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LETTERS TO THE EDITOR

Association Between Nonstenosing Carotid Artery Plaque on MR Angiography and Acute Ischemic Stroke

Most ischemic stroke classification schemes require an atherosclerotic plaque to cause ≥50% stenosis for the stroke to be ascribed to large-artery atherosclerosis (1). However, recent data (2–4) suggest that some of the 30% of ischemic strokes whose cause is currently classified as unknown may actually arise from nonstenosing large-artery atherosclerotic plaque. Improving our ability to recognize culprit nonstenosing plaque as the cause of stroke has important implications for precision medicine for secondary stroke prevention because such patients may benefit from dual antiplatelet drugs and emerging drugs for lowering serum cholesterol.

We examined the association between nonstenosing, vulnerable large-artery plaque and ischemic stroke using data from our prospective stroke registry. We reviewed all available medical records and assigned a stroke etiology using a standard ischemic stroke classification scheme (1). Because we were interested in stroke risk from atherosclerotic plaques that are currently not recognized as a cause of stroke, we excluded patients with large-artery atherosclerosis based on these standardized criteria, and instead focused on patients with stroke from cardioembolism, small-vessel occlusion, and undetermined cause. To reduce the risk of unmeasured confounding between patients, we performed a within-subjects comparison of the prevalence of vulnerable internal carotid artery (ICA) plaque on the side ipsilateral to an infarct versus the contralateral side. We therefore limited our study to patients with acute brain infarction(s) limited to the vascular territory of a single ICA as confirmed on magnetic resonance imaging (MRI).

We ascertained vulnerable plaque using sequences from routine magnetic resonance angiograms (MRAs). The details of our imaging technique are provided in a previous report (2). Briefly, all brain MRI and neck MRA studies were performed using standard MRI equipment without high-resolution surface carotid coils or gadolinium. We ascertained complicated carotid plaque based on the qualitative assessment of intraplaque high-intensity signal (IHIS) on axial 3-dimensional-time-of-flight images, a presumed marker for intraplaque hemorrhage (2). To be classified as IHIS, an atherosclerotic lesion's signal had to meet a certain threshold (50% greater than the background signal intensity of the sternocleidomastoid muscle using region-of-interest analysis) and be distinguishable from the normal flow-related enhancement visible in the patent ICA lumen.

We identified 109 eligible patients (50.0% females, mean age 69.5 ± 14.7 years). Patients with cardioembolic stroke had significantly higher National Institutes of Health Stroke Scale scores and a higher proportion of atrial fibrillation. Patients with cryptogenic stroke had a slightly higher proportion of patients receiving echocardiography compared with other stroke subtypes. The stroke subtypes were otherwise comparable in demographics, vascular risk factors, and the extent of diagnostic evaluation. The median interval between MRI brain and MRA neck and between stroke onset and MRA neck was 0 and 1 day, respectively.

Overall, 22 of 109 patients (20.2%) had <50% ICA plaque with IHIS ipsilateral to the side of infarction, compared with 9 of 109 (8.3%) patients who had IHIS in <50% ICA plaque contralateral to the side of infarction ($p = 0.01$) (Table 1). The median degree of vessel luminal narrowing was not significantly different on the ipsilateral versus contralateral side of the infarction ($p = 0.67$). Subgroup analysis revealed a

TABLE 1 Carotid Artery Characteristics Ipsilateral and Contralateral to This Side of Cerebral Infarction

	ICA Ipsilateral to Stroke	ICA Contralateral to Stroke	p Value*
Overall (N = 109)			
Prevalence of IHIS	22/109	9/109	0.0124
Median carotid stenosis	0 (0 to 47.5; 0)	0 (0 to 49; 0)	0.6694
TOAST stroke subtype			
Cryptogenic (n = 50)			
Prevalence of IHIS	11/50	0/50	0.0009
Median carotid stenosis	0 (0 to 47.5; 15.6)	0 (0 to 49; 5.6)	0.4896
Cardioembolic (n = 37)			
Prevalence of IHIS	7/37	6/37	0.7630
Median carotid stenosis	0 (0 to 41; 0)	0 (0 to 34.8; 0)	0.4360
Small vessel occlusion (n = 22)			
Prevalence of IHIS	4/22	3/22	0.6547
Median carotid stenosis	0 (0 to 17.4; 0)	0 (0 to 39.1; 0)	0.1250

Values are n/N or % (range; IQR). *p value by McNemar's test for correlated proportions or Wilcoxon signed rank sum test, as appropriate. Carotid stenosis calculated using standard North American Symptomatic Carotid Endarterectomy Trial criteria.

ICA = internal carotid artery; IHIS = intraplaque high intensity signal; IQR = interquartile range; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

significantly higher proportion of IHIS in ICA plaques ipsilateral to the side of infarction in cryptogenic stroke patients ($p < 0.001$), but not in patients with strokes from cardioembolism ($p = 0.76$) or small-vessel occlusion ($p = 0.49$).

Our results suggest that some strokes from large-artery atherosclerosis are currently not being recognized as such because the plaque causes <50% stenosis. Our findings also suggest that useful plaque composition data can be extracted using only a standard luminal imaging technique (time-of-flight MRA) that can be integrated into a rapid acute stroke imaging protocol. Because our IHIS-positive subgroup was small ($n = 31$), larger confirmatory prospective studies are now warranted which should also investigate stroke recurrence rates in such patients. Such studies are important because if patients who are currently labeled as cryptogenic stroke are more correctly identified as harboring a culprit large-artery atherosclerotic lesion, they may benefit from intensified and targeted therapy aimed at reducing their risk of recurrent stroke and other major adverse cardiovascular events.

Ajay Gupta, MD*
Gino Gialdini, MD
Ashley E. Giambrone, PhD
Michael P. Lerario, MD
Hediyeh Baradaran, MD
Babak B. Navi, MD, MS
Randolph S. Marshall, MD, MS
Costantino Iadecola, MD
Hooman Kamel, MD

*Department of Radiology
Weill Cornell Medical College
525 East 68th Street
Starr 8A, Box 141
New York, New York 10065
E-mail: ajg9004@med.cornell.edu

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Vortex Formation Time Index in Patients With Hypertrophic Cardiomyopathy

Vortex ring formation in early diastole helps with left ventricular (LV) filling without an increase in left atrial (LA) pressure. Vortex formation time (VFT) is a dimensionless parameter derived from LV geometry and indexes of LV systolic and diastolic performance (1). The optimal range was reported at $3.3 < VFT < 5.5$ but varies on the basis of cardiac pathology. VFT application in hypertrophic cardiomyopathy (HCM) has not been evaluated. We sought to study VFT in relation to exercise tolerance in HCM.

We included 116 HCM patients (mean age 58 years; 39.7% female). Patients willing and able to exercise ($n = 77$) underwent exercise testing using a modified Bruce protocol within 2 months or less of a transthoracic echocardiography (TTE) study. Cardiac magnetic resonance findings were noted for 94 patients who underwent imaging within 4 days of TTE. Patients with previous septal reduction, more than mild valve disease, prosthetic valves, moderate or worse annular calcification, and atrial fibrillation were excluded. Normal healthy subjects ($n = 20$, 48 ± 7.4 years of age) were included. To examine the impact of septal reduction on VFT, patients who underwent alcohol septal ablation ($n = 24$) or surgical myectomy ($n = 7$) were examined. Analysis was performed, blinded to clinical data, for LV and LA volumes and left ventricular ejection fraction (LVEF), mitral annulus diastolic diameter (D) and velocities (mitral peak early diastolic velocity [E], mitral peak late diastolic velocity [A], ratio of mitral peak early diastolic velocity to mitral peak late diastolic velocity [E/A], atrial filling fraction [AFF]), mitral annulus early diastolic velocity (e′), (pulse Doppler: septal, lateral, average), and ratio of mitral peak early diastolic velocity to mitral annulus early diastolic velocity (E/e′). left ventricular outflow tract (LVOT) gradient was measured at rest and with the Valsalva maneuver. LV diastolic function was graded per guidelines (2). The VFT was obtained: $4 \times (1 - \beta) \times \alpha^3 \times LVEF/\pi$ (1), ($\alpha = LVEDV$ [LV end-diastolic volume]$^{1/3}$/D, β is the fraction of stroke volume due to AFF). The study population was divided into VFT <3.3 and 3.3 to 5.5. The Wilcoxon rank sum and Student *t* tests were used to determine the differences in continuous variables. Differences before and after treatment were tested