Carotid Artery Anatomy and Geometry as Risk Factors for Carotid Atherosclerotic Disease

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Background and Purpose—Traditional vascular risk factors do not completely explain the asymmetry, racial, and sex differences in carotid artery disease. Carotid anatomy and geometry may play a role in the pathogenesis of internal carotid artery (ICA) stenosis, but their effects are unknown. We hypothesized that carotid artery anatomy and geometry would be independently associated with ICA stenosis.

Method—This is a retrospective study of patients with CT angiography at Monash Medical Centre, 2006 to 2007. Carotid arteries were segmented using semiautomated methods to estimate measures of carotid anatomy and geometry. Measurements of carotid artery geometry were performed according to the recent article by Thomas and colleagues. ICA stenosis was dichotomized as <30% or ≥30% stenosis. Cluster logistic regression was used to examine the associations of anatomy and geometry with stenosis accounting for the paired arteries within subjects, adjusting for age, sex, and vascular risk factors.

Results—Mean age of the sample (n=178) was 68.4 years (SD, 14 years). The following were independently associated with ICA stenosis: ICA radius at the bifurcation (OR, 0.20; 95% CI, 0.14–0.29), ICA angle (OR, 1.05 per degree increment; 95% CI, 1.04–1.07), age (OR, 1.05 per year increment; 95% CI, 1.03–1.07), male sex (OR, 1.72; 95% CI, 1.08–2.8), and ever-smoker (OR, 1.85; 95% CI, 1.15–2.96).

Conclusions—Carotid anatomy and geometry may enhance the risk of stenosis independent of traditional vascular risk factors and may be of help in very early identification of patients at high risk of developing carotid artery atherosclerosis for aggressive intervention. (Stroke. 2012;43:1596-1601.)

Key Words: anatomy ■ angiography ■ carotid stenosis

Atherosclerotic disease of large arteries such as the carotid artery is responsible for one fourth of stroke cases.1 The “traditional” Framingham risk factors for atherosclerotic disease do not explain differences in disease prevalence between vascular beds (carotid versus mesenteric vascular bed),2 side-to-side variation in carotid artery atherosclerotic disease in the same individual, interracial differences in the location of plaque along the carotid artery,3 or sex differences in carotid artery atherosclerosis.3,4 Plaques do not form randomly in the carotid artery but preferentially around the carotid artery bifurcation (extracranial site) and the carotid artery siphon (intracranial site). At the carotid artery bifurcation, plaque builds up on the outer aspect of the internal carotid artery (ICA) rather than at the point of bifurcation. High wall shear stress (frictional force of flowing blood on vessel wall) and laminar flow (smooth parabolic profile) are likely to dominate at the carotid artery bifurcation and may provide “protection” in this region from plaque formation.5,6 By contrast, low wall shear stress predominates at the outer aspect (lateral wall) of the ICA7 and may promote atherosclerosis. The inference from these studies is that carotid artery anatomy may influence hemodynamic forces and play a role in the development of carotid artery atherosclerosis. However, these studies on carotid anatomy have not accounted for the contribution of traditional Framingham risk factors to ICA stenosis.

There are fewer data on the association of carotid artery geometry with carotid artery stenosis.8 These data come from studies comparing carotid geometry in young people with older healthy subjects rather than directly studying people with atherosclerotic disease.8 Consequently, the association of carotid artery geometry with carotid artery stenosis is...
inferred rather than known. In this study, we set out to explore this possible relationship in a clinical setting. We hypothesized that measures of carotid anatomy and geometry would be associated with ICA stenosis in people at high risk of atherosclerotic disease independent of traditional cardiovascular risk factors.

Methods
The sample was derived from patients who underwent CT angiography (CTA) at the time of attending the stroke and vascular clinics at Monash Medical Centre from 2006 to 2007. Demographic variables (age, sex) and a history of traditional risk factors (hypertension, diabetes mellitus, hyperlipidemia, and ever smoking) were collected from medical records. The study was approved by the Southern Health Human Research Ethics committee.

Imaging Protocol
CT scans were performed on 16 multirow and 64 multirow detector General Electric scanners with the field of view covering from the aortic arch to the level of the level of the basal ganglia with voxel resolution of 2 mm×0.5 mm×0.5 mm. A tube voltage of 140 kV and automatic mA setting (range, 100–700 mA) were used and 75 mL of intravenous contrast delivered through a power injector at 3 mL/s. Images were acquired and displayed in a 512 matrix. On the axial plane, the images were reconstructed to 0.625 mm thickness.

Reconstruction of 3-Dimensional Carotid Artery
The carotid artery was segmented using semiautomated software developed in-house. This software requires identifications of points within the ICA, external carotid artery (ECA), and common carotid artery (CCA). The user-defined points were automatically connected using a path of lowest cost to form a "sketch" of the artery tree. Next, we used watershed transform from markers to refine the sketch of the artery tree so that the entire artery was segmented. The watershed transform was controlled by gradient information from the CTA image. Segmentation and measurement tools were developed using the Insight Toolkit and associated classes. Segmentation methods were validated by comparing semiautomated segmentation with manual segmentation performed by an experienced interventional radiologist in a set of 11 randomly selected subjects from the studied group.

Measurement of Carotid Artery Geometry
The 3-dimensional geometric characteristics of the arterial tree were computed from the skeleton of the carotid artery generated by the segmentation software. The measures of carotid artery geometry were defined according to methods described previously. The bifurcation angle was the angle between the ICA and ECA. The ICA angle was the angle of deviation of the ICA from a vertical line drawn through the center of the CCA (Figure 1). As can be seen from Figure 1, the ICA angle is a subset of the bifurcation angle. The ICA planarity is the angle between the out-of-plane components of the CCA and ICA vector (see Figure 1). Tortuosity of the CCA or ICA was defined as the ratio between the length of a straight line drawn between vessel end points and the actual length of the vessel. The ICA angle of origin (named as the ICA–ECA angle in this study to avoid confusion with the ICA angle) describes a line connecting the centers of the lumen of the ICA and ECA relative to the horizontal line drawn by the plane of the ultrasound probe. In this study, we used 3-dimensional reconstruction of the arterial geometry to standardize the measurement of the ICA–ECA angle.

Measurement of Carotid Artery Bifurcation Anatomy
The anatomy of the carotid bifurcation was defined in terms of radius of ICA, ECA, and CCA at locations equidistant from the carotid bifurcation as described and illustrated in Figure 1. The ICA–CCA diameter ratio was generated from these measurements. The ICA volume was generated from the radius of the ICA and length (bifurcation radius) measurement at the bifurcation using the formula for a cylinder. The carotid bifurcation was taken to be the bifurcation point of the skeleton of the arterial tree. The point at which the radius of each artery was measured was distance, r, along the skeleton from the bifurcation point. The distance, r, was the radius of the largest sphere, centered on the bifurcation point, that could be inscribed within the bifurcation. Artery diameters and radii at these locations were computed automatically using the radius of the largest sphere centered on the measurement point that could be inscribed inside the artery segmentation. Measurement points were defined in terms of the size of the bifurcation and were therefore dependent on the size of an individual’s arteries. In addition to the radius of the ICA, the minimum radius of the ICA was determined. The minimum radius of the ICA, and not the ICA radius at the bifurcation, was used in calculation of ICA stenosis.

Measurement of Arterial Stenosis
The degree of ICA stenosis was measured using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criterion.
Table 1. Relationship Among ICA Anatomy, ICA Angle, and ICA Stenosis

<table>
<thead>
<tr>
<th>ICA Stenosis</th>
<th>0%</th>
<th>10%–49%</th>
<th>50%–79%</th>
<th>&gt;80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA radius at the bifurcation, mm</td>
<td>3.11±0.76</td>
<td>2.44±0.52</td>
<td>2.21±0.71</td>
<td>1.84±0.95</td>
</tr>
<tr>
<td>ICA volume at bifurcation, mm³</td>
<td>128.22±89.49</td>
<td>64.46±35.25</td>
<td>54.59±44.11</td>
<td>45.95±55.58</td>
</tr>
<tr>
<td>Ratio diameter ICA–CCA</td>
<td>0.85±0.11</td>
<td>0.79±0.12</td>
<td>0.78±0.16</td>
<td>0.66±0.23</td>
</tr>
<tr>
<td>ICA angle</td>
<td>23.3°±14.01°</td>
<td>31.25°±21.60°</td>
<td>35.47°±19.01°</td>
<td>43.17°±24.69°</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; CCA, common carotid artery.

The mean degree of difference in asymmetry between the paired arteries was 1.168 (95% CI, 1.001–1.336; P<0.01).

There was excellent agreement between manual and automated segmentations with intraclass correlation coefficient of 0.96 (95% CI, 0.93–0.98) and a median similarity index of 0.86 (interquartile range, 0.80–0.91).

Linear relationships were observed between degree of ICA stenosis and ICA radius at the bifurcation, ICA angle, ICA volume at bifurcation, CCA radius, and the ICA–CCA diameter ratio (Table 1; Figure 2) The univariable predictors (P<0.10 of carotid artery stenosis were (Table 2): age (OR, 1.05 per year increment; 95% CI, 1.03–1.07), hypertension (OR, 1.73; 95% CI, 1.08–2.76), male sex (OR, 2.31; 95% CI, 1.44–3.72), smoker (OR, 1.85; 95% CI, 1.15–2.96), diabetes mellitus (OR, 1.87; 95% CI, 1.11–3.16), hyperlipidemia (OR, 1.80; 95% CI, 1.14–2.84), ICA angle (OR, 1.05 per degree increment; 95% CI, 1.04–1.07), bifurcation angle (OR, 1.02 per degree increment; 95% CI, 1.00–1.03), ICA radius at the bifurcation (OR, 0.20 per mm decrement; 95% CI, 0.14–0.29), and CCA radius (OR, 0.30 per mm decrement; 95% CI, 0.22–0.41). The associations of tortuosity, ICA planarity, and ICA–ECA angle with ICA stenosis were not statistically important at the P<0.10 level.

In multivariable regression, radius of ICA (OR, 0.20 per mm decrement; 95% CI, 0.14–0.29), ICA angle (OR, 1.05 per degree increment; 95% CI, 1.04–1.07), age (OR, 1.05 per year increment; 95% CI, 1.03–1.07), male sex (OR, 1.72; 95% CI, 1.08–2.8), and ever smoker (OR, 1.85; 95% CI, 1.15–2.96) were independent predictors (P<0.05) of carotid artery stenosis (Table 3). The analysis yielded the same results when carotid stenosis was dichotomized at a threshold of 10% (presence) versus no stenosis (data not shown). This model was also repeated with volume of ICA at the bifurcation or the ICA–CCA diameter ratio (OR, 0.019 per ICA–CCA ratio decrement; 95% CI, 0.003–0.106) and ICA–CCA area ratio (OR, 0.79 per ICA–CCA area ratio decrement; 95% CI, 0.718–0.888) as measures of anatomy instead of ICA radius at the bifurcation, again with statistically significant results. The CCA radius at the bifurcation was not independently associated with ICA stenosis when both ICA and CCA radius at the bifurcation were used as covariates. However, CCA radius at the bifurcation was independently associated with ICA stenosis (OR, 0.32 per mm decrement; 95% CI, 0.22–0.46) when ICA radius at the bifurcation was removed from the regression model.

In post hoc analyses, factors that were independently associated with ICA angle were age (slope=0.23°/year increment; 95% CI, 0.08–0.38; P=0.002), hypertension (differ-
ence=5.63°; 95% CI, 1.28–9.98; P=0.01), and ICA radius at the bifurcation (−7.68° per change in mm; 95% CI, −9.81 to −5.52; P<0.001). Factors that were independently associated with ICA radius were age (slope 0.01 mm/year increment; 95% CI, 0.15 to −0.02; P=0.01), diabetes (difference=−0.25 mm; 95% CI, −0.45 to −0.05; P=0.01), male sex (difference=0.0301 mm; 95% CI, 0.121–0.480; P<0.01), and ICA angle (slope=−0.02 mm per degree change; 95% CI, −0.02 to −0.01; P<0.01).

Table 2. Univariable Factors Associated With Carotid Artery Stenosis and ICA Angle

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td>Age, y</td>
<td>1.05 (1.03–1.07)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.73 (1.08–2.76)</td>
<td>0.02</td>
</tr>
<tr>
<td>Traditional risk factors</td>
<td>Hypertension</td>
<td>2.31 (1.44–3.72)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.85 (1.15–2.96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.87 (1.11–3.16)</td>
<td>0.02</td>
</tr>
<tr>
<td>Carotid bifurcation geometry</td>
<td>ICA angle</td>
<td>1.05 (1.04–1.07)</td>
</tr>
<tr>
<td>Bifurcation angle</td>
<td>1.02 (1.00–1.03)</td>
<td>0.01</td>
</tr>
<tr>
<td>Carotid bifurcation anatomy</td>
<td>ICA radius at the bifurcation</td>
<td>0.20 (0.14–0.29)</td>
</tr>
</tbody>
</table>

Table 3. Independent Factors Associated With Carotid Artery Stenosis

<table>
<thead>
<tr>
<th>Covariates</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic factors</td>
<td>Age, y</td>
<td>1.03</td>
</tr>
<tr>
<td>Male sex</td>
<td>2.63</td>
<td>0.427–4.85</td>
</tr>
<tr>
<td>Traditional risk factors</td>
<td>Smoker</td>
<td>1.427–4.85</td>
</tr>
<tr>
<td>Carotid bifurcation anatomy</td>
<td>ICA radius at the bifurcation</td>
<td>0.21</td>
</tr>
<tr>
<td>Carotid bifurcation geometry</td>
<td>ICA angle</td>
<td>1.03</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery.
A limitation of our study is its retrospective nature, cross-sectional design, and consequent possibility of selection bias. The majority of the patients came from vascular and stroke clinics in a tertiary hospital. As a result of this, these patients were likely at higher vascular risk than the general population. Therefore, our results may need to be examined and validated in different samples. Furthermore, a causal relationship between carotid artery geometry and disease may best be demonstrated in a longitudinal study. However, the finding of an independent association of geometry and anatomy to ICA stenosis raises interesting leads to pursue in explaining mechanisms of ICA stenosis, particularly with regard to innate risk factors. The strengths of our study were the relatively large sample, the use of cluster regression taking into account paired artery data, and importantly a highly accurate segmentation method for carotid arteries.

In this study we have not assessed the effect of the Glagov compensatory enlargement mechanism on carotid artery stenosis. The Glagov phenomenon is an important mechanism to maintain the size of the arterial lumen in the face of progression of atherosclerosis but can be difficult to assess with CTA. Atherosclerotic plaque can be difficult to measure automatically when using CTA. This is because atherosclerotic plaque has tissue density very similar to the surrounding tissue. By contrast, measurement of the arterial lumen is relatively easy because the contrast agent illuminates the arterial lumen.

In summary, in high-risk vascular patients, carotid artery anatomy and geometry are independently associated with ICA stenosis. These intrinsic factors need to be considered in future studies of the mechanisms underlying development of carotid artery atherosclerosis.

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Disclosures
None.

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