Carotid Atherosclerosis Does Not Predict Coronary, Vertebral, or Aortic Atherosclerosis in Patients With Acute Stroke Symptoms

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Background and Purpose—The purpose of this study was to determine whether significant atherosclerotic disease in the carotid arteries predicts significant atherosclerotic disease in the coronary arteries, vertebral arteries, or aorta in patients with symptoms of acute ischemic stroke.

Methods—Atherosclerotic disease was imaged using CT angiography in a prospective study of 120 consecutive patients undergoing emergent CT evaluation for symptoms of stroke. Using a comprehensive CT angiography protocol that captured the carotid arteries, coronary arteries, vertebral arteries, and aorta, we evaluated these arteries for the presence and severity of atherosclerotic disease. Significant atherosclerotic disease was defined as >50% stenosis in the carotid, coronary, and vertebral arteries, or ≥4 mm thickness and encroaching in the aorta. Presence of any and significant atherosclerotic disease was compared in the different types of arteries assessed.

Results—Of these 120 patients, 79 had CT angiography examinations of adequate image quality and were evaluated in this study. Of these 79 patients, 33 had significant atherosclerotic disease. In 26 of these 33 patients (79%), significant disease was isolated to 1 type of artery, most often to the coronary arteries (N=14; 54%). Nonsignificant atherosclerotic disease was more systemic and involved multiple arteries.

Conclusions—Significant atherosclerotic disease in the carotid arteries does not predict significant atherosclerotic disease in the coronary arteries, vertebral arteries, or aorta in patients with symptoms of acute ischemic stroke. Significant atherosclerotic disease is most often isolated to 1 type of artery in these patients, whereas nonsignificant atherosclerotic disease tends to be more systemic. (Stroke. 2010;41:1604-1609.)

Key Words: atherosclerosis ▪ carotid artery ▪ carotid stenosis ▪ computed tomography ▪ coronary artery ▪ imaging ▪ vertrobrobasilary disease

Atherosclerotic disease is the leading cause of death in industrialized countries and causes the large majority of ischemic strokes and myocardial infarctions.1–3 Atherosclerotic disease is typically considered a systemic disease.4–6 However, there is some debate regarding the relationship between carotid, vertebral, and aortic artery atherosclerosis (involved in stroke) and coronary artery atherosclerosis (involved in myocardial infarctions).

Studies have proposed the carotid artery intima-media thickness as a surrogate marker for coronary artery disease.5–9 However, other studies have questioned the use of the intima-media thickness as a marker for coronary artery disease because the underlying disease process of intima-media thickening is thought to differ from that leading to atherosclerotic plaques.10–12

Carotid plaque has been suggested as an alternate marker for coronary artery disease.12 This is illustrated by the Rotterdam study, in which carotid plaques and carotid intima-media thickness were found to be strong predictors of myocardial infarctions.13–18 Studies have also found an association between atherosclerosis in the aorta and in the carotid arteries,19 and between aortic plaque and coronary artery disease.8,20–22 Aortic plaque that is encroaching and ≥4 mm in thickness, as imaged by transesophageal echocardiography, has been shown to predict cardiac events and cardiac death.23

The inconsistencies among studies in terms of the degree of association between carotid, vertebral, aortic, and coronary artery atherosclerosis is largely attributable to the fact that the presence of atherosclerosis in the different types of arteries in
these studies was assessed using different imaging modalities for each artery, and the different types of arteries were usually imaged at different time points.\textsuperscript{6–10, 12, 19–22}

CT angiography (CTA) has emerged as a reliable tool in the evaluation of atherosclerotic disease. CTA has been shown to have a high concordance with histology when evaluating carotid artery plaque characteristics.\textsuperscript{24} It has also been shown to provide high-quality images of the coronary arteries and to allow for the detection of significant coronary artery stenosis.\textsuperscript{25–27} CTA can also provide good-quality images of the vertebral arteries\textsuperscript{28} and aorta.\textsuperscript{29}

The purpose of this study was to determine whether significant atherosclerotic disease in the carotid arteries predicts significant atherosclerotic disease in the coronary arteries, vertebral arteries, and aorta in patients undergoing emergent CT evaluation for symptoms suggestive of acute ischemic stroke. For this purpose, we used a comprehensive CTA protocol that captured the carotid arteries, vertebral arteries, aorta, and coronary arteries in a single study at a single time point.

**Materials and Methods**

**Study Population**

All consecutive patients with symptoms suggestive of acute ischemic stroke aged 45 years or older referred for standard-of-care emergent CT evaluation between August 1, 2006 and September 31, 2008 were considered for enrollment in this prospective study. Standard exclusion criteria for contrast-enhanced cardiac CTA were applied (previous allergic reaction to iodinated contrast, renal disease with serum creatinine level $>1.5$ mg/dL, heart rate $>100$ beats per minute, or irregular heart rate). Also, hyperacute stroke patients eligible for reperfusion therapy were not considered for this study, at least until the neurologists in charge of these patients confirmed that they could be approached for consent without delaying treatment. Our Institutional Review Board approved this study and informed consent was obtained for each patient. Patients’ charts were reviewed for discharge diagnoses.

**CT Imaging Protocol**

CT studies were performed on a 64-slice multidetector CT scanner (Lightspeed; General Electric). These studies were performed without previous administration of $\beta$-blockers or nitroglycerin. A combined carotid–coronary CTA series was obtained, consisting of 2 helical acquisitions and dual-phase contrast injection (Supplemental Figure I available online at http://stroke.ahajournals.org). The first acquisition was non-ECG-gated, ascending from the top of the aortic arch to the vertex of the head. The second acquisition was performed during a single breath-hold and was retrospectively ECG-gated, descending from the top of the aortic arch to the diaphragm. The acquisition parameters were as follows: $64$-mm×$0.625$-mm collimation, 0.33-second gantry rotation time, 120-kV tube voltage, and 850-mA tube current. A slice-thickness of 1.25 mm and a pitch of 0.92 were used for the aortic arch, carotid, and intracranial arteries, whereas a slice-thickness of 0.625 mm and a pitch of 0.2 were used for the coronary arteries. The time of maximal enhancement on a bolus test was used to calculate the contrast transit time. This contrast transit time determined the delay between initial contrast injection and the first acquisition. The dual-phase contrast injection consisted of 2 boluses of $30$ mL and $60$ mL iodinated contrast material (iohexol, Omnipaque; Amersham Health; 350 mg/mL of iodine) injected into the right or left (preferably the right) cubital vein, followed by saline injection phases of $15$ mL and $60$ mL, respectively. The injection rate was $5$ mL/sec for both the contrast and saline. The scanning mode for the heart was selected based on the heart rate observed during a test breath-hold. One-sector reconstruction was performed if the heart rate was $\leq 65$ bpm and 2-sector reconstruction was performed if the heart rate was $>65$ bpm.

Axial images of the heart were retrospectively reconstructed using a slice-thickness of $1.25$ mm in $1.0$-mm increments from $5\%$ to $95\%$ every $10\%$ of the cardiac cycle. Data were transferred to and postprocessed on an off-line workstation (Advantage Workstation, 4.4-version software; General Electric). Curved multiplanar reformatted images of each coronary artery were rendered, and the cardiac phase providing the highest-quality images was selected for each artery.

**Assessment of the Carotid and Cardiac CTA Studies**

The atherosclerotic plaque burden of the common and internal carotid arteries and vertebral arteries was assessed by 2 radiologists blinded to the patients’ clinical information. The atherosclerotic plaque burden of the aorta and coronary arteries was assessed by 2 chest radiologists blinded to the patients’ clinical information. The curved multiplanar reformatted images of the following coronary arteries were evaluated: the right coronary artery, left main coronary artery, left anterior descending coronary artery, and circumflex coronary artery. The proximal, mid, and distal segments of the right coronary artery, left anterior descending coronary artery, and left circumflex coronary artery were evaluated separately (Supplemental Figure II available online at http://stroke.ahajournals.org).

When atherosclerotic disease was detected, its severity was characterized by measuring the degree of maximal stenosis. Depending on the degree, the artery was then distributed into 1 of the $6$ following categories: $<25\%$, $26\%$ to $50\%$, $51\%$ to $74\%$, $75\%$ to $95\%$, $96\%$ to $99\%$ (subocclusion), and $100\%$ (complete occlusion). Atherosclerotic plaque in the ascending, transverse, and descending aorta was given 1 of the following 4 grades: grade I ($<4$ mm in thickness), grade II ($\leq 4$ mm, not encroaching), grade III ($\geq 4$ mm, encroaching), and grade IV ($\geq 4$ mm, thrombus).\textsuperscript{30–31} Significant disease was defined as $>50\%$ vessel stenosis in the carotid,\textsuperscript{32} vertebral,\textsuperscript{33,34} and coronary arteries.\textsuperscript{6,12,22} or aortic atheroma $\geq 4$ mm in thickness\textsuperscript{35,36} (grade III or IV).

**Analysis of Atherosclerotic Disease Prevalence**

The analysis of disease prevalence in our study population was performed on a vessel level and patient level. In the vessel-level analysis, each type of artery was considered separately. For example, the internal carotid arteries of all patients were grouped together, and the disease prevalence was calculated. The same was performed for the common carotid arteries, vertebral arteries, aortic arch, horizontal aorta, descending aorta, right coronary artery, left coronary artery, left anterior descending coronary artery, and left circumflex coronary artery. In addition to comparing the prevalence of any level of disease, the prevalence of significant disease was compared among these arteries.

In the patient-level analysis, the prevalence of disease in each type of artery was compared within each patient. There were 6 comparisons as follows: the carotid arteries vs the coronary arteries, carotid arteries vs aorta, coronary arteries vs aorta, carotid arteries vs vertebral arteries, coronary arteries vs vertebral arteries, and aorta vs vertebral arteries. These 6 comparisons were completed in 2 ways.

First, the fractions of each type of artery containing any level of disease were calculated, and these fractions were compared within each patient. The fractions of carotid arteries (common and 2 internal carotid arteries per patient) containing any level of disease were calculated as follows: 0 (no disease), 0.25 (disease in 1 artery), 0.5 (disease in 2 arteries), 0.75 (disease in 3 arteries), and 1 (disease in all 4 arteries). The fractions of coronary arteries (10 segments per patient; Figure II) containing any level of disease were calculated as follows: 0 (no disease), 0.2 (disease in 1 or 2 segments), 0.4 (disease in 3 or 4 segments), 0.6 (disease in 5 or 6 segments), 0.8 (disease in 7–9 segments), and 1 (disease in all segments). The fractions of vertebral arteries (2 per patient) containing any level of disease were calculated as follows: 0 (no disease), 0.5 (disease in 1 artery), and 1 (disease in both arteries). The fraction of aorta (3 segments per
patient: ascending, horizontal, and descending) containing any level of disease was calculated as follows: 0 (no disease), 0.33 (disease in 1 segment), 0.67 (disease in 2 segments), and 1 (disease in all 3 segments).

Second, the same analysis was repeated but considered only significant disease. The fractions of each type of artery containing significant disease, with > 50% stenosis in the carotid, vertebral, and coronary arteries, and grade III or higher in the aorta were calculated, and these fractions were compared within each patient.

Fisher exact tests were used to assess the statistical significance of the comparisons between fractions listed. \( p < 0.05 \) was the threshold for significance in our statistical analysis.

Results

Patient Characteristics

Two hundred ten consecutive patients evaluated in the emergency department because of suspected stroke between August 1, 2006 and September 31, 2008 were considered as potential candidates for this study. Forty-three patients had hyperacute stroke and were excluded because the consent process could have delayed stroke reperfusion therapy. Thirty-three patients were excluded because they were non-English speakers and could not give consent. Among the 134 patients who were approached to enroll in our study, 120 consented and 14 refused to enroll. In our study population of 120 patients, 79 had appropriate CTA image quality that allowed either partial or total assessment of the coronary arteries (Figure 1). Five patients were excluded because they had coronary artery bypass grafts. In 36 patients, the cardiac portion of the CTA protocol succeeded, but the cardiac portion failed. In 79 patients, both the carotid and the coronary portions of the CTA protocol succeeded. These 79 patients were evaluated in our study (yellow).

The average age was 65 ± 13 (SD) years, with a range of 43 to 89 years. Forty-four patients were male (56%) and 35 were female (44%). Discharge diagnoses in our patient population were as follows. Twenty-nine of our 79 patients (37%) had ischemic stroke diagnosed at the time of their CT evaluation. Eighteen (23%) had transient ischemic attack diagnosed. Of the remaining patients, 11 (14%) had migraine headaches, 4 (5%) had aneurysms, 4 (5%) had brain tumors, and 13 (16%) had other diagnoses such as syncope, Bell’s palsy, and cervical radiculopathy.

Vessel-Level Analysis of Disease Prevalence

More than 50% of the internal carotid arteries, horizontal aortas, and left anterior descending coronary arteries were diseased, giving them the highest prevalence of disease in our patient population (Figure 2). Between 25% and 50% of the descending aortas, common carotid arteries, left main coronary arteries, and left circumflex coronary arteries were diseased. Less than 25% of the right coronary arteries, vertebral arteries, and ascending aortas were diseased, giving them the lowest prevalence of disease in our patient population.

When considering the prevalence of significant disease, the descending aorta (13.9%) had the greatest prevalence in our patient population, followed by the left anterior descending coronary artery (9.9%) and internal carotid arteries (7.0%; Figure 3). Next, the left circumflex coronary artery had a
Shifting focus from any level of disease to only significant disease revealed a different pattern. Significant disease was found mainly isolated to 1 type of artery rather than together in different types of arteries. This tendency of significant disease to be isolated to 1 type of artery (reflected by nonstatistically significant associations) was seen in the carotid–coronary (Fisher exact test for association between significant carotid disease and significant coronary disease, \(P=0.100;\) Table 2), carotid–aorta (Fisher exact test, \(P=0.082;\) Supplemental Table VI available online at http://stroke.ahajournals.org), coronary–aorta (Fisher exact test, \(P=0.334),\) carotid–vertebral (Fisher exact test, \(P=0.569),\) coronary–vertebral (Fisher exact test, \(P=0.585),\) and aorta–vertebral comparisons (Fisher exact test, \(P=0.136).\)

Of the 79 patients evaluated in this study, 26 (33%) had significant disease isolated in 1 type of artery. The majority of these 26 patients had significant disease in their coronary arteries (\(N=14; 54\%\)). Of the other 12 patients, 6 had significant disease isolated to their carotid arteries, 3 had significant disease isolated to their aorta, and 3 had significant disease isolated to their vertebral arteries.

Seven patients (9%) had significant disease in \(>1\) artery. There was 2-artery disease in 5 patients; their combinations were as follows: carotid–coronary (\(N=1),\) carotid–aorta (\(N=1)),\) coronary–aorta (\(N=2),\) and aorta–vertebral (\(N=1).\) There was 3-artery disease in 2 patients; their combinations were as follows: carotid—coronary–aorta (\(N=1)\) and carotid—aorta—vertebral (\(N=1).\)

**Discussion**

This study of patients undergoing emergent CT evaluation for symptoms of acute ischemic stroke shows that significant atherosclerotic disease in the carotid arteries does not predict significant atherosclerotic disease in the coronary arteries, vertebral arteries, or aorta. Moreover, our results indicate that although nonsignificant atherosclerotic disease tends to be systemic, significant disease tends to be isolated to 1 of the 4 types of arteries we evaluated—the carotid arteries, coronary arteries, vertebral arteries, and aorta. When comparing significant disease in the carotid and coronary arteries, we found that 26 of our 79 patients (33%) had significant disease in their carotid, coronary, or both types of arteries. Eight of these 26 patients (30.7%) had significant disease isolated to their carotid arteries and 16 (61.5%) had significant disease isolated to their coronary arteries. Only 2 of these 26 patients (7.8%) had significant disease in both the carotid and coro-
nary arteries. When evaluating for significant disease in all 4 types of arteries, we found that 26 of our 79 patients (33%) had significant disease in 1 type of artery, and only 7 of our 79 patients (9%) had significant disease in >1 type of artery. These results have clinical implications. Although the presence of significant carotid artery disease alone was not an adequate predictor of significant coronary artery disease in our population of patients undergoing emergent evaluation for suspected stroke, 18 of our 79 patients (23%) had significant coronary artery disease, and only 2 of these 18 (11%) had concomitant significant carotid artery disease. Therefore, it is important to image the carotid and coronary arteries in patients with symptoms of acute stroke. However, these results also indicate that in a patient with significant carotid artery disease, extensive work-up for coronary disease may not be warranted.

The results of this study also have implications for expanding our knowledge of the pathogenesis of atherosclerosis. Atherosclerosis has been viewed as a systemic disease for a number of years.\textsuperscript{37–41} Our results indicate that although atherosclerosis is a diffuse process, it tends to be significant in 1 type of artery at a time. This suggests that the progression of atherosclerosis is not synchronous in all arteries but predominates in different arteries in different patients. Previous studies have also shown this propensity for atherosclerosis to be severe in one vascular bed but not in others.\textsuperscript{37,41} Further studies are required to determine why some patients tend to have significant atherosclerosis in different arteries. Also, our study design was cross-sectional, and we cannot assess the evolution of time of the severity of atherosclerotic disease; we do not know whether patients with severe disease in 1 type of artery are more likely to have severe disease in other arteries, or if severe disease would remain confined in the 1 type of artery.

There are limitations to the applicability of our results to other patient populations. Our study was conducted in a select group of patients undergoing emergent CT evaluation for suspected stroke. Because of their symptoms, such patients are more likely to have atherosclerotic disease compared to the general population. We felt that it would not be ethical to expose patients without symptoms to the radiation dose associated with our stroke CT protocol. However, in order to minimize the selection bias, we included all patients referred for a CTA regardless of whether their final diagnosis was stroke/transient ischemic attack or not. It is likely that the overall prevalence of atherosclerotic disease would have been higher if we had considered only patients with a final diagnosis of stroke/transient ischemic attack. Our study was also limited by its sample size. A large-scale study to confirm our results would be useful.

**Conclusion**

In conclusion, significant atherosclerotic disease in the carotid arteries does not predict significant disease in the coronary arteries, vertebral arteries, or aorta. Significant atherosclerotic disease is more often isolated to 1 type of artery. However, nonsignificant atherosclerotic disease tends to be a systemic process.

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**Disclosure**

The content of the article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke, the National Center for Research Resources, the National Institutes of Health, or the other sponsors.

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