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

Abstract

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 computed tomography angiography (CTA) in a prospective study of 120 consecutive patients undergoing emergent CT evaluation for symptoms of stroke. Using a comprehensive CTA 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 ≥ 4mm thickness and encroaching in the aorta. Presence of any and significant atherosclerotic disease were compared in the different types of arteries assessed.

RESULTS—Of these 120 patients, 79 had CTA exams 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 one type of artery, most often to the coronary arteries (N = 14; 54%). Non-significant 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 one type of artery in these patients, while non-significant atherosclerotic disease tends to be more systemic.

Introduction

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

Studies have proposed the carotid artery intima-media thickness (IMT) as a surrogate marker for coronary artery disease (CAD).(6-9) However, other studies have questioned the use of the IMT as a marker for CAD 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 CAD.(12) This is illustrated by the Rotterdam study, where carotid plaques and carotid IMT were found to be strong predictors of MI.(13-18) Studies have also found an association between atherosclerosis in the aorta and in the carotid arteries(19), and between aortic plaque and CAD.(8, 20-22) Aortic plaque that is encroaching and greater than or equal to 4mm 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 due 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.(6-10, 12, 19-22)

Computed tomography 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.(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.(25-27) CTA can also provide good quality images of the vertebral arteries (28) and aorta.(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 employed a comprehensive CTA protocol that captured the carotid arteries, vertebral arteries, aorta, and coronary arteries in one single study at one single time point.

Materials and Methods

Study Population

All consecutive patients with symptoms suggestive of acute ischemic stroke aged 45 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 CT angiography were applied (previous allergic reaction to iodinated contrast, renal disease with serum creatinine level > 1.5 mg/mL, 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

Computed tomography (CT) studies were performed on a 64-slice multi-detector CT scanner ("Lightspeed," General Electric). These studies were done without prior administration of beta-blockers or nitroglycerin. A combined carotid-coronary CT angiography (CTA) series was obtained, consisting of 2 helical acquisitions and dual phase contrast injection (Figure 1). The first acquisition was non ECG-gated, ascending from the top of th 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: 64mm × 0.625mm collimation, 0.33-second gantry rotation-time, 120kV tube voltage, and 850mA 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 0.625mm 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 two boluses of 30cc and 60cc iodinated contrast material (iohexol, Omnipaque, Amersham Health, Princeton, NJ; 350mg/ml of iodine) injected into the right or left (preferably the right) cubital vein, followed by saline injection phases of 15cc and 60cc, respectively. The injection rate was 5cc/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 less than or equal to 65 beats per minute (bpm) and two-sector reconstruction if the heart rate was greater than 65bpm.

Axial images of the heart were retrospectively reconstructed using a slice-thickness of 1.25mm in 1.0mm increments from 5% to 95% every 10% of the cardiac cycle. Data were transferred to and post-processed 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 two radiologists blinded to the patients' clinical information. The atherosclerotic plaque burden of the aorta and coronary arteries was assessed by two chest radiologists blinded to the patients' clinical information. The curved multiplanar reformatted images of the following coronary arteries were evaluated: the right coronary artery (RCA), left main coronary artery (LM), left anterior descending coronary artery (LAD), and left circumflex coronary artery (LCX). The proximal, mid and distal segments of the RCA, LAD, and LCX were evaluated separately (Figure 2).

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 one of the six following categories: <25%, 26-50%, 51-74%, 75-95%, 96-99% (sub-occlusion), and 100% (complete occlusion). Atherosclerotic plaque in the ascending, transverse, and descending aorta was given one of the following four grades: Grade I (< 4mm in thickness), Grade II (≥ 4mm, not encroaching), Grade III (≥ 4mm, encroaching), and Grade IV (≥ 4mm, thrombus).(30, 31)

Significant disease was defined as > 50% vessel stenosis in the carotid (32), vertebral (33, 34), and coronary arteries (6, 12, 22) or aortic atheroma ≥ 4mm in thickness (35, 36) (Grade III or IV).

Analysis of Atherosclerotic Disease Prevalence

The analysis of disease prevalence in our study population was performed on both 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 done for the common carotid arteries, vertebral arteries, ascending aorta, horizontal aorta, descending aorta, RCA, LM, LAD, and LCX. 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 six 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 six comparisons were completed in two 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 (2 common and 2 internal carotid arteries per patient) containing *any* level of disease were calculated as follows: 0 (no disease), 0.25 (disease in one artery), 0.5 (disease in two arteries), 0.75 (disease in three arteries), and 1 (disease in all four arteries). The fractions of coronary arteries (10 segments per patient; Figure 2) containing *any* level of disease were calculated as follows: 0 (no disease), 0.2 (disease in 1-2 segments), 0.4 (disease in 3-4 segments), 0.6 (disease in 5-6 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 one 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 considering only *significant* disease. The fractions of each type of artery containing significant disease, > 50% stenosis in the carotid, vertebral, and coronary arteries and ≥ Grade III in the aorta, were calculated, and these fractions were compared within each patient.

Fisher's exact tests were used to assess the statistical significance of the comparisons between fractions listed above. A p-value of 0.05 was the threshold for significance in our statistical analysis.

Results

Patient Characteristics

Two hundred and 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 were hyperacute stroke patients 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 be consented. 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 3). Five patients were excluded because they had coronary artery bypass grafts. In 36 patients, the cardiac portion of the CTA failed because of technical issues (n = 21) or poor image quality (n = 15). Our analysis was conducted on the 79 successful cases (Figure 3).

The average age was 65 ± 13 (SD) years, with a range of 43 to 89 years. Forty-four patients were male (56%) and thirty-five were female (44%). Discharge diagnoses in our patient population were as follows. Twenty-nine of our 79 patients (37%) were diagnosed with ischemic stroke at the time of their CT evaluation Eighteen (23%) were diagnosed with transient ischemic attack. 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, cervical radiculopathy.

Vessel-Level Analysis of Disease Prevalence

Greater 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 4). 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 5). Next, the left circumflex coronary artery had a prevalence of 5.7%, the right coronary artery 4.2%, vertebral arteries 3.8%, horizontal aorta 3.8%, and left main coronary artery 2.5%. The common carotid arteries only contained 0.6% significant disease, and the ascending aorta had no significant disease.

Patient-Level Analysis of Disease Prevalence

Considering the type of arteries with *any* level of disease within each patient, more patients tended to have disease in both the carotid and coronary arteries (N = 50/79 patients, or 63%) than isolated to one or the other type of artery (N = 22/79 patients, or 37%, including 14 patients with any disease in the carotid arteries and no disease in the coronary arteries, 8 patients with any disease in the coronary arteries and no disease in the carotid arteries) (Fisher's exact test for association between any level of carotid disease and any level of coronary disease, $p = 0.100$) (Table 1). This trend became significant in the carotid-aorta comparison (Fisher's exact test, $p = 0.015$) (Table 2) and in the coronary-aorta comparison (Fisher's exact test, $p = 0.001$) (Table 3).

In contrast, disease in the vertebral artery was much rarer. Disease was more often seen or tended to be more often seen just in the carotid arteries (Fisher's exact test for association between any level of carotid disease and any level of vertebral disease, $p = 0.002$) (Table 4), just in the coronary arteries (Fisher's exact test, $p = 0.111$) (Table 5), or just in the aorta (Fisher's exact test, $p = 0.006$ (Table 6), rather than together in these same arteries and the vertebral arteries. Vertebral artery disease without coronary disease (N = 4; 7%) or without aortic disease (N = 4; 7%) was only seen in a small number of cases. Vertebral artery disease only without concomitant carotid disease was never seen.

Shifting focus from *any* level of disease to only *significant* disease revealed a different pattern. Significant disease was found mainly isolated to one type of artery, rather than together in different types of arteries. This tendency of significant disease to be isolated to one type of artery (reflected by non statistically significant associations) was seen in the carotid-coronary (Fisher's exact test for association between significant carotid disease and significant coronary disease, $p = 1.000$) (Table 7), carotid-aorta (Fisher's exact test, $p = 0.082$) (Table 8), coronary-aorta (Fisher's exact test, $p = 0.334$), carotid-vertebral (Fisher's exact test, $p = 0.569$), coronary-vertebral (Fisher's exact test, $p = 0.585$), and aorta-vertebral comparisons (Fisher's exact test, $p = 0.136$).

Of the 79 patients evaluated in this study, 26 (33%) had significant disease isolated in one 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 to their aorta, and 3 to their vertebral arteries.

Seven patients (9%) had significant disease in more than one artery. There was two-artery disease in five 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 three-artery disease in two 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, while non-significant atherosclerotic disease tends to be systemic, significant disease tends to be isolated to one of the four 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%) to their coronary arteries. Only 2 of these 26 patients (7.8%) had significant disease in both the carotid and coronary arteries. When evaluating for significant disease in all four types of arteries, we found that 26 of our 79 patients (33%) had significant disease in one type of artery, and only 7 of our 79 patients (9%) had significant disease in more than one type of artery.

These results have clinical implications. While 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 both the carotid and coronary arteries in patients with symptoms of acute stroke. But, 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.(37-41) Our results indicate that while atherosclerosis is a diffuse process, it tends to be significant in one 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 while not in others.(37, 41) Further studies are required to determine why some patients tend to develop 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 one type of artery are more likely to develop severe disease in other arteries, or if severe disease would remain confined in the one 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. On the other hand, we included all patients referred for a CTA independently on whether their final diagnosis was stroke/transient ischemic attack or not, in order to minimize the selection bias. 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.

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 one type of artery. On the other hand, non-significant atherosclerotic disease tends to be a systemic process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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