Differences in Near-Wall Shear Rate in the Carotid Artery Within Subjects Are Associated With Different Intima-Media Thicknesses

Lilian Kornet, Jacques Lambregts, Arnold P.G. Hoeks, Robert S. Reneman

Abstract—In the common carotid artery, reflections originating from the periphery and the flow divider may affect the shape of the flow velocity profile and, hence, near-wall shear rate (WSR) differently just before the bifurcation (location B) than 20 to 30 mm farther upstream (location A). Recent developments in ultrasound technology allow the assessment of WSR and intima-media thickness (IMT) at the same site in the carotid artery in vivo. We therefore determined WSR at locations A and B and investigated whether the differences between both sites, if any, were associated with different IMTs and different mechanical properties of the arterial wall. The effect of age on the possible differences was assessed as well. The study was performed on presumably healthy volunteers (n=53). In all individuals, IMT was larger at location B than at location A. The relative difference in IMT between both locations was not affected by age. No significant differences in diameter and distension were found between locations. Near peak systolic and near mean WSR at the posterior wall (PWSRp and MWSRp, respectively) were significantly lower at location B than at location A. The relative differences in PWSRp and MWSRp between both locations within subjects were independent of age. The velocity profiles were more blunted at location A than at location B. PWSRp and MWSRp significantly decreased and IMT significantly increased with age at both locations. IMT was negatively correlated with PWSRp and MWSRp at location B, but this correlation was not significant at location A. In summary, in the common carotid artery, the lower WSR near the bifurcation, as compared with 20 to 30 mm upstream, is associated with a larger IMT than at the more proximal site. The relative difference between both locations within subjects is independent of age. (Arterioscler Thromb Vasc Biol. 1998;18:1877-1884.)

Key Words: carotid artery ■ intima-media thickness ■ shear rate ■ ultrasound

Flowing blood induces a tangentially directed shear stress on the inner vessel wall. By relating stationary flow behavior in scale models of human carotid bifurcations to intimal thickening in a corresponding series of autopsy specimens, Zarins et al1 and Ku et al2 concluded that maximal intimal thickening occurs in regions of flow separation and a relatively low mean wall shear stress. In studies of pulsatile flow, a negative correlation between intimal thickening and the amplitude of cyclic changes in wall shear stress was found in a human coronary artery branch3 and in a human aortic bifurcation.4 In a recent in vivo study with a limited number of persons,5 intima-media thickness (IMT) of the common carotid artery, as assessed at 1 site in this artery, was also found to correlate negatively with average wall shear stress. Wall shear stress was estimated from mean center stream velocity, assuming a fully developed velocity profile.

Recent developments in ultrasonography have made it possible to assess noninvasively IMT and near-wall shear rate (WSR), and hence, near-wall shear stress, in humans at the same site in the common carotid artery.6 This makes it possible to relate areas of low or high WSR to IMT in humans at various sites in 1 artery. In the common carotid artery, reflections originating from the periphery and the flow divider may affect the shape of the time-dependent flow velocity profile, and hence, the time-dependent WSR, differently just before the bifurcation and 20 to 30 mm farther proximally. Therefore, we investigated whether both locations are indeed subjected to a different WSR, and hence, a different near-wall shear stress, and whether this difference, if any, affects IMT and mechanical arterial wall properties differently at these locations. Moreover, the effect of age on the possible differences was assessed because IMT is known to increase with age.7-11 The common carotid artery was chosen for this study because it is easy to assess with ultrasonography and because of the pronounced difference in the echocardiographic density of the intima and media, which facilitates assessment of IMT.

Methods

Subject Population

Sixty-two normotensive volunteers were invited to participate in the study. Nine persons were excluded because of a blood pressure
Characterizing the Behavior of Blood

Shear stress is the product of shear rate and viscosity. Local blood viscosity is difficult to assess. The assumption that viscosity is the same at 2 locations closely spaced within 1 carotid artery allows the use of shear rate as an indicator of shear stress for direct comparison at both locations. WSR is the radial derivative of velocity \( \nu(r) \) at the wall: \( \text{WSR} = \frac{d\nu}{dR} |_{r=R} \), where \( \nu(r) \) is the velocity distribution, determined as a function of radial position \( r \), and \( R \) is the local radius of the artery. WSR can be determined directly by considering the velocity gradient of blood at the wall-lumen boundary as determined by ultrasonography (see below).

Protocol

Data gathering started after an acclimation period of 10 to 15 minutes. Subjects were in the supine position with the head slightly tilted in the contralateral direction. Each subject was connected to an electrocardiograph to generate a pulse to signal the onset of a cardiac cycle. In each subject, only 1 carotid artery was investigated, because in a previous study, no significant differences in the parameters to be measured were found between the left and right carotid arteries.12 Measurements were obtained using the right carotid artery because the coefficient of variation of WSR was slightly smaller for the right than for the left common carotid artery in case the investigator was right-handed.13 First, the wall of the common carotid artery was visualized just proximal to the carotid artery bifurcation (Figure 1, location B), where the artery was not yet widened, and the carotid artery bifurcation was checked for the presence of plaque or stenosis. If present, the subject was excluded. If not, the IMT of the posterior wall was determined 6 times at location B.14 Next, the IMT was measured were found between the left and right carotid arteries.12 so no distinction was made between sexes in this study. Informed consent was obtained from all subjects before they entered the study. The study was approved by the joint medical ethical committee of the academic hospital of Maastricht and Maastricht University.

Assessment of IMT

The method used to assess IMT is described in detail elsewhere.14 In brief, the common carotid artery was visualized in B mode (ATL Mark 9, Advanced Technology Laboratories). Using the tip of the flow divider as a landmark, the position of the L10-5 38-mm probe (operating frequency, 5 to 10 MHz) was manipulated until a suitable line of sight was obtained (Figure 1, solid vertical lines). Along this line, starting synchronously with a trigger derived from the top of the R wave on the electrocardiogram, radiofrequency (RF) data were collected at a sample frequency of 20 MHz over a period of 4 seconds. After acquisition of RF data, the first line was displayed on a personal computer screen, allowing identification of a window of 3 mm covering the posterior lumen-wall transition. Data from this window over time were then stored on hard disk for further off-line processing. Because of arterial wall motion, averaging the power distribution over time along a line will reduce speckle artifacts. Wall motion, however, will complicate processing, because echocardiographic signals will be displaced over time along the line of view. To avoid the latter complication, RF signals were aligned in phase before averaging on the basis of the displacement detected between observations. Subsequently, an edge detection algorithm was applied to the average envelope (amplitude distribution) of the processed RF signals. The intima position was assumed to be halfway along the first up slope, where the spatial derivative of the envelope exceeded for the first time a preselected level. The same procedure was repeated for the next significant upstroke, which is the media-adventitia transition. The outer boundary of the adventitia cannot be distinguished. The difference between the intima position and the media-adventitia transition was taken as the IMT. In vivo registrations exhibit a variation in the order of 45 μm.14

Assessment of WSR, Diameter, and Distension

The ultrasonic Shear Rate Estimating System has been described in detail elsewhere.6,13 The ultrasonic echo system (ATL Mark 9, HDI), in combination with dedicated signal processing,6 is able to measure the blood flow velocity distribution along a selected line of observation across the center of the vessel with a spatial resolution of 300 μm and a temporal resolution of 10 milliseconds. To obtain a more detailed velocity distribution in both the spatial resolution and temporal direction, intermediate values were calculated using half-overlapping data segments. The common carotid artery was first visualized in B mode using the C9-5 ICT probe (operating frequency, 5 to 9 MHz). After positioning the M line (Figure 1, dashed line), the ultrasound system was switched to echo M mode with a high pulse-repetition frequency. A registration started synchronously with a trigger derived from the top of the R wave on the electrocardiogram, facilitating the detection of the maximum (systolic) and minimum (diastolic) velocity as well as the initial diameter. The captured RF signals (reflected and scattered ultrasound signals) were digitized at 20 MHz and transferred to the memory of the computer. The size of the memory allows recording over 1.2 seconds, which is normally sufficient for capturing 1 complete heart beat. The first digitized RF line, as a function of depth, was displayed on the computer screen. From the shape and position in depth of the reflections, the wall-lumen interfaces on both sides were identified manually by placing sample volumes, indicated by markers, on the reflections of the anterior and posterior vessel walls. The distance between both markers, corrected for the angle of observation (70°), was considered the initial (end-diastolic) diameter of the vessel. Processing of the RF data within the sample volumes as a function of time, with the sample volumes adaptively tracking the observed displacement, resulted in the time-dependent change of the arterial wall position (displacement waveform). The difference between the displacement curves of both walls reflected the pulsatile change in diameter over time (ie, distension as a function of time). To obtain
Figure 2. Velocity profiles (A), velocity distributions (B), and shear rate distributions (C) as recorded in the common carotid artery of a presumably healthy volunteer (age 31) near the bifurcation (left) and at a location 20 to 30 mm proximal to the bifurcation (right).
the time-dependent blood flow velocity distribution, a modeled cross-correlation function was applied to the RF data between the markers to estimate the mean velocity over time segments of 10 milliseconds spaced at 5-milliseconds (50% overlap) time intervals. The length of the RF segments corresponded to 300 μm in depth, and the segments were spaced at 150-μm intervals (50% overlap). Calculating the mean velocity of all RF segments resulted in a time-dependent velocity profile, which was corrected for the angle of observation (70°). The shear rate distribution followed from the radial derivative of the velocity profile at each time instant. The maximum value of the first derivative of the flow profile relative to the radius toward the posterior wall of the vessel was considered the estimate of the instantaneous longitudinal WSRp. From the velocity and shear rate distributions, such parameters as PWSRp (per second) and the anterior wall PWSR, (per second) at peak systole, MWSR, (per second), and MWSR, (per second), which is the time-averaged shear rate over 1 cardiac cycle, were determined. The average intrasubject intersession variability per measurement is ~15% for PWSR and ~12% for MWSR. The intrasubject intersession variability for averaged values (n=15) is ~3% for PWSR and ~2% for MWSR. Therefore, in the present study, we averaged >15 measurements. End-diastolic diameter (d, in micrometers) and distension (Δd, in micrometers) were assessed simultaneously with shear rate.

Statistics
To study the differences between a parameter determined at both locations, a paired t test was used. Linear regression was used to study the influence of age. A significant correlation with age was present if the derivative of the linear regression line was significantly different from zero. Significance was reached at P≤0.05.

Results
No significant difference was observed between the diameters and distensions at both locations. Heart rate, brachial pulse, and mean and systolic blood pressure did not change significantly within an individual (ie, during measurements at locations B and A) or between individuals of various ages. IMT was larger at location B than at location A (Figure 3A and 3B). In all individuals, the relative spatial difference in IMT was not significantly affected by age (Figure 3B). At
Figure 4. PWSRₚ (A) and MWSRₚ (C) at the posterior wall (PWSRₚ) as a function of age as recorded in the common carotid artery of presumably healthy volunteers of various ages near the bifurcation (location B) and at a location 20 to 30 mm proximal to the bifurcation (location A). Also shown are PWSRₚ (B) and MWSRₚ (D) at location B as percentages of the values at location A ([(PWSRₚB/PWSRₚA)²] and [(MWSRₚB/MWSRₚA)²], respectively). The solid and dashed lines in Figure 4B and 4D show the mean and 95% confidence intervals of the standard errors, respectively.
both locations, IMT, determined at the posterior wall, increased significantly with age (Figure 3A).

PWSRₚ (per second) and MWSRₚ (per second) were significantly lower at location B than at location A (Figure 4A through 4D). The relative spatial differences in PWSRₚ and MWSRₚ were not affected by age. PWSRₚ and MWSRₚ decreased significantly with age at both locations (Figure 4A and 4C). PWSRₚ and MWSRₚ were not correlated with heart rate.

IMT was negatively correlated with PWSRₚ (Figure 5A) and MWSRₚ (Figure 5B) at location B but not at location A. At both locations, IMT was positively correlated with age (Figure 3A), systolic blood pressure, and body mass index, which was defined as

![Figure 4](image_url)

Continued.

![Figure 5](image_url)

Figure 4. IMT as a function of PWSRₚ (A) and MWSRₚ at the posterior wall (B) as recorded in the common carotid artery of presumably healthy volunteers of various ages near the bifurcation (location B) and at a location 20 to 30 mm proximal to the bifurcation (location A).
body weight divided by squared height (data not shown). At both locations, IMT was not correlated with heart rate.

The WSRs determined at locations B and A at the anterior and posterior walls, as well as the differences between them, are shown in the Table. MWSR and PWSR at both the posterior and anterior walls were significantly higher at location A than at location B. The differences between the MWSRs and PWSRs between both locations were a factor of 2 to 3 larger at the posterior wall than at the anterior wall. At location A, MWSR was significantly higher at the posterior wall than at the anterior wall, but at location B, the MWSR values were not significantly different between the walls. At both locations, PWSR was significantly higher at the posterior wall than at the anterior wall. The absolute difference was a factor of 3 larger at location A than at location B.

### Discussion

The findings of this in vivo study show that in the common carotid artery, WSR is lower near the carotid artery bifurcation than 20 to 30 mm farther proximally. At the site of lower WSR, IMT is larger than at the more proximal site and is negatively correlated with WSR. The relative difference between both locations within subjects is independent of age. We propose that the difference in WSR between both locations is caused by different effects of reflections originating from the external carotid artery.

Wall shear stress is the product of viscosity and WSR. Whole-blood viscosity is influenced by wall shear rate. Because of the larger WSR at location A than at location B, we calculated the viscosity to be, on average, 4.1% (95% confidence interval, 2.8% to 5.4%) smaller at location A than at location B. Therefore, the difference in near-wall shear stress between locations A and B, measured to be 23% of that at location A than at location B, is overestimated by 3%. Furthermore, it should be noted that the maximum first derivative of the flow profile, not the actual WSR, was considered. Shear rate at the wall cannot be determined because of the low scanning resolution relative to the arterial diameter. Because the system is activated with a short pulse and because the spatial resolution, determined by the length of the data window, matches the system resolution, the eventual resolution along the ultrasound beam is ≈0.3 mm. The spatial resolution is hardly affected by the ultrasound beam width (≈1 mm) because of the steep observation angle (70°), but this makes the measurement more sensitive to minor deviations of the observation angle. To overcome the problem of low scanning resolution, the maximum shear rate as assessed was considered as WSR. At the posterior wall, we may assume the maximum shear rate to be ≈0.3 mm from the blood-intima boundary. This implies that the measured shear rate may underestimate WSR when the actual velocity gradient is steeper distally than at the site of assessment of maximum shear rate. Therefore, the shear rate as presented may be considered the lowest possible estimate, because theoretically it is unlikely that the velocity gradient will be less steep closer to the wall.

The lower PWSR (Figure 4A and 4B) and MWSR (Figure 4C and 4D) at the posterior wall near the bifurcation than at 20 to 30 mm farther proximally cannot be explained by a difference in diameter or distension of the artery because these parameters were not significantly different between both locations. We therefore conclude that the relatively lower PWSR at the posterior wall near the bifurcation is related to a difference in shape of the time-dependent velocity profile. Typical examples of flow profiles at locations A and B are shown in Figure 2B. The profiles presented in this figure show that the velocity profile is more blunted at the more proximal location in the common carotid artery (location A) than near the bifurcation (location B). These differences in velocity profiles as recorded near the bifurcation and more upstream were observed in all vessels studied. These differences in velocity profile may be explained by a different influence of reflections originating from the external carotid artery (Figure 6). This explanation, however, is speculative because we were not able to quantify the shape of the velocity profiles because they change with time and are asymmetric (Figure 2B). At location B, only a relatively small

### Differences in MWSRs and PWSRs Between Walls and Locations in the Common Carotid Artery

<table>
<thead>
<tr>
<th>Location</th>
<th>MWSR</th>
<th>PWSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location B</td>
<td>253</td>
<td>677</td>
</tr>
<tr>
<td>Location A</td>
<td>283</td>
<td>799</td>
</tr>
<tr>
<td>A/B</td>
<td>-30 (11%)</td>
<td>-122 (17%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>-57 to -3</td>
<td>-182 to -62</td>
</tr>
<tr>
<td>P</td>
<td>0.03</td>
<td>0.00</td>
</tr>
</tbody>
</table>

*Anterior wall side.
†Posterior wall side.
‡Just before bifurcation of carotid artery.
§Proximal (20 to 30 mm) to bifurcation of carotid artery.
part of the velocity profile is affected, and MWSR is not significantly different between the posterior and anterior walls (the Table). At location A, the reflections are “diluted” and more spread out over the whole cross section of the vessel, leading to a more blunted velocity profile and higher PWSRs and MWSRs at both walls than at location A. The increase is more pronounced at the posterior wall than at the anterior wall (the Table), because reflections are not completely axially oriented but oriented more toward the posterior than the anterior wall.

By relating stationary flow behavior in scale models of human carotid artery bifurcations to intimal thickening in a corresponding series of autopsy specimens, lower WSR, and thus near-wall shear stress, was also found to be correlated inversely with IMT.1,2 In the current study, however, we were able to demonstrate that there is a direct relation between the level of WSR and the degree of intima-media thickening because of the comparable circumstances at both sites of measurement. It is of interest to note that average differences in PWSR and MWSR of only 23% result in a difference in IMT of 29%. The correlation between IMT on one hand and PWSR and MWSR on the other was significant only near the bifurcation and more upstream in the common carotid artery, despite a significant difference in IMT, may be explained by the finding that mainly glycosaminoglycans, a relatively elastic protein, accumulates in the vascular extracellular matrix with increasing age.17 Riley et al18 also observed that thicker vessel walls are not necessarily stiffer than thinner ones.

Two explanations for the negative correlation between WSR or stress and wall thickness may be considered. First, the increased residence time of particles on the inner side of the vessel wall might lead to diffusion of particles into the wall, resulting in a thicker wall. Platelets and macrophages, key elements of atherosclerotic lesions, are more likely to adhere to the arterial wall in regions of increased residence time.19 Second, wall shear stress causes the endothelial cells to orient in the prevailing direction of flow.20,21 Regions of enhanced shear stress are characterized by more elongated endothelial cells, whereas regions of relatively low shear stress are associated with more rounded endothelial cells.22 In the latter regions, cell turnover rates are higher than in the former ones.23 During cell turnover, intercellular junctions become leaky, allowing for an enhanced influx of lipids and other macromolecules. Therefore, the entrance into the wall of macromolecules, as lipids, may be enhanced in low-shear regions.24 Whether accumulation of compounds actually occurs depends on the resistance of the underlying wall, especially the media, to the transport of such molecules across the wall to the adventitia, where they will be removed.25

In summary, in the common carotid artery of humans, WSR is lower near the bifurcation than at more proximal locations. IMT is greater at the site of lower WSR. The relative differences between both locations within a subject are independent of age. We propose that the differences in WSR between both locations are caused by a different effect of reflections originating from the external carotid artery.

References
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