Internal Carotid Artery Angle of Origin
A Novel Risk Factor for Early Carotid Atherosclerosis

Matthias Sitzer, MD; Damir Puac, MD; Alexandra Buehler, MD; Donata A. Steckel, MD; Stephan von Kegler, MD; Hugh S. Markus, FRCP; Helmut Steinmetz, MD

Background and Purpose—Established “systemic” vascular risk factors do not fully explain the occurrence of atherosclerosis at the carotid bifurcation. Local anatomic and hemodynamic factors may also influence the initiation of the atherosclerotic process. We determined whether the angle of internal carotid artery (ICA) origin is a risk factor for early atherosclerosis.

Methods—In 1300 individuals from a normal population aged 40 to 70 years, we measured both carotid intima-media thickness (IMT) at 3 arterial sites (common carotid artery; carotid bifurcation; ICA bulb) and the presence of any atherosclerotic plaque within the ICA bulb bilaterally by means of high-resolution ultrasound. A standardized transverse insonation was used to determine the angle of ICA origin, expressed as the angle of rotation relative to the external carotid artery.

Results—This angle was positively associated with ICA bulb IMT but not with IMT at other sites. After we controlled for age, sex, and other cardiovascular risk factors, a dorsal/dorsomedial ICA origin (angle ≥60°) conferred an odds ratio for having an ICA bulb IMT in the highest quartile of 2.99 (95% CI, 1.86 to 4.83) on the left and 2.01 (95% CI, 1.31 to 3.09) on the right side (both P<0.001). A similar relationship was found for plaque; odds ratios on multivariate analysis were 3.67 (95% CI, 1.49 to 9.03) on the left and 2.07 (95% CI, 1.10 to 4.83) on the right side (both P=0.035).

Conclusions—This study suggests that the angle of ICA origin may be an independent risk factor for early atherosclerotic changes at the ICA bulb. This new hypothesis should be tested in prospective studies. (Stroke. 2003;34:950-955.)

Key Words: atherosclerosis ■ carotid arteries ■ carotid artery plaque ■ epidemiology ■ ultrasonography

The internal carotid artery (ICA) bulb is a predilection site for atheroma,1–3 and stenosis at its origin accounts for at least 10% to 15% of all ischemic strokes.4 Much of the risk of carotid atherosclerosis is not explained by conventional vascular risk factors.5 Other responsible factors remain unknown. Considerable evidence suggests that local hemodynamic factors play a role in the pathogenesis of atheroma at the carotid bifurcation, and these are likely to be influenced by anatomic variation.6 Therefore, normal anatomic variation of the carotid bifurcation between individuals could influence the initiation and progression of carotid atherosclerosis and account for some of the unexplained risk of carotid atherosclerosis.

This hypothesis is best examined in a normal population with early atheromatous changes because in the presence of severe stenosis secondary hemodynamic factors and adaptive changes of the vessel morphology may complicate interpretation. Therefore, in a large normal population sample, we examined whether the angle of ICA origin is a risk factor for early atherosclerosis. We estimated both intima-media thickness (IMT) and early atheromatous plaque using high-resolution duplex ultrasound.

Subjects and Methods

Study Population
All members of 2 German health insurance companies who lived within a radius of 50 km from 5 study sites in western Germany (n=35 608; mean age, 43.2 years; SD 18.5 years; 49.8% women) were invited to participate (Carotid Atherosclerosis Progression Study [CAPS]).7 Within a predefined time limit, 6962 subjects (19.6%; mean age, 51.0 years; SD 12.9 years; 50.9% women) agreed to participate. The first consecutive 1300 subjects enrolled in the study aged 40 to 70 years (mean age, 53.4 years; SD 7.7 years; 50.5% women) in whom there was no past history of stroke, transient ischemic attack, coronary heart disease, or peripheral arterial disease were included in this study.7 Vascular risk factors were assessed by means of a standardized computer-assisted interview technique. Risk factors determined included the following: duration of smoking (sum of all years smoked by both smokers and ex-smokers); history of arterial hypertension (treatment with antihypertensive medication or blood pressure >160 mm Hg systolic or >95 mm Hg diastolic); history of diabetes mellitus; and body mass index (BMI).7,8 Additionally, fasting (>10 hours) blood samples were drawn from each subject, and serum total cholesterol was determined enzymatically with the use of a commercial kit (Boehringer Mannheim). Informed consent was obtained from all participants before study entry. The study was approved by the local institutional review committee.
Baseline demographic characteristics of the population were as follows: 309 (23.8%) were hypertensive, 36 (2.8%) had diabetes mellitus, 248 (19.1%) were current smokers, and 459 (35.3%) were ex-smokers. Mean duration of smoking was 29.5 (SD 9.4) years among smokers and 17.9 (SD 10.3) years among ex-smokers. Mean BMI was 27.1 (SD 4.2) kg/m²; mean total cholesterol was 219.9 (SD 38.5) mg/dL.

Ultrasound Imaging
For ultrasonic examinations, a 7.5- to 10.0-MHz linear array transducer was used (P700SE, Phillips Medical System). Preprocessing configurations (log gain compensation [60 dB] and image persistence) were held constant during all examinations. The gain was adjusted so that the least dense arterial wall interface was just visible. With the use of antero-oblique insonation, far-wall carotid IMT was visualized within the common carotid artery (CCA IMT) 20 to 60 mm proximally from the flow divider, the carotid bifurcation (bifurcation IMT) 0 to 20 mm proximally from the flow divider, and the ICA bulb (ICA bulb IMT) 0 to 20 mm distally from the flow divider, bilaterally. The images were digitally captured during the systole of a single heartbeat on a personal computer with the use of S-VHS PC-EYE 2-frame grabber (ELTEC Elektronik GmbH) in 16-bit red-green-blue packing mode (748×576 pixel) for offline measurements. Vertical and horizontal calibration measurements were performed every 100th measurement with the use of an ultrasound assurance phantom.

Carotid IMT measurements were performed offline with the use of automated image analysis software (Matlab, The Mathworks, Inc). With this software, both the blood/intimal and the medial/adventitial borderline were automatically detected with a gray value–based edge detection algorithm combined with higher-degree polynomial fitting along these borders. The mean distance between the blood/intimal and the medial/adventitial interfaces was calculated and defined as the IMT of the corresponding arterial segment. The mean length of the arterial segment in which IMT was determined was 14.35 mm for the left CCA IMT, 12.85 mm for the right CCA IMT, 5.75 mm for the left bifurcation IMT, 5.8 mm for the right bifurcation IMT, and 3.45 mm for the ICA bulb IMT on both sides.

Interobserver reproducibility was determined in a separate sample of 15 subjects (54 arterial segments) in whom carotid IMT was independently depicted and measured by 4 blinded observers. Linear regression analyses revealed high correlation coefficients (r = 0.92 to 0.99), and according to the method described by Bland and Altman, the 2 SD of the difference between 2 observers varied between 0.03 and 0.06 mm. Additionally, the intraobserver retest reproducibility was determined from repeated examinations of 35 subjects (102 arterial segments) by 3 independent observers; the time interval between both examinations ranged from 4 to 6 months. Linear regression showed high correlation (r = 0.91 to 0.98). The 2 SD of the difference between the first and second examination varied between 0.04 and 0.06 mm. For IMT measurements, image quality was sufficient for analysis in the following number of cases: left CCA IMT, n = 1201; right CCA IMT, n = 1201; left bifurcation IMT, n = 1043; right bifurcation IMT, n = 1057; right ICA bulb IMT, n = 1263; right ICA bulb IMT, n = 1226.

At the same time, the extent of any carotid plaque was measured by means of a previously described method that has been applied previously in large-scale community studies. Carotid plaque was defined as any obscuration of the free luminal vessel surface with a distance between the luminal-interface and the medial-adventitial interface > 1.7 mm. In the presence of plaque, the degree of ICA stenosis was determined as the maximum cross-sectional luminal area reduction. Interobserver reliability for 4 different observers for 30 carotid plaques was determined (linear regression r = 0.76 to 0.90; 2 SD of the mean of the difference between 2 observers was 5% to 10%). Of the 1300 subjects included in the study, 40 had ICA plaque formation on the left side (> 50% luminal narrowing; n = 5), and 49 had plaque on the right side (> 50% luminal narrowing; n = 8).

The angle of ICA origin was determined from a standardized transverse insonation of the carotid system, as displayed in Figure 1. The transducer was oriented so that the lateral side of the artery was displayed on the left for both sides. The transducer was adjusted until a line connecting the anterior border of the thyroid gland and the dorsal border of the sternocleidomastoid muscle was parallel with the horizontal margin of the ultrasound image at the level of the proximal CCA (1). The transducer was then moved cranially (2, 3) to a level where the ECA and the ICA (*) were clearly distinguishable (4). A line was then drawn connecting the center of the lumen of each vessel, and the angle between this line and the horizontal was used as a measurement of the ICA angle of origin. Left, Typical example of a lateral origin of the ICA (angle 0° to 15°) is shown; right, part of a typical example of a dorsomedial ICA origin (angle 135°) is shown.
for 2 different observers for 28 carotid bifurcations revealed a high concordance by linear regression \((r = 0.87)\).

**Statistical Analyses**

The relationships between anatomic variability of the ICA origin, carotid IMT, and ICA plaque were determined. Initially univariate analysis was performed, followed by multivariate analysis with the use of logistic regression to allow for controlling of other vascular risk factors. The relationship between angle of ICA origin and age, sex, and vascular risk factors was then evaluated by linear regression analysis. If several consecutive analyses were performed, a Bonferroni correction was applied, and the level of significance was \(\alpha\)-adjusted. In a subgroup of subjects with a strict lateral ICA origin, we measured ICA bulb IMT in different insonation angles. To compare these IMT values intraindividually, we calculated the intraclass correlation coefficient. All statistical analyses were performed with the use of SPSS (10.0.7) software.

**Results**

**Anatomic Variability of ICA Origin**

The distribution of the angle of ICA origin across the entire study population is displayed in Figure 2. The majority of ICAs originated in a lateral position with the angle lying between \(-60^\circ\) and \(+60^\circ\) for 94% of origins on the left side and 91.8% on the right side. A dorsal/dorsomedial origin of the ICA was significantly more frequent on the right side (6.0% versus 8.2%; \(P = 0.001\), Wilcoxon test).

**Anatomic Variability of ICA Origin, Carotid IMT, and ICA Plaque**

In a first step, the prevalence of a dorsal/dorsomedial ICA origin (\(\geqslant 60^\circ\)) was determined for IMT quartiles for each arterial segment on both sides (Table 1). This analysis revealed that a dorsal/dorsomedial ICA origin was particularly associated with a markedly increased ICA bulb IMT (in the upper quartile). The mean ICA bulb IMT in increasing 15° categories of ICA angle of origin is depicted in Figure 3. This demonstrates the nonlinear nature of the relationship and shows that ICA bulb IMT increased markedly above an angle of \(60^\circ\). There was a trend toward smaller ICA bulb IMT values above \(120^\circ\), but the number of subjects in these

![Figure 2. Distribution of angle of ICA origin on both sides for a middle-aged (40 to 70 years) community population (n = 1300). A strict lateral origin corresponds to 0°.](image)

![Figure 3. Mean ICA bulb IMT in increasing 15° categories of ICA angle of origin. Error bars show corresponding SD. Extreme categories (165°, 180°) are not shown because of the very small number of subjects.](image)

**TABLE 1. Prevalence of Dorsal/dorsomedial ICA Origin for Increasing Quartiles of the Corresponding IMT Distribution at 3 Different Arterial Sites**

<table>
<thead>
<tr>
<th>IMT Quartile</th>
<th>Dorsal/Dorsomedial ICA Origin, yes/no</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CCA</td>
<td>BIF</td>
</tr>
<tr>
<td>1st</td>
<td></td>
<td>16/291</td>
<td>16/271</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5.5)</td>
<td>(5.9)</td>
</tr>
<tr>
<td>2nd</td>
<td></td>
<td>20/299</td>
<td>9/265</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6.7)</td>
<td>(3.4)</td>
</tr>
<tr>
<td>3rd</td>
<td></td>
<td>12/316</td>
<td>15/250</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.8)</td>
<td>(6.0)</td>
</tr>
<tr>
<td>4th</td>
<td></td>
<td>21/296</td>
<td>19/271</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7.1)</td>
<td>(7.0)</td>
</tr>
<tr>
<td>(P^*)</td>
<td></td>
<td>0.420</td>
<td>0.383</td>
</tr>
</tbody>
</table>

Dorsal/dorsomedial internal carotid artery (ICA) origin is defined as an angle of origin \(\geqslant 60^\circ\). Values in parentheses are percentages.

\(*\chi^2\) statistics; because 6 consecutive tests were performed, a \(P\) value of 0.05/6 = 0.008 has been used to indicate significance.

CCA indicates common carotid artery; BIF, carotid bifurcation; BULB, ICA bulb.
extreme groups was very small. On logistic regression analyses, a dorsal/dorsomedial ICA origin (≥60°) conferred an odds ratio (OR) for having an IMT in the highest quartile of 3.30 (95% CI, 2.09 to 5.21; P<0.001) for the left ICA bulb IMT and 2.24 (95% CI, 1.49 to 3.38; P<0.001) for the right ICA bulb IMT. These positive relationships remained after we controlled for age, sex, history of arterial hypertension, duration of smoking, history of diabetes mellitus, serum cholesterol, and BMI: left ICA, OR=2.99 (95% CI, 1.86 to 4.83); right ICA, OR=2.01 (95% CI, 1.31 to 3.09); P<0.001 for both sides. To further explore the relationship between a dorsal/dorsomedial ICA origin and elevated ICA bulb IMT, we performed intrapatient comparisons between the left and right sides in individuals with a dorsal/dorsomedial ICA origin on one side and a lateral origin on the other side. In 168 subjects with this combination, the mean ICA bulb IMT on the side with the dorsal/dorsomedial ICA origin was 1.05 mm (SD 0.58) compared with 0.91 mm (SD 0.44) on the side with a lateral origin (P=0.037, Wilcoxon test).

In contrast to the highly significant relationship between ICA bulb IMT and the angle of ICA origin, similar relationships were not found at other arterial sites. There was no relationship between angle of origin and CCA and bifurcation IMT, respectively (Table 1).

A similar relationship was found for carotid plaque. On univariate analysis, the OR for the presence of plaque associated with a dorsal/dorsomedial ICA origin was 4.06 (95% CI, 1.81 to 9.14; P=0.001) on the left and 2.27 (95% CI, 1.04 to 4.97; P=0.041) on the right. These associations persisted after we controlled for the aforementioned cardiovascular risk factors: left ICA, OR=3.67 (95% CI, 1.49 to 9.03); right ICA, OR=2.07 (95% CI, 1.10 to 4.83); P=0.035 for both sides.

In a subgroup of 20 subjects with a lateral origin of the ICA (angle between −30° and +30°), both far- and near-wall ICA bulb IMT values were determined by means of postero-oblique and lateral angles of insonation in addition to the standard antero-oblique insonation. The mean far-wall ICA bulb IMT was 0.61 mm (range, 0.4 to 1.0 mm) in antero-oblique, 0.61 mm (range, 0.4 to 0.9 mm) in lateral, and 0.60 mm (range, 0.4 to 1.1 mm) in postero-oblique insonation (intraclass correlation coefficient=0.78; 95% CI of intraclass correlation coefficient, 0.53 to 0.91; P<0.001). For the corresponding near-wall ICA bulb IMT, the mean was 0.61 mm (range, 0.3 to 1.1 mm) in antero-oblique, 0.62 mm (range, 0.4 to 0.85 mm) in lateral, and 0.62 mm (range, 0.4 to 1.1 mm) in postero-oblique insonation (intraclass correlation coefficient=0.91; 95% CI of intraclass correlation coefficient, 0.80 to 0.96; P<0.001).

### Table 2. Relationship of Age, Sex, Vascular Risk Factors, and the Angle of the ICA Origin on Both Sides as Determined by Multiple Regression

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Angle of ICA Origin (−60° to 180°)</th>
<th>B (95% CI of B)</th>
<th>P</th>
<th>B (95% CI of B)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td></td>
<td></td>
<td>Right</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>0.00</td>
<td>0.01</td>
<td></td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.13</td>
<td>(−0.01 to 0.01)</td>
<td>0.50</td>
<td>(0.00 to 0.02)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.12</td>
<td>(−0.26 to 0.00)</td>
<td>0.03</td>
<td>(−0.25 to 0.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>Duration of smoking, y</td>
<td>0.12</td>
<td>(−0.04 to 0.28)</td>
<td>0.05</td>
<td>(−0.21 to 0.15)</td>
<td>0.92</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>−0.15</td>
<td>(−0.54 to 0.23)</td>
<td>0.38</td>
<td>(−0.33 to 0.57)</td>
<td>0.94</td>
</tr>
<tr>
<td>Serum cholesterol, mg/dL</td>
<td>0.00</td>
<td>(0.00 to 0.00)</td>
<td>0.14</td>
<td>(0.00 to 0.00)</td>
<td>0.66</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>−0.01</td>
<td>(−0.03 to 0.01)</td>
<td>0.35</td>
<td>(−0.03 to 0.09)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Because 2 consecutive statistical procedures were performed, a P value of 0.05/2=0.025 has been considered as indicating statistical significance. Values given are B coefficients (95% CI of B) and the corresponding P value.

ICA indicates internal carotid artery.

Anatomic Variability of ICA Origin and Vascular Risk Factors

There was no relationship between age, sex, other cardiovascular risk factors, and ICA angle of origin (Table 2).

### Discussion

This study provides the first evidence that an “anomalous” ICA origin may be a novel risk factor for carotid atherosclerosis. A dorsal/dorsomedial ICA origin was associated with both increased ICA bulb IMT and the presence of plaque, and these relationships persisted after we controlled for other cardiovascular risk factors. Consistent relationships were found for both...
right and left ICA bulb IMT, but similar relationships were not found for CCA IMT or bifurcation IMT.

The site specificity of the relationship, which is present only for ICA bulb IMT, is consistent with a more dorsal angle of origin resulting in local hemodynamic changes, which themselves increase the risk of atherosclerosis. This is consistent with previous experimental work. It has been shown that intimal thickness around bifurcations is mainly modulated by local longitudinal wall shear stress. Studies of scale models of carotid bifurcations show that the normally axially aligned, unidirectional blood flow of the CCA changes at the bifurcation; complex secondary flow patterns consisting of vortices (or recirculating zones) develop at the bifurcation opposite the flow divider. Thereby, the blood flow features a stagnation point that oscillates in strength and position, leading to an alteration and reduction of the longitudinal wall shear. Unidirectional laminar flow, as seen on the side of the flow divider, is associated with relatively high shear stresses and sparing from adaptive intimal-medial thickening and atherosclerotic plaque development. One of the major determinants of the local shear stress at the ICA origin is the ratio between the outflow area of the carotid bifurcation, which is the sum of the cross-sectional areas of the ICA plus ECA, and the inflow area, which corresponds to the cross-sectional area of the CCA. Postmortem studies revealed a close relationship between the occurrence of intimal thickening or plaque formation and a reduced outflow/inflow ratio, suggesting that a greater outflow area covers longitudinal shear stress on the daughter vessels, promoting the local atherosclerotic process. These findings have been recently confirmed in a large-scale angiographic study. Furthermore, the insertion angle of the ICA may also influence local hemodynamics, leading to an extension of the flow separation zone with an increasing insertion angle. It is possible that the influence of the angle of ICA origin on local hemodynamics is partially mediated by the aforementioned factors.

A large portion of risk of carotid atherosclerosis, and approximately half of the variance in carotid IMT, is unexplained by cardiovascular risk factors. Recent studies suggest that much of this unexplained risk is mediated by genetic factors. A recent twin study has shown that carotid IMT has a high heritability. The anatomic configuration of the carotid bifurcation, including the angle of ICA origin, is likely to have a strong genetic component. Variation in this angle may therefore account for some of this unexplained genetic predisposition to increased IMT and plaque.

There is a possible alternative explanation for the relationship between ICA angle of origin and ICA bulb IMT. As mentioned above, around bifurcations an eccentric thickening of the intimal layer can occur, with a relative increase in thickness involving the wall opposite the flow divider. This thickening of both the parent and proximal daughter vessel can extend for a short distance along the length of the artery proximal and distal to the flow divider. In the case of a lateral origin of the ICA, if an antero-oblique angle of insonation is used, as in our study, the far-wall IMT is obtained from the dorsomedial wall of the ICA bulb near the flow divider. In contrast, as the angle of origin becomes more dorsal, the far-wall IMT is obtained from a wall segment that becomes more and more opposite to the flow divider. Therefore, our finding could merely be a consequence of the site of insonation and not reflect true increases in IMT. To exclude this explanation, in a subgroup of 20 subjects with a lateral ICA origin, we determined both the far- and near-wall IMT using 3 ultrasound insonation angles. There were no differences in near- and far-wall IMT when it was measured with different angles of insonation. This finding implies that eccentric thickening of the intimal layer opposite the flow divider does not influence the measurable IMT in our population. In addition, the relationship between ICA angle of origin and carotid plaque would not be explained by eccentric thickening of the intimal layer.

In this cross-sectional study we investigated associations in a large population-based cohort with mild atherosclerosis. We studied the first 1300 consecutively enrolled middle-aged individuals. The overall recruitment rate was 20%, which is in accord with previous IMT studies. There was no difference between the age and sex distribution of those who took part and nonresponders. Additional information on the risk factor profiles of nonresponders was not available. Our results provide the first evidence that the angle of ICA origin may be a novel risk factor for carotid atherosclerosis. However, whether this relationship is causal cannot be proven by a cross-sectional study design. This hypothesis now should be tested in prospective populations.

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References


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