely to have a history of heart disease, atrial fibrillation, and larger volumes of acute infarction.

Twenty-five (22.5%) of the 111 study subjects had acute insula infarction (table 2). There were several statistically significant differences between subjects who had acute insula infarction compared to subjects who did not: patients with acute insula infarction were less likely to have a prior history of stroke, diabetes, or hypertension, but they were more likely to have atrial fibrillation. Many differences were noted in the neuroimaging results as well. Importantly, acute insula infarctions were larger than noninsula infarctions (mean volume 59.7 vs. 12.4 cm^3). The involvement of regions around the insula in cases of insula infarction are shown in table 3.

Table 2. Association of demographic factors, prior medical history, and neuroimaging data with acute insula infarction

	Total	Insula infarction		p[a]
		yes	no	
Total	111 (100.0)	25 (22.5)	86 (77.5)	
Baseline characteristics				
Age, mean ± SEM (range 29–98), years	64.1 ± 1.3	62.8 ± 3.0	64.5 ± 1.4	0.60[b]
Female	62 (55.9)	16 (64.0)	46 (53.5)	0.35
Prior medical history				
Heart disease (MI/CAD)	38 (34.2)	7 (28.0)	31 (36.0)	0.46
Previous stroke	50 (45.1)	6 (24.0)	44 (51.1)	<0.05
Diabetes mellitus	33 (29.7)	3 (12.0)	30 (34.9)	<0.05
Smoking	38 (34.2)	6 (24.0)	32 (37.2)	0.22
Hypertension	76 (68.5)	12 (48.0)	64 (74.4)	<0.05
Dyslipidemia	45 (40.5)	8 (32.0)	37 (43.0)	0.32
Atrial fibrillation	17 (15.3)	8 (32.0)	9 (10.5)	<0.01
Heart failure	13 (11.7)	5 (20.0)	8 (9.3)	0.14
Stroke outcome				
Modified Rankin Scale at discharge[d]				0.24[c]
0–1	29 (27.1)	3 (13.0)	26 (30.9)	
2–3	45 (42.1)	12 (52.2)	33 (39.3)	
4–5	33 (30.8)	8 (34.8)	25 (29.8)	
Neuroimaging studies				
Type of neuroimaging				
Serial CTs	16 (14.4)	6 (24.0)	10 (11.6)	0.12
MRI	95 (85.6)	19 (76.0)	76 (88.4)	
Number of acute infarcts				
1	86 (77.4)	22 (88.0)	64 (74.4)	0.18[c]
>1	25 (22.6)	3 (12.0)	22 (25.6)	
Side of acute infarction				
Left	49 (44.1)	14 (56.0)	35 (40.7)	
Right	53 (47.8)	11 (44.0)	42 (48.8)	0.18[c]
Bilateral	9 (8.1)	0 (0)	9 (10.5)	
Total acute infarct volume[e], mean ± SEM, cm^3	22.9 ± 3.6	59.7 ± 11.7	12.4 ± 2.0	<0.0001[b]
Quartile 1 (range 0.1–1.0)	27 (24.3)	1 (4.0)	26 (30.2)	
Quartile 2 (range 1.1–7.1)	29 (26.2)	2 (8.0)	27 (31.4)	<0.0001[c]
Quartile 3 (range 7.9–22.7)	27 (24.3)	6 (24.0)	21 (24.4)	
Quartile 4 (range 23.5–205.7)	28 (25.2)	16 (64.0)	12 (13.9)	
Other areas of acute infarction				
Peri-insular cortex	22 (19.8)	18 (72.0)	4 (5.8)	<0.0001[c]
Anterior internal capsule	12 (10.8)	5 (20.0)	7 (8.1)	0.09
Posterior internal capsule	25 (22.5)	8 (32.0)	17 (19.7)	0.20
Thalamus	13 (11.7)	0 (0)	13 (15.1)	<0.05[c]
Striatum	27 (24.3)	14 (56.0)	13 (15.1)	<0.0001
Corona radiata	68 (61.3)	21 (84.0)	47 (54.7)	<0.01
Frontal cortex	24 (21.6)	10 (40.0)	14 (16.3)	<0.05
Temporal cortex	15 (13.5)	5 (20.0)	10 (11.6)	0.28
Parietal cortex	20 (18.0)	5 (20.0)	15 (17.4)	0.77
Occipital cortex	5 (4.5)	0 (0)	5 (5.8)	0.59
Brainstem	12 (10.8)	0 (0)	12 (13.9)	0.06
Cerebellum	15 (13.5)	0 (0)	15 (17.4)	<0.05
Chronic infarction present	35 (31.5)	3 (12.0)	32 (37.2)	<0.05[c]

Unless otherwise stated, figures represent number of subjects. Figures in parentheses are percentages.

[a] p value from χ^2 test, unless otherwise noted; [b] p value from Student t test; [c] p value from Fisher's exact test; [d] Modified Rankin Scale missing for 4 patients (2 with insula infarction and 2 without); [e] Variable log-transformed prior to statistical analysis but untransformed means are presented in the table.

Table 3. Topography of infarctions that involve the insula (n = 25)

If infarct extended into ...	Anterior IC (n = 5)	Posterior IC (n = 8)	Striatum (n = 14)	Caudate (n = 4)	Corona radiata (n = 21)	Frontal cortex (n = 10)	Parietal cortex (n = 10)	Temporal cortex (n = 9)
It also involved ...								
Anterior IC	n/a	3	5	4	5	0	1	3
Posterior IC	3	n/a	6	3	8	2	3	2
Striatum	5	6	n/a	4	13	5	5	6
Caudate	4	3	4	n/a	4	0	1	3
Corona radiata	5	8	13	4	n/a	8	10	9
Frontal cortex	0	2	5	0	8	n/a	6	4
Parietal cortex	1	3	5	1	10	6	n/a	5
Temporal cortex	3	2	6	3	9	4	5	n/a
Mean volume, cm^3	92.0	38.1	39.1	48.3	78.6	96.0	91.1	75.3
SEM	25.8	17.4	16.2	11.0	13.1	22.5	19.0	23.4

IC = Internal capsule.

Table 4. Proportional hazards models for survival to 1 year after stroke

	HR	95% CI	p[a]
Unadjusted			
Insula infarction	2.1	0.6–7.0	0.25
Infarct volume in top quartile (>23.5 cm^3)	3.9	1.2–12.6	<0.05
Chronic infarction present	0.5	0.1–1.7	0.48
Atrial fibrillation[b]	5.1	1.6–16.7	<0.01
Heart disease (MI/CAD)	3.6	1.1–12.4	<0.05
Model 1: Stroke risk factors and insula infarction			
Insula infarction	2.0	0.5–7.5	0.29
Atrial fibrillation[b]	4.5	1.4–15.1	<0.05
Heart disease (MI/CAD)	4.3	1.2–15.9	<0.05
Model 2: Neuroimaging data			
Insula infarction	1.0	0.2–4.1	1.00
Infarct volume in top quartile (>23.5 cm^3)	3.9	1.0–15.0	0.05

[a] p value from Wald χ^2 test.
[b] Pre-existing diagnosis or diagnosed during index hospitalization.

Survival Analysis

HRs quantifying the relative risk of death are shown in table 4. In unadjusted analysis, subjects with acute insula infarction had a twofold increased hazard of 1-year mortality (HR = 2.1, 95% CI 0.6–7.0) that was nevertheless nonsignificant ($p = 0.25$).

The only clinical and demographic variables that were retained in Model 1 were heart disease and atrial fibrillation. When acute insula infarction was added to this model, its HR was essentially the same as in the aforementioned unadjusted analysis (HR = 2.0, 95% CI 0.5–7.5; p = 0.29), indicating that these risk factors are not acting as confounders on acute insula infarction. For Model 2, the only neuroimaging variable that was retained in the model was infarct volume. When acute insula infarction was added into this model, its HR was reduced to the null value (HR = 1.0, 95% CI 0.2–4.1; p = 1.00), indicating that acute insula infarction may have been confounded by infarct volume.

Discussion

We found a nonsignificant unadjusted association between acute insula infarction and 1-year mortality, with a magnitude of effect (HR = 2.1) similar to that found in previous studies [6, 7, 9]. More importantly, however, we found that this apparent association could be accounted for by infarct volume, which was considerably larger in the insula infarction group.

In comparison with infarctions in other brain regions, infarctions involving the insula are larger [6, 10]. In our study, the mean volume of acute infarctions that involved the insula was nearly fivefold larger than that of infarctions that did not involve the insula. This was an expected finding given that the insula is supplied by early branches of the middle cerebral artery [28] upon which it appears to be highly dependent [29], the occlusion of which can cause infarction of wide-spread cortical areas

and deep brain regions. Indeed, in our study, only 1 of the 25 subjects with acute insula infarction did not have involvement of contiguous brain regions, whereas another study could not find a single stroke patient who had infarction strictly limited to the insula region [10].

Infarct volume has been reported to be predictive of poor outcome following stroke [16, 17], however, infarct volume was not considered in most previous studies of the effect of insula infarction on survival [6, 9–11]. In fact, only two such studies considered infarct volume, and then only because they limited their analysis to infarctions greater than 3 cm in diameter [7, 12]. When we accounted for the association between acute infarction in the insula and infarct volume, there was no longer any relationship between insula infarction and survival. The simplest interpretation for this observation, then, would be that much of the effect of infarction involving the insula was attributable to the larger overall volume of infarction in these subjects.

We limited our study population to those patients who survived the post-stroke hospitalization period (mean ± SEM 9.4 ± 5.2 days). Thus, acute stroke mortality was not measured in our study. This also appears to have been a limitation of the studies that found an effect of insula infarction on survival. A cursory reading of those reports might give the impression that survival was measured from the time of the index stroke, thereby including acute causes of mortality, however, all those research protocols required that their stroke patients undergo a neuroimaging evaluation as a condition of enrollment, and often they required that their stroke patients also undergo a follow-up neuroimaging evaluation, often days after the stroke. In Laowattana et al. [9], the initial neuroimaging evaluation was performed on average 3.6 ± 2.6 days (mean ± SEM) after hospitalization. Accordingly, death occurring within a few days after stroke could not have been reliably captured in that study. Similarly, in the study of Christensen et al. [8], after the initial neuroimaging evaluation a follow-up neuroimaging evaluation was required between 5 and 8 days after stroke onset. In Colivicchi et al. [7], cardiovascular monitoring was instituted within 3 days of admission and continued for at least 1 day; therefore, patients had to survive for at least 1 day after stroke, and likely had to survive as long as 4 days after stroke. In Christensen et al. [8] and Colivicchi et al. [7], the actual length of time from the index stroke to the onset of the collection of post-stroke mortality is difficult to determine from the published reports, however, it is clear that they could not have reliably captured deaths occurring within a few days after stroke because of these necessary features of study design. Thus, as in our study, acute post-stroke mortality does not appear to have been reliably measured in those studies that found an effect of insula infarction on survival.

Our analysis and those of previous studies represent the effects of insula infarction on survival in the subacute period only, and early causes of post-stroke mortality are likely excluded. The causes of death after stroke are known to change over time: death within 1 week of stroke is usually related to brain herniation, whereas death within 2–3 weeks from stroke is typically caused by pneumonia, pulmonary embolus, or sepsis [20]. After about 4 weeks following stroke, the predominant cause of death becomes heart disease. Insula infarction has been proposed to induce 'neurocardiogenic death' or 'cerebrogenic' sudden cardiac death [14, 15], that is, the dysregulation of cardiovascular function through the autonomic nervous system. Given the known causes of death after stroke, then, it might be expected that so-called neurocardiogenic/cerebrogenic deaths would occur in the subacute or even chronic post-stroke period, perhaps being hidden under the guise of common heart disease. Neurocardiogenic/cerebrogenic deaths would accordingly be well-measured by our study design.

Another limitation of our study is the small number of subjects, which may have decreased our ability to detect a significant effect. However, the HR of insula infarction in our study was comparable to two of the studies that demonstrated relationships between insula infarction and decreased survival using HRs (HR = 1.57 in Abboud et al. [6]; HR = 2.01 in Colivicchi et al. [7]). Our population of 111 subjects was also comparable in size to two of those positive studies (n = 42 in Christensen et al. [8]; n = 116 in Laowattana et al. [9]). Furthermore, infarct volumes were similar between our study and at least one study that demonstrated relationships between insula infarction and decreased survival (approximately 40–65 cm^3 in Abboud et al. [6]; infarct volume not reported in other studies [7–9]).

Additional limitations of our study may be the variability of types of neuroimaging studies used to evaluate the MASCOTS stroke patients and the variability of the timing at which these studies were obtained following stroke. Again, these appear to be limitations of most other studies pertaining to this topic. Head CT may have missed smaller lesions, although the neurovascular anatomy is such that such lesions would be unlikely to occur in the insula [28]. The inconsistent timing of neuroimaging studies may also have contributed to variability in infarct volume measurement. Such limitations would not

clearly affect the results of our study toward a specific outcome, however.

In summary, we found a nonsignificant association of acute insula infarction with mortality, but after adjusting for infarct volume this association vanished. Infarct volume as well as other prognostic variables that have a significant effect on mortality should be considered in future studies of insula infarction and mortality.

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