Geometry of the Carotid Bifurcation Predicts Its Exposure to Disturbed Flow

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Background and Purpose—That certain vessels might be at so-called geometric risk of atherosclerosis rests on assumptions of wide interindividual variations in disturbed flow and of a direct relationship between disturbed flow and lumen geometry. In testing these often-implicit assumptions, the present study aimed to determine whether investigations of local risk factors in atherosclerosis can indeed rely on surrogate geometric markers of disturbed flow.

Methods—Computational fluid dynamics simulations were performed on carotid bifurcation geometries derived from MRI of 25 young adults. Disturbed flow was quantified as the surface area exposed to low and oscillatory shear beyond objectively-defined thresholds. Interindividual variations in disturbed flow were contextualized with respect to effects of uncertainties in imaging and geometric reconstruction. Relationships between disturbed flow and various geometric factors were tested via multiple regression.

Results—Relatively wide variations in disturbed flow were observed among the 50 vessels. Multiple regression revealed a significant ($P<0.002$) relationship between disturbed flow and both proximal area ratio ($β=0.5$) and bifurcation tortuosity ($β=-0.4$), but not bifurcation angle, planarity, or distal area ratio. These findings were shown to be insensitive to assumptions about the flow conditions and to the choice of disturbed flow indicator and threshold.

Conclusions—Certain geometric features of the young adult carotid bifurcation are robust surrogate markers of its exposure to disturbed flow. It may therefore be reasonable to consider large-scale retrospective or prospective imaging studies of local risk factors for atherosclerosis without the need for time-consuming and expensive flow imaging or CFD studies. (Stroke. 2008;39:2341-2347.)

Key Words: atherosclerosis ■ hemodynamics ■ imaging ■ MRI ■ carotid artery ■ risk factors

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The geometric risk hypothesis also hinges on the assumption of a direct relationship between exposure to disturbed flow and purported geometric risk factors. This too has not been tested directly. Rather, it has been intuited from parametric studies of often-idealized vascular models for which geometric factors have been varied independently. The power of such relationships, if indeed they exist, remains unclear, which may explain the lack of consensus regarding the role of geometric factors in the development of atherosclerosis.

The objective of this study was therefore to test these often-implicit assumptions in a statistically meaningful manner. In so doing, we aimed to determine whether investigations of local risk factors can indeed rely on the use of surrogate geometric markers of disturbed flow.

Subjects and Methods

The “subjects” of this study were 50 carotid bifurcation lumen geometries digitally reconstructed from black blood MRI of 25 ostensibly healthy volunteers (24±4 years; range, 19 to 38 years; 14:11 M:F), whose carotid bifurcation geometries were presumably...
free of secondary effects of atherosclerosis. A representative geometry is presented in Figure 1, which also shows transverse sections through the common (CCA), internal (ICA), and external (ECA) carotid arteries used for later quantitative analysis. Details of the imaging and lumen reconstruction, as well as the definition and quantification of Geometry

Computational Fluid Dynamics
Pulsatile blood flow dynamics were simulated for each of the 50 carotid bifurcation geometries using a well-validated finite-element-based computational fluid dynamics (CFD) solver. Quadratic tetrahedral-element meshes were generated by a commercial mesh generator (ICEM-CFD; ANSYS) using a uniform node spacing of 0.2 mm, previously shown to be sufficient for resolving wall shear stresses. Fully-developed (Womersley) velocity boundary conditions were imposed at the CCA inlet and ECA outlet; traction-free boundary conditions were imposed at the ICA outlet. Rigid walls and a constant blood viscosity of 3.5 mm²/s were assumed. Further details of the meshing and specification of boundary conditions are provided elsewhere.

Flow rates were not available for these subjects, so inlet/outlet pulsatile flow rates were defined for each case based on the following observations: flow waveform shape is relatively consistent across normal subjects; and mean flow rate scales approximately with lumen cross-sectional area. Inlet/outlet flow rate waveforms were first defined for an average case by combining the normal ICA flow waveform of Ford et al. with the time-varying ICA:CCA flow division data of Marshall et al. (Figure 2). Then, for each individual case, these average CCA and ICA waveforms were scaled by, respectively, the ratios of the CCA3 and ICA5 cross-sectional areas (see Figure 1) to their respective averages over the 50 cases. The individual ECA waveform was then calculated as the difference between the individual CCA and ICA waveforms. The present study focused on simulations carried out using these scaled flow rates; however, simulations were also carried out using the same average flow waveforms (ie, those in Figure 2) across all 50 cases, as a way of testing the sensitivity of the findings to the assumed flow conditions.

CFD simulations were carried out using up to 4800 timesteps per cardiac cycle, and 3 cycles were required to damp initial transients. For each CFD model we then computed the surface distributions of the following hemodynamic parameters: time-averaged wall shear stress magnitude (WSS) and oscillatory shear index (OSI). OSI, a measure of directional changes in wall shear stress over the cardiac cycle, is a dimensionless quantity. WSS, on the other hand, is a dimensional quantity, and its baseline value depends on an individual’s vessel size and flow rate. For this reason, and consistent with the notion of disturbed flow as “flow that differs from the ‘undisturbed’ pulsatile flow that is seen in relatively straight vessel segments,” for each case WSS was normalized by its nominal value at the respective CCA3 section. To ensure a consistent axial extent for all cases—the length of each model depended on the number of MRI slices acquired for each subject—each CFD model was clipped at its respective CCA3 and ICA5 sections before further quantitative analysis.

Quantification of Disturbed Flow
While it is widely accepted that low and oscillatory shear promotes an atherogenic endothelial cell phenotype, there remains no definitive quantitative relationship between disturbed flow and risk of atherosclerosis. Following the approach of Stone et al., we pooled together the surfaces of all 50 models, and identified threshold values of OSI and normalized WSS to which up to 80% or 90% of this cumulative surface was exposed. (Two different percentiles were chosen to test the sensitivity of the findings to choice of threshold.) Then, for a given model, disturbed flow was quantified as its surface area (SA) exposed to normalized WSS below (or OSI above) the respective threshold values. Finally, to factor out the influence of vessel size—for the same geometry, a larger vessel will experience more disturbed flow—a relative exposure (SArel) was defined as this absolute exposure (SAabs) divided by the total surface area of the respective model.

Quantification of Geometry
A variety of geometric factors defining each bifurcation was extracted automatically, as described previously. Here we focused on those factors characterizing the bifurcation as a whole (Figure 1): angle, planarity, tortuosity, and area ratio. Tortuosity was defined as L/D, where L is the length of the centerline from CCA3 to ICA5,
and D is the straight-line distance between these 2 points. (Tortuosity may thus be thought of as the fractional extra distance blood must travel in the real vessel versus a theoretical, straight-line path.) Previously, area ratio was defined as the sum of the ECA1 and distal ICA5 section areas, divided by the CCA3 section area, these locations chosen to be consistent with Schulz and Rothwell.4 Noting that disturbed flow typically occurs near the level of the flow divider, the present study also defined an area ratio using the more proximal ICA1 section instead. Hereafter these distal and proximal area ratios are referred to as AR5 and AR1, reflecting the ICA section used in their respective definitions. Descriptive statistics for tortuosity and AR1 were 0.025 ± 0.018 (range 0.009 to 0.058) and 1.82 ± 0.28 (range 1.17 to 2.42), respectively (see Thomas et al for angle, planarity, and AR5).

Statistical Analysis
Interindividual variations were quantified as the standard deviations of both SAabs and SArel across the 50 cases. The magnitude of these variations was contextualized by similarly calculating these quantities for 3 separate cases for which reproducibility of the entire image-based CFD process was previously assessed via 3 repeated acquisitions.17 Specifically, interindividual variations were quantified as the square root of the within-subject variances in SAabs and SArel averaged across those 3 subjects.

Multiple linear regression was used to quantify the relationship between exposure to disturbed flow (SArel) and angle, planarity, tortuosity, and either of AR5 or AR1 as independent predictors. The overall quality of the regression was assessed using Pearson's correlation coefficient, adjusted by the number of independent predictors (R^2_pr). The relative contributions of the geometric predictors was determined from the standardized (β) regression coefficients.

These analyses were performed separately for the 4 permutations of hemodynamic parameter and threshold criterion (hereafter identified as WSS80, WSS90, OSI80, and OSI90) to test the sensitivity of findings to the choice of disturbed flow indicator. Statistical analyses were carried out using Microsoft Excel 2003 with StatistiXL v1.7 add-on.

Results
Interindividual Variations in Disturbed Flow
Figure 3 confirms, qualitatively at least, the wide interindividual variations in low and oscillating shear among the 50 normal carotid bifurcations studied. Models for some cases (eg, 2L and 24R) showed almost no disturbed flow, whereas for others (eg, 11L and 23L) much of the bifurcation region was exposed to disturbed flow. Still, in most cases, disturbed flow was concentrated around the outer walls of the ICA and ECA as expected.18,19 Moreover, on a case-by-case basis, the extent and distribution of low normalized WSS appeared to largely mirror that of high OSI, which was confirmed by correlation analysis: Pearson R^2 values were 0.642 (WSS80 versus OSI80) and 0.526 (WSS90 versus OSI90), both highly significant (P < 0.0001).

As enumerated in Table 1, interindividual variations in disturbed flow were uniformly above the level of intraindividual variations attributable to uncertainty in the CFD model geometries, irrespective of the threshold or hemodynamic parameter. As quantified by SAabs, these interindividual variations were typically 2 to 3 times greater than the intraindividual variations. Even after adjusting for individual vessel size, interindividual variations in SArel were still 1.5 to 2 times greater.

Relationship Between Geometry and Disturbed Flow
As summarized in Table 2, multiple regressions revealed a significant inverse relationship between exposure to disturbed flow and vessel tortuosity, but not angle, planarity or distal area ratio (AR5), irrespective of the hemodynamic parameter or threshold criterion. Multiple regressions using AR1 instead of AR5 (Table 3) revealed that the combination of tortuosity and proximal area ratio was a far stronger predictor of exposure to disturbed flow.

Discussion
The present study has demonstrated wide interindividual variations in the exposure of the young adult carotid bifurcation to disturbed flow—at least wide with respect to variations that could be attributed to uncertainty in imaging and reconstruction processes. This is significant, because our previous work had suggested the difficulty of reconciling narrow variations in young adult carotid bifurcation geometry with the concept of local risk for atherosclerosis.5 Nevertheless, although our findings are consistent with this idea, in no way do they prove it.

Of course, the presence of wide variations in normal carotid bifurcation hemodynamics is widely appreciated, especially by sonographers and radiologists, as demonstrated by Steinke and colleagues.19 In that study, disturbed flow was assessed semiquantitatively from the durations and extents of retrograde flow observed in 2-dimensional longitudinal and cross-sectional color Doppler ultrasound images. In the present study, a combination of MRI and CFD was used to determine the 3-dimensional distributions and relative intensities of the disturbed wall shear stresses themselves.

More importantly, our study has shown that the exposure of an individual carotid bifurcation to disturbed flow can be predicted by a relatively simple relationship:

SA_{rel} = AR1 - C \times \text{Tortuosity}

where C is a positive constant falling between 19 and 27, depending on the choice of disturbed flow indicator. In other words, bifurcations with larger proximal area ratios are more susceptible to disturbed flow, but this can be ameliorated by the presence of a curved or tortuous path along the CCA and ICA. Proximal area ratio (AR1) may itself be viewed as a measure of bifurcation flare, which is well known to promote flow separation,20 the consequence of which is low and oscillating shear. Similarly, tortuosity may be seen as an indirect marker of swirling flow, which can be instrumental in suppressing flow disturbances21 (and perhaps their consequences22).

The finding of a significant relationship between area ratio and exposure to disturbed flow echoes conclusions drawn from idealized model studies.6,23 On the other hand, previous model studies had also suggested an important role for branch angle,8 which is contrary to our finding here. This may be attributed to the fact that only angle was varied in that study, whereas, strictly speaking, one would have to probe an N-dimensional space of possible geometries to investigate the relative importance of N parameters. For example, Karino and Goldsmith demonstrated the relative importance of di-
ameter ratio versus angle on vortex formation using an idealized bifurcation geometry for which those two geometric parameters were each varied over a wide range. Here we were able to efficiently sample a potentially huge 4-dimensional parameter space by using a representative set of actual carotid bifurcation geometries.

Our results are also consistent with the geometric risk study of Fisher and Fieman, which found that intraindividual variations in exposure to low and oscillating shear for the 50 cases, identified at the bottom left of each panel. Dark (red) highlights those areas exposed to low normalized WSS (left of each panel) and high OSI (right of each panel) outside the 90th percentile. The lighter (yellow) penumbra incorporates areas exposed outside the 80th percentile. Translucent rendering highlights disturbed flow on the back walls of the models. CFD models are shown clipped at the CCA3 and ICA5 sections and not necessarily to the same physical scale. The full CFD domains are shown to scale in Thomas et al.
individual asymmetry in stenosis severity was associated with area ratio asymmetry, but not branch angle asymmetry. In an earlier study,25 Harrison and Marshall found no significant difference between the bifurcation angles of normal patients versus those with (angiographic) plaque, but noted “the line of the common carotid and internal carotid artery was straighter in those with atheroma,” consistent with our finding of a significant inverse relationship between ICA-CCA tortuosity and disturbed flow. On the other hand Smedby and Bergstrand demonstrated the influence of tortuosity on the development of atherosclerosis26; however, that study was biased by our assumed flow conditions.

What remains then is the reliance on a scaling law to estimate the mean flow rates for each subject. Regarding the choice of scaling law (ie, flow rate scales with cross-sectional area14), we note that interindividual variations among the n=50 anatomically-scaled ICA flow rates (σ=54 mL/min, range 181 to 416) were remarkably consistent with interindividual variations in flow rates measured by phase contrast MRI (PC-MRI) in a separate group of n=17 young adults (σ=56 mL/min, range 167 to 445).13 Similarly, variations in the scaled ICA:CCA flow ratios (σ=0.49 to 0.91) compared favorably with those derived from independent PC-MRI measurements (σ=0.098, range 0.58 to 0.89; Dr Ian Marshall, unpublished data, 2007).

Although this circumstantial evidence supports our choice of scaling law, it ultimately says little about the sensitivity of our findings to the assumed flow rates and flow divisions. As noted in the Methods, to test this more directly we applied the model quality 

Table 2. Multiple Regressions of Exposure to Disturbed Flow (SAabs), With Angle, Planarity, Tortuosity, and Distal Area Ratio (AR5) as Independent Predictors

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<thead>
<tr>
<th>Model Quality</th>
<th>Standardized Coefficients</th>
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<tr>
<td></td>
<td>βWSS0</td>
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<tr>
<td>P Value</td>
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<tr>
<td>R², adj</td>
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<tr>
<td>P Value</td>
<td>0.049</td>
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<td>βWSS0</td>
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Use of fixed flow waveform shapes was justified by the observation that interindividual variations in carotid flow rate dynamics can be attributed mainly to variations in mean flow; variations in waveform shape are close to the level of measurement uncertainty or normal physiological fluctuations.13,32 Implicit in the use of fixed waveform shapes is a fixed heart rate, here set to 68 bpm. Younis et al33 reported “minimal” changes in OSI for a carotid bifurcation model exposed to resting (72 bpm) versus exercise (104 bpm) conditions, suggesting that the effect of more modest normal variations in heart rate can be considered negligible.

Modeling Assumptions and Potential Shortcomings

As noted in the Methods, a number of modeling assumptions (rigid walls, Newtonian rheology, fully-developed entry flow) were made to render the analysis tractable. These were considered reasonable, in the sense that they have been shown to have only a minor effect on the resulting carotid bifurcation flow dynamics.12,28–30 On the other hand, although it is widely accepted that flow rate has a similarly minor influence,31 we considered the possibility that our findings were biased by our assumed flow conditions.
to the assumed flow conditions and further reinforces the primacy of geometry in determining exposure of a vessel to disturbed flow.

Aside from the modeling assumptions, a potential shortcoming was that intraindividual variations used to contextualize our findings were based on data from a separate reproducibility study of three ostensibly normal, but elderly (74 to 77 years), subjects.17 Those subjects tended to have less disturbed flow, as evidenced by the higher normalized WSS and lower OSI threshold values enumerated in Table 1. Nevertheless, these data likely provide a conservative estimate of intraindividual variability for young adults since, in our experience anyway, image quality (and hence reconstruction variability) tends to be poorer for older subjects.

By design, our study also did not consider the spatial distribution of disturbed flow. For example, as demonstrated by Steinke and colleagues,19 and consistent with Figure 3, disturbed flow tends to be ICA-dominant, although often it is distributed circumferentially around the bifurcation. Interestingly, those authors also noted an association between flow separation and carotid bulb size, but not bifurcation angle, which parallels our finding of a relationship between SArel and carotid bulb size, but not bifurcation angle, which parallels our finding of a relationship between SArel and carotid bulb size, but not bifurcation angle.

Finally, absent a definitive quantitative relationship between disturbed flow and atherosclerosis risk, our study was forced to rely on a simple, threshold-based criterion to discriminate disturbed flow, albeit one informed by broadly-accepted qualitative criteria,1 and consistent with previous work.16 Nevertheless, our findings were robust to reasonable choices for the percentile-based thresholds. Our findings were also robust to the choice of hemodynamic parameter, although this was almost certainly a reflection of a strong correlation between normalized WSS and OSI. Although low and oscillatory shear is widely thought to promote endothelial dysfunction,1 there are other disturbed flow indicators (eg, based on WSS gradients,34 residence times,35 or WSS harmonic content36) that may ultimately be more closely linked to the underlying mechanisms. However, these too may also be strongly inter-related,37 something we are presently investigating with our models.

### Implications for Geometric/Hemodynamic Risk of Atherosclerosis

As noted above, the present study neither proves nor disproves the notion that individuals may be exposed to differential risk of atherosclerosis by virtue of their local arterial geometry or hemodynamics. Rather, like Schulz and Rothwell,4 we have confirmed a necessary, but not sufficient, condition for this local risk hypothesis, in this case that there do exist wide interindividual variations in exposure to disturbed flow. Moreover, this was demonstrated in a group for which secondary effects of atherosclerosis on geometry were presumably negligible.

A less abstract and more immediate implication of our findings is that, for studies aimed at elucidating the role of local risk factors in atherosclerosis, it may be unnecessary to acquire local hemodynamic data. This is important, as direct imaging of carotid bifurcation wall shear stresses remains a significant challenge.38 Similarly, although great advances have been made in the area of image-based CFD,39 such models usually require additional imaging data and remain cumbersome to construct and use. Historically, these constraints have made it difficult to carry out studies of sufficient size to control for other systemic risk factors. On the other hand, noninvasive, 3-dimensional imaging of the carotid bifurcation is becoming increasingly available and practical.40 This opens up the possibility of retrospective studies of local risk factors in atherosclerosis using routinely-acquired clinical images, or prospective studies where it might not be easy or cost-effective to acquire the data necessary for quantifying disturbed flow.

Lastly, it must be stressed that our findings in no way imply that the complexities of carotid bifurcation blood flow dynamics can be encoded into simple geometric factors such as area ratio or tortuosity. Rather, much like stenosis severity and aneurysm size are useful surrogate geometric markers of plaque and aneurysm rupture risk despite only crudely approximating the biophysical factors that ultimately lead to rupture, the use of area ratio and tortuosity is being proposed here as a pragmatic solution to the problem of quantifying disturbed flow for future, evidence-based studies of local risk factors for atherosclerosis.

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