Brief Report

Relationship Between Visceral Infarction and Ischemic Stroke Subtype

Caitlin Finn, BS; Peter Hung, BS; Praneil Patel, MD; Ajay Gupta, MD; Hooman Kamel, MD

Background and Purpose—Most cryptogenic strokes are thought to have an embolic source. We sought to determine whether cryptogenic strokes are associated with visceral infarcts, which are usually embolic.

Methods—Among patients prospectively enrolled in CAESAR (Cornell Acute Stroke Academic Registry), we selected those with a contrast-enhanced abdominal computed tomographic scan within 1 year of admission. Our exposure variable was adjudicated stroke subtype per the Trial of ORG 10172 in Acute Stroke Treatment classification. Our outcome was renal or splenic infarction as assessed by a single radiologist blinded to stroke subtype. We used Fisher exact test and multiple logistic regression to compare the prevalence of visceral infarcts among cardioembolic strokes, strokes of undetermined etiology, and noncardioembolic strokes (large- or small-vessel strokes).

Results—Among 227 patients with ischemic stroke and a contrast-enhanced abdominal computed tomographic scan, 59 had a visceral infarct (35 renal and 27 splenic). The prevalence of visceral infarction was significantly different among cardioembolic strokes (34.2%; 95% confidence interval [CI], 23.7%–44.6%), strokes of undetermined etiology (23.9%; 95% CI, 15.0%–32.8%), and strokes from large-artery atherosclerosis or small-vessel occlusion (12.5%; 95% CI, 1.8%–23.2%; P=0.03). In multiple logistic regression models adjusted for demographics and vascular comorbidities, we found significant associations with visceral infarction for both cardioembolic stroke (odds ratio, 3.5; 95% CI, 1.2–9.9) and stroke of undetermined source (odds ratio , 3.3; 95% CI, 1.1–10.5) as compared with noncardioembolic stroke.

Conclusions—The prevalence of visceral infarction differed significantly across ischemic stroke subtypes. Cardioembolic and cryptogenic strokes were associated with a higher prevalence of visceral infarcts than noncardioembolic strokes. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.117.020035.)**

Key Words: atherosclerosis ■ embolism ■ splenic infarction ■ stroke ■ tomography

Many cryptogenic strokes are thought to originate from emboli with distant origins, such as unrecognized cardiac sources and nonstenotic atherosclerotic plaques.[1] Emboli from a central source may cause limb, mesenteric, renal, and splenic infarcts. Although symptomatic systemic infarcts are rare,[2] asymptomatic visceral infarcts are commonly found in patients with recent stroke,[3,4] raising the possibility of a common embolic source. We hypothesized that visceral infarcts are more common in patients with cardioembolic and cryptogenic strokes than strokes caused by small-vessel occlusion or large-artery atherosclerosis.

Methods

Design

We performed a cross-sectional study of patients prospectively enrolled in CAESAR (Cornell Acute Stroke Academic Registry). Our institutional review board approved this study. Deidentified data are available from the corresponding author on request.

Patient Population

We included all patients with ischemic stroke admitted to our hospital from 2011 to 2015 with a contrast-enhanced abdominal computed tomographic (CT) scan within 1 year of admission (Methods in the online-only Data Supplement).

Measurements

Medical records were reviewed by 3 neurologists who adjudicated ischemic stroke subtype per the Trial of ORG 10172 in Acute Stroke Treatment classification.[5] Neurologists involved in adjudication had no knowledge of the abdominal CT results.

Our primary outcome was the presence of at least 1 visceral infarct (renal or splenic) on abdominal CT. A board-certified radiologist blinded to clinical information, including stroke subtype, graded visceral infarcts as absent, possible, or probable (Methods in the online-only Data Supplement). Our primary definition of visceral infarct comprised possible and probable infarcts to maximize sensitivity.

Statistical Analysis

We used standard descriptive statistics, t test, or rank-sum test for continuous variables, χ^2 or Fisher exact for categorical variables,

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From the Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute, New York, NY (C.F., P.H., H.K.); and Departments of Radiology (P.P., A.G.) and Neurology (A.G., H.K.), Weill Cornell Medical College, New York, NY.

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Correspondence to Hooman Kamel, MD, Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute, 407 E, 61st St, New York, NY 10065. E-mail hok9010@med.cornell.edu

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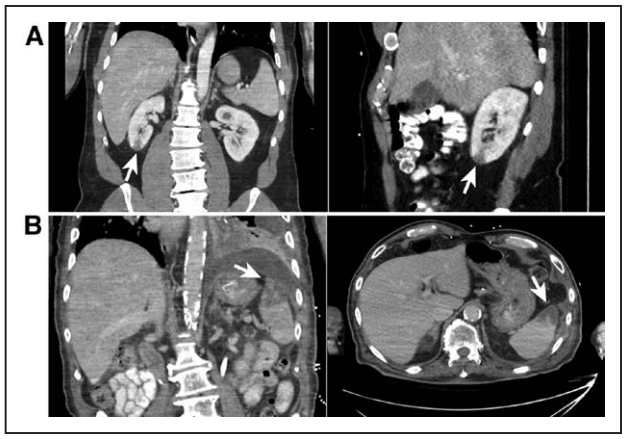

Figure. Representative renal and splenic infarcts. **A**, Renal infarct in coronal and sagittal view (**arrows**). Note morphological difference between renal infarct and contralateral renal cyst. **B**, Splenic infarct in coronal and axial view (**arrows**).

and multiple logistic regression (Methods in the online-only Data Supplement).

Results

Among 1721 patients with ischemic stroke registered in CAESAR from 2011 to 2015, we identified 229 with an abdominal CT within 1 year of admission for stroke. The demographic features, vascular comorbidities, and distribution of stroke subtypes of included patients were similar to ineligible CAESAR patients (Table I in the online-only Data Supplement).

Of 229 eligible patients, we excluded 2 because artifact resulted in nondiagnostic abdominal CT quality. We excluded an additional 24 patients from our analysis of splenic infarcts because 3 were asplenic and 21 scans lacked portal venous imaging. Overall, 59 patients had at least 1 visceral infarct (Figure). Patients with and without visceral infarcts had similar demographics, vascular comorbidities, and indications for abdominal imaging (Table 1).

The prevalence of visceral infarcts differed among patients with stroke caused by cardioembolism (34.2%; 95% confidence interval [CI], 23.7%–44.6%), undetermined source (23.9%; 95% CI, 15.0%–32.8%), and large-artery atherosclerosis or small-vessel occlusion (12.5%; 95% CI, 1.8%–23.2%; P=0.03; Table 2). In multiple logistic regression models adjusted for demographics and vascular comorbidities, we found significant associations with visceral infarction for both cardioembolic stroke (odds ratio, 3.5; 95% CI, 1.2–9.9) and stroke of undetermined source (odds ratio, 3.3; 95% CI, 1.1–10.5).

The detailed results of several secondary and post hoc analyses are presented in Table 2 and discussed in Results in the online-only Data Supplement.

Table 1. Baseline Characteristics of Patients in the CAESAR Stroke Registry Who Had Abdominal Imaging, Stratified by Visceral Infarcts

Characteristic	Visceral Infarct (n=59)	No Visceral Infarct (n=168)	*P* Value
Age, mean (SD), y	70.3 (14.4)	68.7 (16.3)	0.50
Female	28 (47.5)	88 (52.4)	0.52
Race			0.04
White	54 (91.5)	143 (85.1)	
Black	2 (3.4)	15 (8.93)	
Hispanic	2 (3.4)	0 (0)	
Other	1 (1.7)	10 (6.0)	
Active tobacco use	6 (10.2)	15 (8.9)	0.78
Diabetes mellitus	14 (23.7)	43 (25.6)	0.78
Dyslipidemia	28 (47.5)	74 (44.0)	0.65
Hypertension	41 (69.5)	107 (63.7)	0.42
Coronary artery disease	17 (28.8)	35 (20.8)	0.21
Congestive heart failure	4 (6.8)	8 (4.8)	0.55
Chronic kidney disease	0 (0)	5 (3.0)	0.33
Atrial fibrillation	13 (22.0)	30 (17.9)	0.48
Valvular disease	1 (1.7)	6 (3.6)	0.68
Peripheral vascular disease	5 (8.5)	9 (5.4)	0.36
Malignancy	24 (40.7)	54 (32.1)	0.27
Prior stroke	18 (30.5)	40 (23.8)	0.31
Indication for abdominal imaging			0.51
Malignancy	14 (23.7)	25 (14.9)	
Infection	7 (11.9)	19 (11.3)	
Vascular	5 (8.5)	28 (16.7)	
Trauma	2 (3.4)	8 (4.8)	
Autoimmune	0 (0)	2 (1.2)	
Gastrointestinal	13 (22.0)	47 (28.0)	
Renal	2 (3.4)	9 (5.4)	
Neurological	0 (0)	1 (0.6)	
Other	7 (11.9)	15 (8.9)	
Time from stroke to scan, median (IQR), d	23 (108)	25 (116.5)	0.57

Data presented as number (%) unless otherwise specified. CAESAR indicates Cornell Acute Stroke Academic Registry; and IQR, interquartile range.

Discussion

Among patients in a prospective stroke registry, we found significant associations between stroke subtype and visceral infarcts. Patients with cardioembolic stroke showed the highest prevalence of visceral infarcts, followed by cryptogenic stroke, large-artery atherosclerosis, and small-vessel occlusion. These results were consistent across different definitions of cryptogenic stroke.

Prior studies of abdominal magnetic resonance imaging in patients with cardioembolic stroke show a 20% prevalence of visceral infarcts.[3,6] Our results build on these studies by demonstrating the prevalence of visceral infarction differs across ischemic stroke subtypes. We found no visceral infarcts among patients with lacunar stroke, supporting this stroke subtype as a distinct entity resulting from in situ occlusion of the cerebral vasculature. Compared with patients with small-vessel stroke,

Table 2. Prevalence of Visceral Infarcts Among Ischemic Stroke Subtypes

Primary analysis*	CE (n=82)	UND (n=92)		LAA/SVO (n=40)	*P* value
Any visceral infarct	28 (34.2)	22 (23.9)		5 (12.5)	0.03
Secondary analysis 1†	CE (n=82)	ESUS (n=65)		LAA/SVO (n=40)	*P* value
Any visceral infarct	28 (34.2)	17 (26.2)		5 (12.5)	0.04
Secondary analysis 2	CE (n=82)	UND (n=92)		LAA/SVO (n=40)	*P* value
Possible visceral infarct	18 (22.0)	12 (13.0)		2 (5.0)	0.04
Probable visceral infarct	11 (13.4)	10 (10.9)		3 (7.5)	0.62
Post hoc analysis 1	CE (n=82)	UND (n=92)		LAA/SVO (n=40)	*P* value
Renal infarct	24 (29.3)	16 (17.4)		2 (5.0)	0.004
Splenic infarct	13 (15.9)	10 (10.9)		3 (7.5)	0.41
Post hoc analysis 2‡	CE (n=82)	UND (n=92)	LAA (n=25)	SVO (n=15)	*P* value
Any visceral infarct	28 (34.2)	22 (23.9)	5 (20.0)	0 (0)	0.02

Data presented as number (%). CE indicates cardioembolic; ESUS, embolic stroke of undetermined source; LAA, large-artery atherosclerosis; SVO, small-vessel occlusion; and UND, undetermined etiology.

*Stroke classified according to the Trial of ORG 10172 in Acute Stroke Treatment classification.[5]

†Stroke classified according to the ESUS classification.[1]

‡LAA and SVO were considered separately.

those with other stroke subtypes had a significantly higher prevalence of visceral infarcts, suggesting a shared etiology in the form of cardiac embolism and large-artery atherosclerosis. The high prevalence of visceral infarcts in strokes of undetermined etiology supports the emerging consensus that cryptogenic strokes arise from embolic sources.[1]

Our study has several limitations. First, we included only patients who underwent abdominal CT during the course of routine clinical care, thereby potentially introducing selection bias. However, our comparison of included and excluded patients showed no difference in demographics, vascular comorbidities, or distribution of stroke subtype. We found no association between indication for abdominal scans and presence of visceral infarcts. Second, we included CT scans obtained within 1 year of admission for stroke to broadly capture acute or subacute visceral infarcts; changes in patients' health in the year preceding or after admission may affect the prevalence of visceral infarcts. However, analysis of CT scans obtained within 28 days of admission showed generally similar findings although this analysis' small sample precludes definitive conclusions. Third, our results may have included hypoattenuating lesions that mimic infarcts, such as renal cysts. To maximize our sensitivity for visceral infarcts, we included findings with characteristic appearance based on strict criteria (probable) and less characteristic but compatible appearance for infarcts (possible). Our finding that possible infarcts are more discriminative than probable infarcts is likely because of the small sample size resulting from overly strict diagnostic criteria for probable infarcts, which reflects the challenges of diagnosing visceral infarcts on CT. Fourth, our analysis involved a single-center cohort and may not generalize to other populations with stroke.

We found that visceral infarcts were more common among patients with stroke because of cardiac or cryptogenic sources than in noncardioembolic subtypes. In a post hoc analysis, we found that visceral infarction was also more common in large-artery stroke when compared with small-artery stroke, which may reflect multifocal atherosclerosis affecting both proximal and distal sites. Our findings suggest that the detection of visceral infarcts in a patient with cryptogenic stroke might be a clue to an underlying cardioembolic source or aortic atherosclerosis.

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Disclosures

None.

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Relationship Between Visceral Infarction and Ischemic Stroke Subtype

Caitlin Finn, Peter Hung, Praneil Patel, Ajay Gupta and Hooman Kamel

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SUPPLEMENTAL MATERIAL

Relationship between Visceral Infarction and Ischemic Stroke Subtype

Caitlin Finn, BS; Peter Hung, BS; Praneil Patel, MD; Ajay Gupta, MD; Hooman Kamel, MD

Supplemental Methods

Design

We performed a cross-sectional study of the prevalence of visceral infarction among patients with different ischemic stroke subtypes. We studied ischemic stroke patients prospectively enrolled in the Cornell AcuteE Stroke Academic Registry (CAESAR), and supplemented the registry data with retrospectively collected information about the findings of abdominal imaging.

Patient Population

All patients with acute stroke admitted to New York-Presbyterian Hospital/Weill Cornell Medical Center from 2011 to 2015 were prospectively enrolled in the American Heart Association's Get With The Guidelines (GWTG)—Stroke registry. Trained hospital analysts electronically entered into the GWTG database information on patients' demographics, vascular risk factors and comorbidities, time and date of stroke onset, vital signs on admission, National Institutes of Health Stroke Scale (NIHSS) score on admission, date of discharge, and ambulatory status at discharge. In addition to the classification of TOAST subtype as described in the main manuscript, a panel of three neurologists also adjudicated whether an ischemic stroke met recently proposed definitions for embolic stroke of undetermined source (ESUS).[1] These data on adjudicated stroke subtype were then merged with the prospectively collected GWTG data to create the CAESAR registry. The vast majority of patients underwent a complete stroke evaluation, defined as at least 24 hours of telemetry, an echocardiogram, cross-sectional brain imaging, and vascular imaging of the head and neck; this work-up was required for a diagnosis of ESUS.

Ascertainment of Visceral Infarction

We chose to focus on renal and splenic infarcts because of their characteristic appearance on CT imaging.[2, 3] If multiple abdominal CT scans were eligible for evaluation, the study closest to the admission date for stroke was evaluated. Since the spleen is poorly evaluated in the arterial phase, only CT exams with a portal venous phase were used for splenic evaluation. Thus, when multiple CTs were eligible in this context, a more remote study with a portal venous phase was used if necessary for splenic assessment.

Infarcts were graded as absent, possible, or probable based on the presence of typical imaging features. Probable infarcts required single or multiple regions of peripheral wedge-shaped hypoattenuation with the apex directed toward the hilum. An enhancing cortical rim was used to distinguish infarction from pyelonephritis if present. Possible infarcts involved an imaging appearance compatible with, but less specific for, an infarct. Placement in this category was on the basis of a nonspecific morphology with less well-defined or more rounded region(s) of peripheral hypoattenuation. If available, ultrasound was reviewed to assess for a cystic lesion at the location of possible infarct.

The indication of each abdominal CT scan was recorded and sorted for descriptive reporting into categories of known or suspected disease: workup of stroke etiology, malignancy, infection,

vascular injury, trauma, autoimmune disease, gastrointestinal signs or symptoms, renal disease, neurological disease, and other. The number of days between the stroke and scan was recorded for each patient.

Covariates

The CAESAR registry contains prospectively collected information on age, sex, race, insurance status, tobacco use, diabetes mellitus, dyslipidemia, hypertension, coronary artery disease, congestive heart failure, chronic kidney disease, atrial fibrillation, valvular disease, peripheral vascular disease, malignancy, and prior stroke.

Statistical Analysis

We used multiple logistic regression to assess whether stroke of undetermined etiology and cardioembolic stroke were associated with visceral infarction after adjustment for demographics and vascular comorbidities, with the composite of small- and large-vessel stroke as the reference. Stepwise backward elimination was used to minimize overfitting, with the significance level for removal from the model of 0.2. Statistical analysis was performed using Stata/MP (version 14, College Station, TX).

Supplemental Results

The median interval between admission for stroke and abdominal CT scan was 23 days (IQR, 108 days) for patients with visceral infarcts and 25 days (IQR, 117 days) for patients without visceral infarcts.

We performed several secondary and *post hoc* analyses. In a secondary analysis of ESUS instead of TOAST-defined stroke of undetermined etiology, the prevalence of visceral infarcts among ESUS cases (26.2%; 95% CI, 15.2-37.1%) differed significantly from the prevalence in cardioembolic and non-cardioembolic strokes ($P = 0.04$) (Table 2). This remained true after adjustment for demographics and risk factors (OR, 3.3; 95% CI, 1.0-10.3; $P = 0.04$).

In a secondary analysis of possible versus probable visceral infarcts, we found a significant difference among stroke subtypes in regards to possible visceral infarcts (22.0% in cardioembolic strokes, 13.0% in strokes of undetermined etiology, and 5.0% in small-vessel or large-vessel strokes; $P = 0.04$) but not in regards to probable visceral infarcts (13.4% in cardioembolic strokes, 10.9% in strokes of undetermined etiology, and 7.5% in small-vessel or large-vessel strokes; $P = 0.69$) (Table 2).

We performed several *post hoc* analyses. First, we assessed the prevalence of renal and splenic infarcts separately, and found significant differences among stroke subtypes only for renal infarcts ($P = 0.004$) and not splenic infarcts ($P = 0.41$) (Table 2). Second, we examined large- and small-vessel strokes as separate categories instead of grouping them together as in our primary analysis, and found that patients with strokes due to large-artery atherosclerosis had a prevalence of visceral infarcts close to that of patients with stroke of undetermined etiology (Table 2).

In a sensitivity analysis limited to patients who underwent an abdominal CT scan within 28 days of their admission for stroke, we found broadly similar differences in the prevalence of visceral infarcts in patients with cardioembolic stroke (34.8%), cryptogenic stroke (18.0%), and stroke due large-artery atherosclerosis (30.7%) in comparison to patients with stroke due to small-vessel occlusion (0%) ($P = 0.16$) (Supplement, Table II).

Table I. Baseline Characteristics of Included and Excluded Subjects in the CAESAR Stroke Registry.

Characteristic	Excluded Subjects (N = 1495)	Included Subjects (N = 229)	All Subjects (N = 1721)	*P* value
Age, mean (SD), years	71.0	69.1	70.8	0.08
Female	741 (49.6)	116 (51.1)	857 (49.8)	0.17
Race:				0.82
White	1298 (86.9)	197 (86.8)	1495 (86.9)	
Black	92 (6.2)	17 (7.5)	109 (6.3)	
Hispanic	17 (1.1)	2 (0.9)	19 (1.1)	
Other	87 (5.8)	11 (4.9)	98 (5.7)	
Stroke Subtype				0.09
Cardioembolic	493 (34.6)	82 (38.3)	575 (35.1)	
Cryptogenic	550 (38.6)	92 (43.0)	642 (39.2)	
Large-artery atherosclerosis	223 (15.7)	25 (11.7)	248 (15.1)	
Small-vessel occlusion	158 (11.1)	15 (7.0)	173 (10.6)	
Active tobacco use	125 (8.4)	21 (9.3)	146 (8.5)	0.66
Diabetes mellitus	336 (24.5)	57 (25.1)	423 (24.6)	0.84
Dyslipidemia	743 (49.7)	102 (44.9)	845 (49.1)	0.18
Hypertension	1027 (68.7)	148 (65.2)	1175 (68.3)	0.29
Coronary artery disease	300 (20.8)	52 (22.9)	352 (20.5)	0.33
Congestive heart failure	73 (4.9)	12 (5.3)	85 (4.9)	0.80
Chronic kidney disease	37 (2.5)	5 (2.2)	42 (2.4)	0.80
Atrial fibrillation	320 (21.4)	43 (18.9)	363 (21.1)	0.39
Valvular disease	26 (1.7)	7 (3.1)	33 (1.9)	0.17
Peripheral vascular disease	71 (4.8)	14 (6.2)	85 (4.9)	0.36
Prior stroke	332 (22.2)	58 (25.6)	390 (22.7)	0.26

Abbreviations: SD, standard deviation.
Data presented as number (%) unless otherwise specified.

Table II. Prevalence of Visceral Infarcts Within 28 Days of Hospitalization Among Ischemic Stroke Subtypes.

	CE (N = 46)	UND (N = 50)	LAA (N = 13)	SVO (N = 5)	*P* value
Any visceral infarct	16 (34.8)	9 (18.0)	4 (30.7)	0 (0)	0.16
Renal infarct	15 (32.6)	7 (14.0)	2 (15.4)	0 (0)	0.10
Splenic infarct	8 (17.4)	3 (6.0)	2 (15.4)	0 (0)	0.26

Abbreviations: CE, cardioembolic; UND, undetermined etiology; LAA, large-artery atherosclerosis; SVO, small-vessel occlusion.
Data presented as number (%).

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