In Vivo Wall Shear Stress Distribution in the Carotid Artery
Effect of Bifurcation Geometry, Internal Carotid Artery Stenosis, and Recanalization Therapy

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Background—The purpose of this study was to analyze the in vivo distribution of absolute wall shear stress (WSS$_{abs}$) and oscillatory shear index (OSI) in the carotid bifurcation and to evaluate its dependence on bifurcation geometry, the presence of internal carotid artery (ICA) stenosis, and recanalization therapy.

Methods and Results—Time-resolved 3D blood flow was acquired with flow-sensitive 4D MRI in 64 normal carotid bifurcations and 17 carotid arteries with moderate ICA stenosis (48±6%) or after surgical recanalization. Among 64 normal arteries, atherogenic wall parameters were consistently concentrated in proximal bulb regions of the common (CCA) and internal (ICA) carotid arteries. The fraction of the carotid bulb exposed to atherosclerosis-prone wall parameters (low WSS$_{abs}$ below and high OSI above group-defined 20% and 10% thresholds) was correlated with the individual bifurcation geometry. Multiple regressions revealed significant ($P<0.01$) relationships ($\beta$, 0.44 to 0.48) between the areas with atherosclerosis-prone wall parameters and the $d_{\text{ICA}}/d_{\text{CCA}}$ diameter ratio. The size of regions exposed to high OSI demonstrated highly significant ($P\leq0.01$) relationships with all analyzed geometry parameters ($d_{\text{ICA}}/d_{\text{CCA}}$, $\beta$, 0.48; tortuosity $\beta$, $\leq-0.56$; bifurcation angle $\beta$, $\geq0.47$). Moderate ICA stenosis altered the distribution of wall parameters (45%/61% reduction of individually low WSS$_{abs}$/high OSI in the proximal ICA), which were relocated to segments distal to the arterial stenosis. WSS$_{abs}$/OSI topology after recanalization was similar compared with the normal wall parameter distribution.

Conclusions—Flow-sensitive 4D MRI identified alterations in the segmental in vivo WSS distribution associated with atherosclerotic disease, surgical therapy, and individual bifurcation geometry and could be a valuable technique to assess the individual risk of flow-mediated atherosclerosis and carotid plaque progression. (Circ Cardiovasc Imaging. 2010;3:647-655.)

Key Words: magnetic resonance imaging ■ carotid arteries ■ atherosclerosis

The understanding of pathomechanisms that influence the formation of carotid atherosclerosis of the internal carotid artery (ICA) is important because moderate and particularly high-grade stenoses constitute major sources of brain embolism.1 Numerous studies have shown that the development of atherosclerosis in the naturally bulbic ICA may be due to local hemodynamic conditions, such as reduced and oscillating wall shear stress (WSS). Although cardiovascular risk factors typically cause thickening and stiffening of the common carotid artery (CCA) wall, the development of atherosclerosis at the naturally dilated ICA bulb is mainly related to bifurcation geometry.2 The physiological bulbic shape of the proximal ICA required for the measurement of local blood pressure through baroreceptors produces a characteristic helical flow pattern3 associated with reduced and oscillating WSS.4–7 Particularly, low absolute WSS (WSS$_{abs}$) and high oscillatory shear index (OSI) seem to determine the composition of atherosclerotic lesions and the development of high-risk plaques.6,8–12

Clinical Perspective on p 655

Wall shear forces within the carotid bifurcation are dynamic, complex, and 3D. Thus, a detailed analysis strategy requires the assessment of the true magnitude and direction of regional WSS variations. Although these properties were investigated previously, no comprehensive analysis of the segmental distribution of physiological WSS in the entire carotid bifurcation has been presented in vivo.5,8,13 Previous human studies relied on 2D Doppler ultrasound and were based on axial WSS only or averages over the entire lumen circumference.13,14 Computational fluid dynamics (CFD) studies can potentially overcome these limitations15–19 and recently were applied in a comprehensive evaluation of 3D flow patterns and...
WSS distribution in healthy volunteers. There was strong
evidence that certain subjects were exposed to critical wall param-
deters due to their particular bifurcation geometry.18

MRI has the potential to assess both vascular geometry and
time-resolved 3-directional blood flow with high accuracy in
vivo. Previous MRI studies evaluated regional WSS but were
limited to predefined 2D slices and idealized model assump-
tions.16,20–27 To overcome these limitations, we used time-
resolved phase-contrast MRI with 3-directional velocity en-
coding (flow-sensitive 4D MRI) combined with an optimized
data quantification strategy.

The purpose of this study was to evaluate the topographical
distribution of WSS in 64 normal carotid bifurcations in vivo.
Regions with disturbed flow and, thus, potentially athero-
genic WSS were identified based on the definition of group
thresholds for low WSSabs and high OSI. We hypothesized
that the size of the area of the carotid wall exposed to
atherosclerosis-prone wall parameters correlates with mark-
ers for individual bifurcation geometry.

Further, the distribution of wall parameters in normal
volunteers was compared with findings in patients with
moderate ICA stenosis (n=6) and after surgical recanaliza-
tion (n=11). Changes in the topology of low WSSabs and high
OSI were evaluated to test the hypothesis that stenotic
bifurcation geometry and therapeutic intervention can alter
wall parameter distributions.

Methods

Study Cohort

Thirty-two healthy volunteers (age, 25.3±3.4 years; range, 22 to 35
years; female sex, 16) were included in the study. In addition, 13
patients (age, 70.6±7.1 years; range, 60 to 81 years) with moderate
ICA stenosis (n=6 carotid arteries; local degree of stenosis [European
Carotid Surgery Trial criteria24], 48±6%; range, 44% to 55%)
or surgically recanalized former severe ICA stenosis (n=11 carotid
arteries; initially ≥70% lumen narrowing; average degree of steno-
is, 85±9%; range, 70% to 95%) were analyzed. The study was
approved by our local ethics board, and written informed consent
was obtained from all participants.

MRI

All measurements were performed using a 3-T MRI system (TIM-TRIO;
Siemens; Erlangen, Germany) using a combined 12-element head and
6-element neck coil. Following the acquisition of scout images for
anatomic orientation, 3D time-of-flight (TOF) magnetic resonance
angiography (MRA) was executed. Data were acquired in an axial slab
encompassing the left and right carotid bifurcation with the following
parameters: flip angle, 25°; echo time/repetition time, 3.7/20 ms; spatial
resolution, 0.5×0.8×1.0 mm3; slab thickness, 114 mm.

Flow-sensitive 4D MRI was based on a time-resolved ECG-
synchronized radiofrequency-spoiled gradient echo sequence with
interleaved 3-directional velocity encoding.3,29 The 3D imaging
volume was carefully positioned according to the carotid arterial
geometry from the TOF MRA data to include the CCA and the
bifurcation into the ICA and external carotid artery (ECA). Imaging
parameters were as follows: flip angle, 15°; echo time/repetition
time, 3.1/5.7 ms; velocity sensitivity, 150 cm/s; spatial resolution,
1.1×0.9×1.4 mm3; slab thickness, 50.4 mm; 36 slices/slab; temporal
resolution, 45.6 ms.

Data Analysis

WSS

Data processing included noise filtering, correction for eddy currents,
Maxwell terms, and velocity aliasing as described previously.29 For
each subject, 3D phase-contrast MRA (PC-MRA) depicting left- and
right-side carotid bifurcations was calculated from the flow-sensitive
4D MRI data.30 The resulting 3D PC-MRA was depicted as a 3D
isosurface and fused with the measured 3-directional velocity data to
permit a joint visualization of arterial geometry and velocity profiles
(EnSight; CEI, Apex, NC) (Figure 1). In addition, time-resolved 3D
particle traces31 were calculated to depict 3D flow patterns inside the
carotid bifurcation.

To ensure consistent definition of 7 analysis planes (ECA and plan-
es 1 to 6 in ICA) for all subjects as shown in Figure 1B, the flow
diverter (FD) separating ECA and ICA flow was determined and
used as reference. Next, analysis plane 2 was anchored at the FD
point and angulated normal to the ICA. All other analysis planes
were generated by shifting the plane center upstream (ECA and ICA)
or downstream (CCA) in 4-mm intervals. Each plane was manually
angulated normal to the arterial lumen.

For wall parameter quantification, all planes were imported into a
home-built analysis tool programmed in MatLab.32 The location of
the vessel walls were defined by manually outlining lumen contours
on all measured time frames. Time-resolved regional WSS was
derived from the flow-sensitive 4D MRI data as reported previ-
ously.33,34 Briefly, first-order derivatives of measured velocities were
directly mapped onto the segmented lumen contours using cubic
b-spline interpolation. The temporal average over the cardiac cycle
of the absolute (WSSabs in N/m2=1 Pa) and the circumferential
(WSScirc in N/m2) components of WSS and the degree of WSSabs
inversion over the cardiac cycle (OSI in %) were extracted for 12
segments along the vessel circumference, as illustrated in Figure 1.

To ensure consistency of segment position among subjects, the
line connecting the centers of the ICA and ECA above the bifurca-
tion was used as an anatomic landmark. The intersection of this line
with the ICA wall defined the location of segment 1 at the posterior
bulb (Figure 2A). The remaining segments were numbered in a
clockwise or counterclockwise manner for the left- and right-side
carotid arteries, respectively. As a result, the following correspondence
of segments and anatomic locations was achieved: posterior ICA wall
(bulb), segments 12 and 1 to 2; inner ICA wall, segments 3 to 5; anterior
ICA, segments 6 to 8; and outer ICA wall, segments 9 to 11.

Atherosclerosis-Prone Wall Parameters in the ICA Bulb

To evaluate the risk for the development of atherosclerosis-prone
WSS in normal controls, an area at risk was defined as the number
of segments in the posterior CCA and ICA bulb exposed to low
WSSabs and high OSI while following the approach of Stone et al12
and Lee et al.18 Because atherosclerotic lesions typically are located
in the posterior CCA and proximal ICA, only the wall segments (11
to 12, 1 to 3) in slices 1 to 4 comprising this area (bulb region) were
considered for risk stratification (Figure 2A). It was assumed that
a larger number of segments inside the bulb exposed to atherogenic
wall parameters was associated with increased risk. To determine
values that reflect particularly low WSSabs/high OSI for healthy
controls, data from all normal 64 carotid bifurcations were pooled for
each analysis plane. Two different threshold values (20% and 10%)
were used to find the 20% and 10% of segments with the lowest
WSSabs and highest OSI within the volunteer group. These thresh-
olds identified cutoff values for low WSSabs (10% of segments, 0.09
N/m2; 20% of segments, 0.11 N/m2) and high OSI (10% of
segments, 16%; 20% of segments, 10%). WSSabs below and OSI
above these cutoff values were considered atherogenic. The size of
the area exposed to atherosclerosis-prone wall parameters was then
quantified as the number of segments exposed to WSSabs below (or
OSI above) the defined 20%/10% cutoff values.

Distribution of Atherogenic Wall Parameters in the Carotid Bifurcation

To compare the relative distribution of wall parameters between
normal controls and patients in the entire carotid bifurcation, the 12
segments with potentially atherogenic wall parameters (ie, lowest
WSSabs and highest OSI of a total of 84 segments) were identified
for each carotid bifurcation. To compare findings between different
groups of subjects and to permit the calculation of the incidence of
such critical wall parameters for each group, a multislice and multisegment bifurcation model was used as shown in Figure 2B.

**Bifurcation Geometry**

Based on the 3D TOF MRA data, 2 independent observers analyzed bifurcation geometry for all normal 64 carotid arteries included in the study. Each observer was blinded to the other’s results. As shown in Figure 2C, geometric measures included the maximum ICA diameter \(d\) and the CCA and ECA diameters 20 mm below and 10 mm above the FD, respectively. From these measurements, diameter ratios \(d_{ICA}/d_{CCA}\) and \((d_{ICA}/d_{ECA})/d_{CCA}\) were calculated. In addition, bifurcation angle \(\alpha\) and the CCA-ICA tortuosity were assessed by calculating the ratio of the direct and centerline connection of CCA and maximum ICA.\(^{18,35}\)

**Reproducibility: Interscan and Interobserver Variability**

To evaluate the reproducibility (interscan variability) of WSS estimation, MRI and data analysis was repeated in a subgroup of 20 carotid bifurcations of 10 volunteers (age, 23.3±2.7 years). In addition, to evaluate the interobserver variability of the data analysis, lumen segmentation and WSS calculation was independently performed by 2 observers.

**Statistical Analysis**

Continuous variables are reported as mean±SD. Interscan and interobserver variability were evaluated using Bland-Altman analysis by calculating the mean difference and 95% limits of agreement (1.96 SD).\(^{36}\)

Multiple linear regression analysis was used to quantify the relationship between the number of segments affected by atherogenic wall parameters (dependent parameters) and geometric parameters \((d_{ICA}/d_{CCA}\) ratio, bifurcation angle, tortuosity) as independent predictors. Q-Q plots indicated normal distribution of all dependent parameters. The overall quality of the model was quantified using the adjusted \(R^2\). The relative contributions of the geometric parameters were determined from the standardized regression coefficient \(\beta\). A correlation was considered significant for \(P<0.05\). To detect statistically significant differences between repeated continuous variables, paired \(t\) tests were applied.

**Results**

**WSS and Bifurcation Geometry**

The size of regions exposed to atherosclerosis-prone wall parameters varied considerably between individual normal carotid
arteries affecting 0% to 90% (20% threshold) and 0% to 70% (10% threshold) of the bulb region (Table 1). The presence of low WSSabs typically mirrored that of high OSI. There was a significant relationship between the area exposed to low WSSabs and high OSI for the 20% threshold \( (r = 0.49; P < 0.001) \) and to a lesser extent for the 10% threshold \( (r = 0.34; P = 0.006) \).

As illustrated in Figure 3, flow measurements in 2 volunteers showed that increased bifurcation angle and diameter ratio \( d_{ICA}/d_{CCA} \) resulted in a much larger area with reduced WSS in the ICA bulb. As summarized in Table 2, multiple linear regressions revealed a significant relationship between the areas affected by low WSSabs (WSSabs at lower 20th percentile of full range of WSSabs values) and the diameter ratio \( d_{ICA}/d_{CCA} \) but not with angle and tortuosity for both thresholds criteria. The size of regions exposed to high OSI demonstrated significant relationships with all analyzed geometry parameters (OSI at higher 20th and 10th percentile of full range of OSI values).

Figure 2. Segmental wall parameter analysis according to anatomic landmarks (A). Multislice, multisegment model of the carotid bifurcation (B). Standardized display of wall parameters in 7 analysis planes in the CCA, ICA, and ECA. Segments comprising the posterior CCA and ICA bulb that were considered at particular risk for the development of atherosclerosis are highlighted in dark gray. Schematic illustration of the parameters used to characterize the individual carotid bifurcation geometry (C). CCA, ICA, and ECA indicate the locations of the diameter measurements; the bifurcation angle is denoted by \( \alpha \). L and D indicate the CCA-ICA distances along the lumen center and the direct connection, respectively.

Table 1. Descriptive Statistics of the Bifurcation Geometry and Wall Segments of the Bulb Region Exposed to Atherogenic Wall Parameters in 64 Carotid Arteries of the 32 Healthy Volunteers

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Mean ± SD</th>
<th>Range, Min–Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bifurcation geometry</td>
<td></td>
<td></td>
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<tr>
<td>Diameter, mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA</td>
<td>6.8 ± 0.6</td>
<td>5.4–8.5</td>
</tr>
<tr>
<td>Max ICA</td>
<td>7.2 ± 1.1</td>
<td>5.2–11.3</td>
</tr>
<tr>
<td>Diameter ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( d_{ICA}/d_{CCA} )</td>
<td>1.1 ± 0.1</td>
<td>0.9–1.4</td>
</tr>
<tr>
<td>( (d_{ICA} + d_{ECA})/d_{CCA} )</td>
<td>1.8 ± 0.2</td>
<td>1.5–2.2</td>
</tr>
<tr>
<td>Bifurcation angle, °</td>
<td>20 ± 11</td>
<td>5–55</td>
</tr>
<tr>
<td>Tortuosity</td>
<td>1.02 ± 0.01</td>
<td>1.0–1.1</td>
</tr>
<tr>
<td>Wall parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area affected by low WSSabs, % bulb region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% threshold</td>
<td>38.8 ± 22.5</td>
<td>0–90</td>
</tr>
<tr>
<td>10% threshold</td>
<td>19.5 ± 16.6</td>
<td>0–60</td>
</tr>
<tr>
<td>Area affected by high OSI, % bulb region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% threshold</td>
<td>39.9 ± 22.9</td>
<td>0–90</td>
</tr>
<tr>
<td>10% threshold</td>
<td>20.1 ± 16.7</td>
<td>0–70</td>
</tr>
</tbody>
</table>

Figure 4 and 5 summarize the distribution of low WSSabs and high OSI in the entire carotid bifurcation. Volunteers (Figure 4, left) demonstrated a very distinct distribution of wall parameters. Color coding reflects the segmental incidence of atherogenic wall parameters (ie, the fraction [%] of 64 normal carotid bifurcations, which presented with low WSSabs and high OSI). As expected, these were concentrated around the posterior regions oriented toward the inner wall (open arrows) of the ICA and in posterior and anterior regions of the ECA.7,18

For patients with moderate ICA stenosis, the distribution of low WSSabs and high OSI was altered, and atherogenic wall parameters were shifted further downstream (Figure 4, middle, arrows). Plane-by-plane comparison with volunteers (Figure 5) revealed that the highest incidence of low WSSabs (high OSI) in the normal proximal ICA (plane 2) was considerably reduced by 45% (61%) and moved downstream to the distal ICA (Figure 5, arrows).

In patients after recanalization, a more heterogeneous distribution of wall parameters was found (Figure 4, right). The incidence of atherogenic wall parameters in each analysis plane (Figure 5) was similar compared with normal controls.
These findings are mirrored by 3D visualization of flow characteristics inside the carotid bifurcation as exemplarily shown in Figure 6 and the supplemental video. In a normal control (Figure 6A), typical helical blood flow in the ICA bulb can be clearly appreciated (open arrows). In contrast, the altered bifurcation geometry in a patient with 40% ICA stenosis (Figure 6B) resulted in more straight flow through the stenosis but enhanced helix flow directly distal to the stenosis within the poststenotic dilatation. These flow patterns correspond well to the observed relocation of atherogenic wall parameters to more distal locations in such patients (Figure 5, middle, solid arrows). A patient after recanalization (Figure 6C) showed similar flow characteristics compared to the normal control, including helix flow in the bulb (yellow arrows).

**WSS\textsubscript{circ}**

\(WSS\textsubscript{circ}\) constituted a substantial fraction (31±14%; range, 13% to 84%) of \(WSS\textsubscript{abs}\), indicating the presence of helical flow in the bulb and the importance of measuring all velocity parameters.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Flow visualization in a plane longitudinally transecting the 3D geometry of the carotid bifurcation for 2 healthy volunteers. Vector fields and color coding of velocity magnitude illustrate the influence of carotid bifurcation geometry on blood flow patterns and resulting wall parameters (left) in the proximal ICA. Increased \(d\text{ICA}/d\text{CCA}\) ratio and bifurcation angle in volunteer 2 resulted in more-complex flow channels and larger areas with low and recirculating flow (open arrows). Consequently, larger regions of the proximal ICA and ECA are exposed to low WSS, indicating a potentially higher risk of atherogenesis in volunteer 2 than in volunteer 1. Geometry parameters (volunteer2/volunteer1) were as follows: bifurcation angle, 41°/23°; tortuosity, 1.03/1.02; \(d\text{ICA}/d\text{CCA}\), 1.2/1.1.

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**Table 2. Multiple Linear Regressions of the Area at Risk (Size of Bulb Region Exposed to Atherogenic Wall Parameters) With Bifurcation Angle, Tortuosity, and \(d\text{ICA}/d\text{CCA}\) Diameter Ratio as Independent Predictors in the 32 Healthy Volunteers (62 Carotid Bifurcations)**

<table>
<thead>
<tr>
<th>Wall Parameter Threshold</th>
<th>Model Quality</th>
<th>(d\text{ICA}/d\text{CCA})</th>
<th>Bifurcation Angle</th>
<th>Tortuosity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted (R^2)</td>
<td>(\beta)</td>
<td>(P)</td>
<td>(\beta)</td>
</tr>
<tr>
<td>(WSS\textsubscript{abs}) 20% (0.11 N/m²)</td>
<td>0.15</td>
<td>0.005</td>
<td>0.44</td>
<td>0.001</td>
</tr>
<tr>
<td>(WSS\textsubscript{abs}) 10% (0.09 N/m²)</td>
<td>0.06</td>
<td>0.081</td>
<td>0.34</td>
<td>0.011</td>
</tr>
<tr>
<td>OSI 20% (10%)</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OSI 10% (16%)</td>
<td>0.28</td>
<td>&lt;0.001</td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The significance of the model was assessed using the overall \(P\) value, and the percent of variance explained using the adjusted \(R^2\). The relative contributions of the geometric parameters are given by the standardized regression coefficient \(\beta\). Significant correlations (\(P<0.05\)) are presented in bold.
components to fully evaluate the absolute value of WSS and its inversion over the cardiac cycle.

Reproducibility: Interscan and Interobserver Variability

The subgroup of 10 subjects undergoing repeated MRI had similar heart rates (scan 1, 65±9 beats/min; scan 2, 62±9 beats/min; P=0.16) but significantly different systolic (scan 1, 115±11 mm Hg; scan 2, 124±14 mm Hg; P<0.01) and diastolic (scan 1, 59±4 mm Hg; scan 2, 63±7 mm Hg; P=0.03) blood pressure. Low interscan and interobserver variability was achieved when comparing data from 20 carotid arteries, 7 slices, and 12 segments (n=1680 data points). Agreement was better for WSS$_{abs}$ (interscan mean difference, −0.05 N/m$^2$; 1.96 SD, −0.22 N/m$^2$ to 0.11 N/m$^2$; interobserver mean difference, 0.05 N/m$^2$; 1.96 SD, −0.04 N/m$^2$ to 0.13 N/m$^2$) compared to OSI (interscan mean difference, 1%; 95% limits of agreement −15% to 16%; interobserver mean difference, −1%; 95% limits of agreement −10% to 7%). For all geometric measures, Bland-Altman analysis demonstrated good agreement between both readers (lumen diameters mean difference, 0.1 mm; 95% limits of agreement, −1.0 to 1.2 mm; angle mean difference, 0.9°; 95% limits of agreement, −7.2 to 9.1°; distances mean difference, 0.4 mm; 95% limits of agreement, −2.3 to 2.7 mm).

Discussion

Flow-sensitive 4D MRI and optimized data analysis allowed for an in vivo assessment of individual hemodynamics in the carotid bifurcation. In addition to the previously described visualization of complex 3D blood flow patterns, such as helical flow in the proximal ICA, it is now possible to quantify WSS at any region of interest along the wall circumference. Consistent with previous studies, we observed that potentially atherogenic wall parameters in normal controls were predominantly concentrated at the posterior wall of the physiologically dilated proximal ICA. This observation is in concordance with the tendency of carotid atherosclerosis to affect the outer walls of arterial bifurcations and to mostly develop in the proximal part of the ICA bulb.6,7

The presence of moderate-proximal ICA stenosis clearly altered wall parameter distribution. Low WSS$_{abs}$ and high OSI moved distal to the ICA plaque potentially linked to future growth of such lesions. The wall parameter distribution in patients after surgical recanalization of former high-grade ICA stenoses was similar to that observed in healthy volunteers. Discrepancies between vessels of healthy volunteers and recanalized stenosis are most probably due to age differences and the small number of patients studied. Moreover, vessel remodeling (dilatation and elongation) as a result
WSS. In case of low axial WSS but simultaneously high measurement or axial WSS only may severely underestimate wall parameter calculation based on unidirectional velocity. Promising tool to individually predict future plaque growth and speculate that in vivo wall parameter analysis could be associated with atherosclerotic disease or therapy. Therefore, we identify regional changes of carotid wall parameters potentially of atherosclerosis may explain the more heterogeneous wall parameter distribution in these patients.

The limited number of patients investigated in this pilot study does not allow conclusions regarding the true clinical impact of the technique. However, the robustness of the findings in volunteers and the redistribution of extreme WSS\textsubscript{abs} and OSI in patients indicate the high sensitivity of the presented method to identify regional changes of carotid wall parameters potentially associated with atherosclerotic disease or therapy. Therefore, we speculate that in vivo wall parameter analysis could be a promising tool to individually predict future plaque growth and the development of vulnerable carotid atheroma.

Compared to previous Doppler ultrasound\textsuperscript{8,10,11,14} and MRI\textsuperscript{24,25,27} studies, an optimized WSS estimation strategy as described by Stalder et al\textsuperscript{12} was used and did not require model assumptions of flow patterns. The necessity to acquire all 3 velocity directions is underlined by our finding that WSS\textsubscript{circ} constituted between 13\% and 84\% of the total WSS\textsubscript{abs}. Thus, wall parameter calculation based on unidirectional velocity measurement or axial WSS only may severely underestimate WSS. In case of low axial WSS but simultaneously high WSS\textsubscript{circ}, the magnitude of WSS may even be falsely classified as potentially atherogenic, although a large WSS component is still present.

CFD provides full 3D blood flow and WSS distribution in realistic carotid bifurcation geometries.\textsuperscript{15,18,38–40} However, it is still debated how boundary conditions needed for the CFD calculations (rigid walls, idealized in-flow velocity profiles, non-Newtonian blood models) affect the results.\textsuperscript{41–43} CFD can provide vital information about the effect of 3D vascular geometry on flow and wall parameters as shown in a systematic and detailed analysis of 50 normal carotid bifurcations in a study by Lee at al.\textsuperscript{18} In their study, a similar data analysis strategy based on 20\% and 10\% group thresholds was used. Thus, we were able to compare the results from our in vivo analysis and to confirm these CFD findings in vivo using flow-sensitive 4D MRI. Consistent with Lee et al, the \(d_{\text{ICA}}/d_{\text{CCA}}\) ratio predicted the occurrence of disturbed flow and wall parameters at the outer wall of the ICA bulb. Further, an increase of the \(d_{\text{ICA}}/d_{\text{CCA}}\) ratio and a decrease of tortuosity were significantly correlated with the presence of atherosclerotic OSI. For OSI, the predictive value of the geometric measures \(d_{\text{ICA}}/d_{\text{CCA}}\) and tortuosity is underlined by their insensitivity to the choice of threshold and critical wall parameter indicator (Table 2). These findings could explain why some individuals develop more pronounced carotid atherosclerosis (ie, ICA stenosis) than others, although cardiovascular risk factors may be similar. In contrast to Lee et al, we also detected a significant relationship between high OSI and increased bifurcation angle. We speculate that in vivo MRI may be advantageous because the true and individual vessel compliance, inflow parameter, and blood composition are considered.

The current spatiotemporal resolution of flow-sensitive 4D MRI can considerably underestimate the true WSS magnitude and limit the accuracy of wall parameter calculations.\textsuperscript{32} Small stenotic lumen diameter or slow recirculation flow may result in increased velocity-to-noise ratio or few pixels available for wall parameter estimation. However, we believe that these limitations do not apply to the most important findings of this study, which are in regions with large aortic diameter and at least moderate flow: the concentration of atherogenic wall parameters in the normal carotid bulb, relocation of atherogenic WSS\textsubscript{abs} and OSI to regions distal to a moderate ICA stenosis, and near-normal wall parameters distribution after recanalization therapy. Nevertheless, the 20\% and 10\% group threshold values for WSS in our study (0.11 and 0.09 N/m\textsuperscript{2}) were lower compared with the findings by Lee et al\textsuperscript{18} (0.48 and 0.33 N/m\textsuperscript{2}) using a similar data analysis strategy based on CFD data providing superior spatial resolution and less partial volume effects. However, the limited resolution in our study does not affect the general WSS distribution or relative regional changes of wall parameters.\textsuperscript{32,34} Thus, our analysis focused on the detection of atherogenic wall parameters relative to other carotid bifurcation segments.

The accuracy of MR-based WSS estimation was not analyzed in this study. However, no gold standard exists for segmental analysis of in vivo WSS. In previous work, we have analyzed the performance of our method under ideal conditions in numeric and in vitro models and found good agreement with expected results.\textsuperscript{35} In addition, the high reproducibility and low interobserver variability found in this study indicate the consistency of the analysis to detect regional variations of WSS. Moreover, the evaluation of relative wall parameter distributions leads to similar results as reported by Lee et al\textsuperscript{18} regarding the relationship of bifurcation geometry and presence of critical wall parameters, indicating the validity of our in vivo MR approach. Nevertheless, additional studies based on more realistic models of the carotid bifurcation are needed to verify the accuracy of the presented technique.
Further in vivo MRI studies that include large cohorts of healthy volunteers of different age groups now are required to obtain normal values of WSS distribution along the carotid bifurcation. Particularly, longitudinal studies evaluating the correlation of changes in WSS patterns and plaque progression are needed to identify both causality and the predictive value of WSS measurements with respect to plaque development, composition, and the risk of plaque rupture. Wall parameter quantification could then be particularly valuable to identify individuals requiring an intensified monitoring of ICA stenosis and an antiatherogenic medical treatment.

In conclusion, the size of the area of the normal carotid wall exposed to potentially hazardous wall parameters clearly correlated with markers for individual bifurcation geometry. Changes in the topology of atherogenic wall parameters indicated that altered stenotic bifurcation geometry can result in the relocation of critical wall parameters to segments distal to the atherosclerotic lesion and that therapeutic intervention can result in similar wall parameter distribution as observed in healthy volunteers.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

These studies used flow-sensitive 4D MRI to analyze the in vivo distribution of wall shear stress in the carotid bifurcation and to evaluate its dependence on individual bifurcation geometry, the presence of internal carotid artery stenosis, and recanalization therapy. The size of the area of the normal carotid wall exposed to potentially hazardous wall parameters clearly correlated with markers for individual bifurcation geometry. The diameter ratio of the internal and common carotid artery, the bifurcation angle, and tortuosity may provide early predictors for regions prone to atherosclerosis. Changes in the topology of atherogenic wall parameters indicated that stenosis in the carotid bifurcation can result in the relocation of critical wall parameters to segments distal to the atherosclerotic lesion and that therapeutic intervention can result in similar wall parameter distribution as observed in healthy volunteers. Flow-sensitive 4D MRI may become a valuable technique to assess the individual risk of flow-mediated atherosclerosis and carotid plaque progression.
SUPPLEMENTAL MATERIAL

**Supplemental video:** Dynamic 3d blood flow visualization using time-resolved 3D particle traces in the carotid bifurcation in a normal volunteer, a patient with moderate ICA stenosis, and in a patient following surgical recanalization after severe ICA stenosis.