Optimal carotid artery coverage for carotid plaque CT-imaging in predicting ischemic stroke

Optimisation de la hauteur d’exploration de la plaque carotide en scanner pour la prédiction de l’accident vasculaire cérébral ischémique

S. Arora, J.D. Chien, S.-C. Cheng, K.A. Chun, M. Wintermark

University of California—San Francisco, Department of Radiology, Neuroradiology Section, 505, Parnassus Avenue, Box 0628, San Francisco, CA 94143, United States

University of California—San Francisco, Department of Epidemiology and Biostatistics, San Francisco, CA 94143, United States

State University of New York, Stony Brook University, School of Medicine, New York, United States

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KEYWORDS
Carotid arteries; Atherosclerosis; Ischemic stroke; Computed tomography

Summary
Objective. — To determine the optimal spatial coverage for CT-imaging of carotid atherosclerosis, allowing the most accurate prediction of the associated risk of ischemic stroke.

Methods. — In a cross-sectional study, we retrospectively identified 136 consecutive patients admitted to our emergency department with suspected stroke who underwent a CT-angiogram (CTA) of the cervical and intracranial carotid arteries. CTA studies of the carotid arteries were processed using a custom, CT-based automated computer classifier algorithm that quantitatively assesses a battery of carotid CT features. We used this algorithm to individually analyze different lengths of the common and internal carotid arteries for carotid wall features previously shown to be significantly associated with the risk of stroke. Acute stroke patients were categorized into ”acute carotid stroke patients” and ”non-acute carotid stroke patients” independently of carotid wall CT features. Univariate and multivariate analyses were used to compare the different spatial coverages in terms of their ability to distinguish between the carotid stroke patients and the noncarotid stroke patients using a receiver-operating characteristic curve (ROC) approach.

Results. — The carotid wall volume was excellent at distinguishing between carotid stroke patients and noncarotid stroke patients, especially for coverages 20 mm or less. The number and location of lipid clusters had a good discrimination power, mainly for coverages 15 mm or greater. Measurement of minimal fibrous cap thickness was most associated with carotid stroke when assessed using intermediate coverages. Typically, a 20 mm coverage on each side of the carotid bifurcation offered the optimal compromise between the individual carotid features.

* Corresponding author.
E-mail address: Max.Wintermark@radiology.ucsf.edu (M. Wintermark).

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Introduction

Stroke is the third leading cause of mortality in industrialized country and the leading cause of long-term disability [1]. The number of strokes related to carotid atherosclerosis approaches 30% of all strokes [1–3]. However, the relationship between carotid atherosclerotic disease and neurological manifestations remains the object of active investigation, due to our incomplete knowledge about plaque “vulnerability”. In addition to the degree of luminal narrowing, which is currently the principal imaging descriptor used to characterize carotid atherosclerotic disease, different candidate descriptors of the carotid artery wall have been proposed to describe the associated risk of ischemic stroke, including: the volume of the plaque; the extent of plaque surface irregularity; the thickness of the fibrous cap and the size and location of the necrotic core [4–20]. These features of the carotid plaques have been studied using either ultrasound [5, 6, 9, 13, 14] or magnetic resonance imaging (MRI) [4, 7, 8, 15, 16, 19, 20] and, more recently, computed tomography (CT) [10–12, 17, 18]. CT has been reported to assess, in a quantitatively accurate and standardized fashion, the histological composition (including noncalcified components) and characteristics of carotid artery atherosclerotic plaques [18]. CT assessment of carotid atherosclerotic plaques has also been demonstrated as being clinically relevant, showing significant differences, in patients with acute carotid stroke when compared with either non-acute carotid stroke patients or the carotid wall contralateral to the infarct side [17]. CT assessment of carotid arteries should ideally assess the complete length of the common and internal carotid arteries. However, considering thin slices offered by modern multislice CT-scanners and the resulting high number of slices, it would be desirable to be able to focus attention on a coverage shorter than the whole carotid length. This would for instance significantly shorten the processing time in case of automatic interpretation of the carotid CT studies by a computer algorithm.

The goal of this study was to determine the optimal spatial coverage for CT-imaging of carotid atherosclerosis, allowing the most accurate prediction of the associated risk of ischemic stroke.

Materials and methods

Study design

Clinical and imaging data, obtained as part of standard clinical stroke care at our institution, was retrospectively reviewed with the approval of the institutional review board. At our institution, patients with suspicion of acute stroke and no history of significant renal insufficiency or contrast allergy routinely undergo a stroke CT survey including the following imaging protocol: noncontrast CT, perfusion-CT at two cross-sectional positions, CT-angiogram (CTA) of the cervical and intracranial vessels and a postcontrast cerebral CT.

We retrospectively identified all consecutive patients admitted to our emergency department from August 2006 through January 2007 who underwent a CTA study to evaluate their carotid arteries.

This patient population was already used in a previous published study [17].

CTA-imaging protocol

The CTA studies of the carotid arteries were obtained on a 16-slice CT-scanner (General Electric Medical Systems, Milwaukee, WI). The image acquisition protocol was as follows: spiral mode, 0.6-second gantry rotation, collimation: 16 × 0.625 mm, pitch: 1.375:1, slice thickness: 0.625 mm, reconstruction interval: 0.5 mm, acquisition parameters: 120 kVp/240 mA. A caudocranial scanning direction was selected, covering the midchest to the vertex of the brain. Seventy milliliters (mL) of iohexol (Omnipaque, Amersham Health, Princeton, NJ; 300 mg/mL of iodine) was injected into an antecubital vein with a power injector at a rate of 4 mL per second. Optimal timing of the CTA acquisition was achieved using a test bolus technique.

Image review

The CT studies of the brain parenchyma obtained at baseline and the brain imaging studies obtained within the first week after the baseline CT were reviewed by a neuroradiologist for the presence or absence of an acute infarct and its distribution (unilateral or bilateral, single or multiple vascular territories and location of vascular territory). The neuroradiologist also reviewed the intracranial portion of the baseline CTA for the degree of completeness of the circle of Willis. Based on the brain CT or MRI findings, the anatomy of the circle of Willis and published criteria [21, 22], the neuroradiologist decided whether the distribution of an acute infarct was consistent with a carotid origin.

The neuroradiologist reviewed the same studies of the brain parenchyma for remote infarcts and determined whether their distribution was consistent with a carotid origin. Patients with remote infarcts in a carotid distribution were excluded from our analysis because carotid atherosclerotic disease is an evolving process and the carotid artery condition may have evolved in the time interval between when the remote infarct occurred and the time of our CTA study. This could have interfered with our identification of the carotid wall features associated with stroke.

Conclusion. — We recommend assessment of 20 mm of each side of the carotid bifurcation to best characterize carotid atherosclerotic disease and the associated risk of ischemic stroke.

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Finally, the neuroradiologist assessed the degree of carotid stenosis on the cervical portion of the baseline CTA but did not record any information regarding the carotid wall. During the review, the neuroradiologist was blinded to the results of the automatic analysis of the carotid wall produced by the computer algorithm.

**Patient classification**

Patients medical records were reviewed to determine the likely etiologic origin of the stroke, using the causative classification system for ischemic stroke [23] and its electronic implementation available online (http://www.strokedatabase.org/index.html) [24]. Based on the review of the imaging studies of the brain parenchyma by the neuroradiologist, degree of carotid stenosis and test results available in patients’ charts (such as EKG and Holter), but independently of carotid wall CT features, patients were categorized as “carotid stroke patients” (cases) if they had an acute ischemic stroke in a carotid distribution and the likely mechanism of stroke was large artery atherosclerosis. Patients with no acute stroke, and patients with an acute stroke from a noncarotid origin were categorized as “noncarotid stroke patients” (controls) (Fig. 1).

**Image postprocessing**

CTA studies of the carotid arteries were processed using a custom, CT-based, automated classifier computer algorithm that was validated using histology derived from carotid endarterectomy specimens as a gold standard [18]. This algorithm automatically segments the inner and outer contours of the carotid artery wall and distinguishes between the histological components of the wall (lipids, calcium) using appropriate thresholds of CT density [18]. The algorithm creates a color overlay affording a visual display of the composition of the carotid wall for each CTA image [18]. It then automatically analyzes several CT features of the carotid arteries — including minimal lumen area, wall volume, minimal fibrous cap thickness, number of lipid clusters, location of the largest lipid cluster, number of calcium clusters — and quantifies them three-dimensionally (not in a plane, as with B-mode ultrasound), independent of any subjective, human interpretation [18]. The location of the largest lipid cluster was described as a percent of the carotid wall thickness, with 0% indicating the center of the cluster immediately adjacent to the inner contour and 100%, the center of the cluster immediately adjacent to the outer contour.

Measurements of individual carotid wall features were performed and recorded individually for each side and for varying spatial coverages (5 mm, 10 mm, 15 mm, 20 mm, 25 mm, 30 mm, 35 mm, 40 mm) of the common carotid artery below the carotid bifurcation and the internal carotid above the carotid bifurcation.

The physician processing the CTA datasets was blinded to the clinical findings of the imaged patients and to the group to which they belonged.

**Statistical analysis**

Two similar analyses were performed. Analysis #1 compared the CT features from the carotid artery ipsilateral to the side of the stroke in “carotid stroke patients” (cases) to the more diseased carotid artery of the “noncarotid stroke patients” (controls) (Fig. 1).

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**Figure 1** Distribution of the initial 136 patients into stroke and nonstroke patients based on the presence or absence of infarct at baseline, infarct distribution and available test results in the patients’ medical records. Of note, patients were classified independently of their carotid wall features noted on CT. None of the 40 “carotid stroke patients” had any history of atrial fibrillation documented in their medical records. Also, according to the causative classification system for ischemic stroke, patients with carotid stenosis between 20% and 50% were classified as “carotid stroke” patients only if they had a prior history of at least one event in the last month as part of two or more ischemic strokes, transient ischemic attacks and/or transient monocular blindness from the territory of index artery.
patients” (controls). Analysis #2 focused on the “carotid stroke patients’”, comparing carotid artery features from the carotid arteries ipsilateral to the stroke side (cases) to contralateral carotid arteries in stroke patients (controls).

In both analyses, CT carotid features previously shown to be significantly different in stroke patients and on the stroke side—minimal lumen area, wall volume, minimal fibrous cap thickness, number and location of the largest lipid clusters, number of calcium clusters—[17] were analyzed individually (univariate analysis) and together as part of a multivariate model (multivariate analysis). For each analysis, the predictive value in terms of stroke group or stroke side was evaluated as the area under the receiver-operating characteristic (ROC) curve calculated for the corresponding carotid feature or multivariate model. The coverage that had the maximal area under the ROC curve (AUC) was considered as the gold standard and AUC’s for the other coverages were compared to the gold standard based on the difference in AUC estimates. For analysis #1 with a paired study design, 95% confidence intervals and p-values were obtained using the a previously published method. Due to the clustered case-control structure in Analysis #2, we bootstrapped the data for inference. A p value less than 0.050 was considered as indicating a statistically significant difference with the gold standard.

Results

Patients and imaging studies

The study population consisted of 136 consecutive patients admitted to our institution’s emergency department between August 2006 and January 2007 who received a CTA of their carotid arteries. Seventy-seven patients were male (56.6%) and 59 were female (44.4%) with a mean age of 66 ± 16 years (range 19—96 years). Of these, 40 “carotid stroke patients” and 50 “noncarotid stroke patients” (Fig. 1) were diagnosed using the patients’ charts, baseline CT studies and all follow-up imaging done within 1 week of the baseline CT. These 90 patients were used for the remainder of the study. All 90 patients (40 “carotid stroke patients” and 50 “noncarotid stroke patients”) underwent perfusion-CT in addition to CTA. Twenty-six of the 40 “carotid stroke patients” underwent MRI of their brain including diffusion-weighted imaging (DWI); 32 underwent a noncontrast CT of their brain prior to discharge. Thirty-four of the 40 “carotid stroke patients” underwent MRI with DWI. None of the 40 “carotid stroke patients” had a history of atrial fibrillation documented in their medical records. Six out of 136 (4.4%) CTA studies were of poor quality, but none of them occurred among the 40 “carotid stroke patients” and 50 “noncarotid stroke patients”.

Statistical analysis #1: comparison between carotid stroke patients and noncarotid stroke patients

The carotid wall volume was most discriminating between carotid stroke and noncarotid stroke patients for shorter coverages (5 mm and 10 mm) and the area under the ROC curve dropped significantly for coverages of 25 mm or more.

<table>
<thead>
<tr>
<th>Carotid Coverage on Each Side of the Illoclusion</th>
<th>5 mm</th>
<th>10 mm</th>
<th>15 mm</th>
<th>20 mm</th>
<th>25 mm</th>
<th>30 mm</th>
<th>35 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Lumen Area</td>
<td>0.621</td>
<td>0.471</td>
<td>0.413</td>
<td>0.362</td>
<td>0.319</td>
<td>0.281</td>
<td>0.229</td>
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<td>Wall Thickness</td>
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<td>0.319</td>
<td>0.281</td>
<td>0.229</td>
</tr>
<tr>
<td>Minimal Fibrous Cap</td>
<td>0.596</td>
<td>0.474</td>
<td>0.393</td>
<td>0.298</td>
<td>0.205</td>
<td>0.150</td>
<td>0.100</td>
</tr>
<tr>
<td>Lipid Cluster</td>
<td>0.517</td>
<td>0.465</td>
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<td>0.214</td>
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</tr>
<tr>
<td>Calcium Cluster</td>
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<td>0.151</td>
<td>0.101</td>
</tr>
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<td>Wall Volume</td>
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<td>0.101</td>
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<tr>
<td>Location of Largest Lipid Cluster</td>
<td>0.578</td>
<td>0.462</td>
<td>0.395</td>
<td>0.316</td>
<td>0.225</td>
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<tr>
<td>Multivariate Analysis</td>
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</tr>
</tbody>
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Figure 2: Results of statistical analysis #1. Individual analyses of 40 carotid stroke patients’ carotid artery ipsilateral to the side of stroke were compared with 50 noncarotid stroke patients’ more diseased carotid artery. Relevant CT-carotid were analyzed individually (univariate analysis) and together as part of a multivariate model (multivariate analysis). For both analyses, the predictive value in terms of stroke group was evaluated as the area under the receiver-operating characteristic (ROC) curve, reported in this table with its 95% confidence interval (in brackets). The coverage that had the maximal area under the ROC curve (AUC) was considered as the gold standard and AUC’s for the other coverages were compared to the gold standard based on the difference in AUC estimates. A p value (reported in bold) less than 0.050 was considered as indicating a statistically significant difference with the gold standard. Coverages that were not significantly different from the gold standard are shaded in gray in this figure.

Statistical analysis #2: comparison between carotid arteries on the ipsi- and contralateral side to stroke, exclusively in stroke patients

The minimal lumen area was most discriminating between carotid stroke and noncarotid stroke patients for larger coverages (30 mm and 35 mm, respectively) and the area under the ROC curve dropped significantly for a coverage less than 10 mm.

In terms of the minimal lumen area, minimal fibrous cap thickness and number of calcium clusters, there was no statistically significant difference between the varying spatial coverages regarding ROC areas.

The multivariate model including all these carotid features was most discriminating between carotid stroke and noncarotid stroke patients for larger coverages (40 mm) and the area under the ROC curve dropped significantly for a coverage inferior to 15 mm.

![Figure 2](image-url)
and the area under the ROC curve dropped significantly for coverages less than 15 mm (20 mm and 25 mm, respectively) and the area under the ROC curve dropped significantly for coverages greater than 20 mm. The number of lipid clusters and location of the largest lipid cluster were most discriminating between the stroke side and the contralateral side in carotid stroke patients, and showed a superior discriminative power for short or intermediate carotid artery coverages. This is likely explained by the observation that the more distal internal carotid arteries can be normal even in patients with advanced carotid disease and therefore do not add any additional information, but mere noise, in terms of ability to discriminate between carotid stroke patients and noncarotid stroke patients and between the stroke side and the contralateral side in carotid stroke patients. This is exemplified by the measurement of the wall volume: If the coverage is extended too far out from the carotid bifurcation, where there is no disease even in patients with severe carotid disease, then normal wall is included in the calculation of the wall volume, both on the stroke side and on the contralateral side, and also in the nonstroke patients, and this parameter loses its ability to discriminate different in carotid stroke patients from noncarotid stroke patients and stroke side from contralateral side.

The minimal lumen area, the minimal fibrous cap thickness and the number of calcium clusters had the lowest association with carotid stroke. The carotid wall volume was excellent at distinguishing between carotid stroke patients and the noncarotid stroke patients, and between the stroke side and the contralateral side in carotid stroke patients, and performed optimally for coverages of 20 mm or less. The number and location of lipid clusters had a good discriminative power, mainly for coverages of 15 mm or greater. Typically, a 20 mm coverage on each side of the carotid bifurcation offered the optimal compromise between the individual carotid features and was also appropriate when considering the multivariate models considering all the carotid features together.

We acknowledge several limitations to our study. Firstly, our results were derived from a cross-sectional sample of patients and will require further validation in a larger, longitudinal study. Also, our study sample was derived from patients receiving carotid artery CTA’s in our institution’s emergency department; a population with a greater risk of ischemic stroke from carotid atherosclerotic disease is offered by an evaluation of the full course of the carotid arteries. However, carotid atherosclerotic disease is known to be concentrated predominantly around the carotid bifurcation, while more distal internal carotid arteries can be normal even in patients with severe carotid disease [25].

Our study shows that, counterintuitively, the carotid features best distinguishing between the carotid stroke patients and the noncarotid stroke patients, and between the stroke side and the contralateral side in carotid stroke patients, showed a superior discriminative power for short or intermediate carotid artery coverages. This is likely explained by the observation that the more distal internal carotid arteries can be normal even in patients with advanced carotid disease and therefore do not add any additional information, but mere noise, in terms of ability to discriminate between carotid stroke patients and noncarotid stroke patients and between the stroke side and the contralateral side in carotid stroke patients. This is exemplified by the measurement of the wall volume: If the coverage is extended too far out from the carotid bifurcation, where there is no disease even in patients with severe carotid disease, then normal wall is included in the calculation of the wall volume, both on the stroke side and on the contralateral side, and also in the nonstroke patients, and this parameter loses its ability to discriminate different in carotid stroke patients from noncarotid stroke patients and stroke side from contralateral side.

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We acknowledge several limitations to our study. Firstly, our results were derived from a cross-sectional sample of patients and will require further validation in a larger, longitudinal study. Also, our study sample was derived from patients receiving carotid artery CTA’s in our institution’s emergency department; a population with a greater risk of stroke than the general population. This limits our ability to generalize from our study but should not affect the study’s internal validity in a hospital setting. Finally, the maximal coverage we considered was 40 mm on each side of the carotid bifurcation was sufficient to assess the cervical carotid arteries in a vast majority of patients, but did not include the cavernous carotid arteries.

In conclusion, we recommend an assessment of 20 mm on each side of the carotid bifurcation in order to best characterize carotid atherosclerotic disease and the associated risk of ischemic stroke.
Acknowledgments

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