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

Thanh G. Phan, FRACP, PhD; Richard J. Beare, PhD; Damien Jolley, MSc (Epidemiol), MSc (Stats); Gita Das, PhD; Mandy Ren, MBBS; Kitty Wong, RN; Winston Chong, FRANZCR; Matthew D. Sinnott, PhD; James E. Hilton, PhD; Velandai Srikanth, FRACP, PhD

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 artery 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. The “traditional” Framingham risk factors for atherosclerotic disease do not explain differences in disease prevalence between vascular beds (carotid versus mesenteric vascular bed), side-to-side variation in carotid artery atherosclerotic disease in the same individual, interracial differences in the location of plaque along the carotid artery, or sex differences in carotid artery atherosclerosis. 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. By contrast, low wall shear stress predominates at the outer aspect (lateral wall) of the ICA 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. These data come from studies comparing carotid geometry in young people with older healthy subjects rather than directly studying people with atherosclerotic disease. Consequently, the association of carotid artery geometry with carotid artery stenosis is
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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 the 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.

Statistical Analysis
We used the intraclass correlation coefficient and a random effects model to compare semiautomated and manual segmentation and the similarity index to test voxel agreement. The comparisons were interpreted using the scales of Landis and Koch. Only variables with a P-value <0.10 on univariable analysis were entered into multivariable models. Based on associations seen in multivariable analysis, we performed post hoc analyses to explore the relationships of relevant carotid anatomy and geometry variables with clinical and demographic factors. Analyses were performed using Stata Version 11.

Results
Demographics
There were 178 patients, mean age 68.4 years (SD, 14 years), with 116 males (65%). Thus, there were 178 paired arteries available for this analysis. A high proportion of the patients (61.8%, n=110) had a history of transient ischemic attack or ischemic stroke as an indication for CTA. The rest had CTA performed using axial CTA source images. For the regression model, we empirically dichotomized stenosis as <30% or ≥30% similar to previous work. To determine asymmetry between the paired carotid arteries, the arteries were categorized as normal, mild (10%–49% stenosis), moderate (50%–80%), and severe (≥81%) based on examination of the distribution of the data. Using this ordinal classification of arterial stenosis, we conservatively calculated the side-to-side asymmetry by subtracting 1 from the other.

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), CCA radius at the bifurcation (OR, 1.02 per per mm decrement; 95% CI, 1.00–1.03), CCA 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 diameter ratio; 95% CI, 0.003–0.016) 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).

### Discussion

We have demonstrated an independent contribution of carotid anatomy and geometry to the presence of carotid artery stenosis in a cross-sectional study of patients with high vascular risk undergoing CTA. In conjunction with the anatomy at the bifurcation, a greater ICA angle may predispose the carotid artery to the effect of proatherosclerotic effect of hemodynamic forces and contribute to the development of atherosclerosis. Carotid anatomy and geometry represent risk factors for carotid artery atherosclerosis intrinsic to the individual. In addition to traditional factors, these intrinsic factors may be of help in very early identification patients at high risk of developing carotid artery atherosclerosis for aggressive intervention.

Our finding is that larger ICA angle (a measure of carotid geometry) is independently associated with higher degree of ICA stenosis and that age, hypertension, and ICA radius also influence ICA angle. These findings extend previous work involving healthy elderly individuals (mean age, 63 years; n=25) showing less variation in ICA angle, bifurcation angle, and arterial tortuosity in older people compared with healthy younger individuals (mean age, 24 years; n=25). Simulation studies have found that larger ICA angles or larger bifurcation angles but not ICA planarity are associated with lower wall shear stress on the sinus wall and higher oscillatory forces.

### Table 2

<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 (β)</td>
<td>0.42 (0.26–0.57)</td>
</tr>
<tr>
<td>Traditional risk factors</td>
<td>Hypertension</td>
<td>10.40 (5.89–14.92)</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia</td>
<td>5.09 (0.82–9.36)</td>
</tr>
<tr>
<td></td>
<td>Ischemic heart disease</td>
<td>3.98 (0.44–8.40)</td>
</tr>
<tr>
<td>Carotid bifurcation geometry</td>
<td>Bifurcation angle</td>
<td>0.60 (0.52–0.68)</td>
</tr>
<tr>
<td>Carotid bifurcation anatomy</td>
<td>ICA radius at the bifurcation</td>
<td>8.95 (11.06 to −6.84)</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery.

### Table 3

<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>
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<tr>
<td></td>
<td>Male sex</td>
<td>2.63</td>
</tr>
<tr>
<td>Traditional risk factors</td>
<td>Smoker</td>
<td>2.44</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.
tery index. It was noted that abnormal wall shear stress was greater in arteries with an ICA angle >25° with greater exposure of the outer aspect of the ICA to the effects of low wall shear stress. In flow simulation study in other vascular bed such as the aortic T-junction, investigators described that “In obtuse angle T-junction, the stagnation point shifted from the flow divider into the side tube, enhancing the flow disturbance there.” In our study, the group with no ICA stenosis had a mean ICA angle of 23.3°, whereas the groups with ICA stenosis had an ICA angle >31.3° (Figure 2). Thus, there may be some interplay between the carotid artery anatomy and geometry in the genesis of the abnormal hemodynamic forces that play a role in atherosclerosis. In this study, we have not been able to replicate a previous observation regarding the independent association between ICA–ECA angle and plaque. A major difference between that study and ours is the use of different imaging modality between the 2 studies and different outcome measures (plaque versus arterial stenosis).

Carotid artery bifurcation anatomy, in the form of ICA radius at the origin, ICA volume, and ICA–CCA diameter, is independently associated with ICA stenosis in our patients. In addition, the asymmetry of ICA stenosis in this patient group lent credence to suggestions regarding the importance of asymmetry in the area ratio at the carotid bifurcation and might help to explain intraindividual asymmetry in carotid atherosclerosis. It can be argued that ICA radius and ICA stenosis may be correlated because they are merely measures of the same construct. However, we used different methods to measure the minimum ICA radius and the ICA radius at the bifurcation to reduce the chance of obtaining the 2 measures at the same site. Furthermore, the finding that the CCA radius at the bifurcation was also independently associated with ICA stenosis (when the ICA radius term was removed from the model) suggested that the intrinsic anatomy at the bifurcation predisposed this region to the type of disturbed flow that promotes atherosclerosis. Our finding is consistent with earlier works on a glass model of aortic T-junction in which investigators proposed that a decrease in the diameter ratio distal to the bifurcation was associated with turbulent flow.

Our finding is consistent with earlier pathological studies comparing carotid anatomy in 60 control and 40 disease subjects and 2 angiographic studies totaling 46 subjects. Taken together in context, these findings suggest that further attention may be needed to the anatomy at critical sites within the carotid artery, particularly in the inflow and outflow areas at the carotid bifurcation. These regions may modulate the local hemodynamic forces important in carotid atherosclerosis. Flow modeling studies shed more light on this issue, showing that the anatomy of the carotid artery (smaller ratio of the diameter of ICA to CCA at the carotid bifurcation) predisposes the outer aspects of the ICA to the effect of low and oscillatory shear stress. This correlates with findings of intimal thickening on the lateral and outer aspects of the ICA. After recanalization procedures to modify the inflow and outflow region at the carotid bifurcation, fluid dynamic simulation showed that parameters such as wall shear stress and oscillatory shear index returned to normal. 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.

Sources of Funding
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Disclosures
None.

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

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<tbody>
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<tr>
<td>Age (y)</td>
<td>1.05 (1.03–1.07)</td>
<td>&lt;0.01</td>
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<td>Male sex</td>
<td>1.73 (1.08–2.76)</td>
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<td>Hypertension</td>
<td>2.31 (1.44–3.72)</td>
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<td>Smoker</td>
<td>1.85 (1.15–2.96)</td>
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<td>Diabetes</td>
<td>1.87 (1.11–3.16)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>1.80 (1.14–2.84)</td>
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<td>Carotid bifurcation anatomy</td>
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<td>ICA radius at the bifurcation</td>
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Univariable Associations of ICA Angle

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<td>Age (β)</td>
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<td>Ischemic heart disease</td>
<td>4.98 (0.44–8.40)</td>
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<td>Bilateral angle</td>
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<td>&lt;0.001</td>
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ICA indicates internal carotid artery.