Analysis of complex flow and the relationship between blood pressure, wall shear stress, and intima-media thickness in the human carotid artery

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Augst AD, Ariff B, Thom SA, Xu XY, Hughes AD. Analysis of complex flow and the relationship between blood pressure, wall shear stress, and intima-media thickness in the human carotid artery. Am J Physiol Heart Circ Physiol 293: H1031–H1037, 2007.—Background: Previous clinical studies have observed relationships between increased intima-media thickness (IMT) in the carotid artery, elevated blood pressure, and low wall shear stress (WSS) calculated from the Poiseuille equation. This study used numerical methods to more accurately determine WSS in the carotid artery and to investigate possible determinants of increased IMT. Methods: IMT [common carotid artery (CCA) and bulb], CCA flow velocity, brachial systolic (SBP) and diastolic blood pressure (DBP), and carotid systolic pressure (cSBP) were measured in 14 healthy subjects (aged 44 ± 16 yr). Flow patterns in the carotid bifurcation were determined by computational fluid dynamics (CFD) based on three-dimensional ultrasound geometry. Instantaneous and time-averaged wall shear stress (WSSav), oscillatory shear index (OSI), and wall shear stress angle gradients (WSSAG) were calculated. Results: IMT was positively related to SBP, DBP, cSBP, and WSSAG and inversely related to WSSav in the CCA. In the bulb, IMT was positively related to SBP and cSBP but was not significantly related to WSSav or WSSAG. IMT was unrelated to OSI in both the CCA and the bulb. Conclusion: Increased carotid artery IMT in healthy subjects with no evidence of focal plaques is primarily a response to elevated pressure.

atherosclerosis; ultrasound; computational fluid dynamics

regions, such as bifurcations or arterial curvature, where complex flow occurs in large arteries correspond closely with locations where atherosclerosis develops in humans and animals (41). It has been proposed that sites exposed to low wall shear rate (13) or shear stress (26), oscillating wall shear stress (WSS) (42), or large angle gradients of shear stress (WSSAG) (10) may be particularly vulnerable to development of intimal thickening and atherosclerosis. Mechanisms proposed include effects on endothelial function (1, 15, 31), increased residence time of atherogenic particles near the wall (13, 17), or alterations in mass transfer (12, 30).

Early studies used laser Doppler velocimetry to determine flow patterns in rigid casts of the human carotid bifurcation and their relation to the distribution of intimal thickening in histological specimens (26, 42). Subsequently, the link between WSS and atheroma formation has been supported by reports of associations between low WSS and increased thickness of the intima-media complex (intima-media thickness; IMT) measured by ultrasound in the human carotid artery. However, in many such clinical studies in vivo, WSS is estimated by assuming Poiseuille flow (11, 21, 24). This assumption is not appropriate in complex geometries, including the bulb of the carotid artery, where atheroma typically develops (10, 13, 41, 42). Moreover, since IMT is a composite measure of intimal and medial layers (33), it is not possible to distinguish between intimal thickening due to atherosclerosis and medial thickening in response to elevated blood pressure (7, 23, 36).

Computational fluid dynamics (CFD) applied to flow data derived from magnetic resonance imaging (MRI) or ultrasound permit the Navier Stokes equations governing three-dimensional (3D) flow patterns to be solved by numerical methods and provide a more accurate assessment of flow patterns and shear stress in complex geometries. We have therefore used this approach to examine the relationships between intima-medial thickening, blood pressure, and measures of WSS in the common carotid artery and in the carotid bulb.

METHODS

Patient recruitment and investigations. The study was approved by the ethics committee at St Mary’s Hospital (London, UK), and all subjects gave informed consent. On the assumption of a correlation of 0.6 between WSS and IMT [based on a previous study in healthy subjects (21)], the estimated required sample size was 13 (alpha = 0.05, beta = 0.8), and consequently, a total of 14 healthy individuals (age 26–75 yr, 9 male) were recruited. Subjects were recruited from the staff of Imperial College London, and subject characteristics are shown in Table 1. None of the subjects was receiving any medication. Prespecified exclusion criteria were inadequate visualization of the carotid artery or presence of a carotid plaque or focal thickening (as this could induce secondary changes in flow patterns and shear stress). A plaque was defined as either a focal thickening of IMT >1.3 mm or a distinct area with an IMT >50% thicker than neighboring sites on initial ultrasound examination.

Clinic blood pressure (BP) was measured from the right arm using a validated fully automated device (Omron HEM-705-CP, Omron Healthcare). Systolic BP (SBP), diastolic BP (DBP), and pulse pressure (PP) were calculated as the average of the last two of three successive readings of BP taken after 5 min of rest and with at least a 1-min interval between readings. Carotid SBP (cSBP) was also measured using application tonometry and calibrated using brachial BP as previously described (25).

The left carotid artery bifurcation of all subjects was scanned using a 3D ultrasound system based on a commercial ultrasound scanner (HD1 5000, ATL-Philips, Bothell, MA) equipped with an electromagnetic position and orientation measurement (EPOM) device (Ascension Technology) attached to an L12–5 (5–12 MHz) broad band linear array ultrasound scan probe to locate acquired ultrasound image slices

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Table 1. Baseline characteristics of subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>44±16</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>142±27</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>82±17</td>
</tr>
<tr>
<td>cSBP, mmHg</td>
<td>128±25</td>
</tr>
<tr>
<td>Peak CCA flow velocity, ms⁻¹</td>
<td>0.74±0.20</td>
</tr>
<tr>
<td>(\frac{LD_{sys} - LD_{dia}}{LD_{dia}})</td>
<td>0.078±0.023</td>
</tr>
<tr>
<td>IMT (CCA), mm</td>
<td>0.55±0.12</td>
</tr>
<tr>
<td>WSSav (CCA), Pa</td>
<td>0.49±0.26</td>
</tr>
<tr>
<td>OSI (CCA)</td>
<td>0.10±0.37</td>
</tr>
<tr>
<td>WSSAG (CCA)</td>
<td>0.37±0.46</td>
</tr>
<tr>
<td>IMT (bulb), mm</td>
<td>0.61±0.12†</td>
</tr>
<tr>
<td>WSSav (bulb), Pa</td>
<td>0.26±0.10†</td>
</tr>
<tr>
<td>OSI (bulb)</td>
<td>0.03±0.03†</td>
</tr>
<tr>
<td>WSSAG (bulb)</td>
<td>1.05±0.76†</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; cSBP, carotid systolic blood pressure; CCA, common carotid artery; \(LD_{sys}\), lumen diameter in systole; \(LD_{dia}\), lumen diameter in diastole; WSSav, time-averaged wall shear stress; OSI, oscillatory shear index; WSSAG, wall shear stress angle gradient. *P = 0.02 and †P < 0.01, comparing CCA with bulb using a paired Student’s t-test.

in 3D space (5). During the scan, the transducer probe was swept slowly over the subject’s neck. Average scan time was ~2 min, during which time ~120 images gated to the peak R wave on ECG were acquired over a scan distance of ~5 cm. Two separate data sets were recorded: a set of 2D images and the 3D positions and orientations of the ultrasound probe (measured by the EPOM device) for each image. The EPOM data were used to accurately determine the location of each acquired ultrasound image within a 3D volume. Ultrasound images were stored digitally on the scanner and later downloaded to a personal computer to be analyzed offline. Acquired images of the carotid bifurcation were segmented, smoothed, and reconstructed into surface splines using software written in MATLAB (MathWorks, Natick, MA). The accuracy of this technique has been reported previously (4).

IMT was measured from digitally acquired B-mode ultrasound images captured using the same ultrasound machine using a 5- to 12-MHz broadband linear array probe to obtain views of the far wall of the distal common carotid artery (CCA) and the carotid bulb (Fig. 1). Images for measurement of IMT were acquired in diastole using retrospective ECG gating and transferred to a personal computer for offline analysis. Lumen diameter (LD) was also measured in both systole and diastole using retrospective ECG gating and distension calculated as the difference between systolic (LDsys) and diastolic diameter (LDdia) with respect to diastolic diameter

\[
\frac{LD_{sys} - LD_{dia}}{LD_{dia}}
\]

IMT and LD were measured over a length of 1 cm in the distal CCA, and IMT was measured over a length of 0.5 cm in the bulb (~1 cm from the start of the dilatation point of the bulb) using AMS II (Chalmers University, Gothenburg, Sweden). This validated semi-automatic tool has excellent reproducibility and subpixel accuracy (40). Blood velocity (u) was measured in the center of the artery in a 1-mm² sample volume at least 3 cm proximal to the bulb of the common and in the distal internal carotid artery using pulsed Doppler. Data were stored as digital cineloops, and an average flow waveform for use as a boundary condition (see below) was constructed from ensemble averaging at least six individual waveforms with a custom program written in MATLAB using the ECG R wave as a fiducial marker. Flow profiles were assumed to be axisymmetric, and we have previously shown that measurements of flow calculated in this manner agree well with MRI phase contrast data (19).

CFD methodology. The reconstructed surface splines of the carotid artery were used with a commercial CAD/CAD package (ICEM-DDN) to produce the input file for the grid generator (ICEM Hexa) (ICEM CFD, ANSYS, Canonsburg, PA). The semi-automatic Hexa tool allows the generation of a grid suitable for the designated solver. The Navier-Stokes equations for time-dependent laminar flow with rigid walls were solved using the commercial CFX-4.4 package (ANSYS) based on the finite volume method. The assumption of rigid walls for CFD modeling is likely to result in a modest overestimation of WSS compared with a compliant wall model (44) but is highly advantageous in terms of computational time. We also employed a non-Newtonian, blood-mimicking fluid (Quemada) model (10)

\[
\eta = \left( \frac{\eta_0 + \eta_{\gamma}}{\sqrt{\lambda + \sqrt{\gamma}}} \right)^2
\]

where \(\eta\) is the apparent viscosity, \(\eta_0\) is the asymptotic viscosity at high shear rates (cm²s⁻¹), \(\tau_0\) is the yield shear stress (\(\tau_0 = 0.0432\) dyn·cm⁻²), \(\lambda\) is the shear rate modifier (\(\lambda = 0.0218\) s⁻¹), and \(\gamma\) is the shear rate. The semi-implicit method for pressure-linked equation consistent (SIMPLEC) computational algorithm was used for velocity-pressure coupling. A quadratic upwind (QUICK) differencing scheme was used for the advection terms. A fully implicit Euler backward scheme was used for the time term. In all cases, time-dependent velocity profiles calculated on the basis of Womersley flow were imposed at the inlet, while outlets were defined as fractional mass flow boundaries with the assumption of zero normal gradients. Since measurement of bulk flow in the external carotid artery (ECA) by ultrasound is subject to large errors, the fraction of mass flow exiting the ECA was estimated in each individual as the difference between CCA inflow and internal carotid artery (ICA) outflow estimated on the basis of the pulsed Doppler velocity data, the diameter...
of the CCA and ICA, and the assumption of Womersley flow (22). All CFD models were simulated for two cycles, the first with time steps of an increment of 0.02 s, the second with equal time steps of a length of 0.01 s. Both mesh generation and flow simulations were carried out on a SUN SPARC Ultra 60 Workstation. For comparison with previous studies, shear stress was also estimated on the basis of the Poiseuille equation, assuming shear stress \( \eta \cdot u / L D_{wa} \) (21).

To permit an acceptable degree of spatial co-registration of IMT with WSS and related parameters, CFD data were averaged over “patches” that corresponded as nearly as possible to the region where IMT was measured. Patches were constructed as previously described (20, 39). In short, “patching” consisted of four steps. First, the three arteries were disconnected from each other; second, the vessel was “cut open” anteriorly and “unwrapped” to obtain a flat irregular shape. Third, this irregular shape was subdivided into 12 rectangular patches of \( 1.5 \) mm dimension (width). Four, the patches most closely corresponding in location with the region of the far wall of the carotid artery where IMT was measured were taken as the relevant site for spatial averaging of WSS and related parameters. While this process has the disadvantage of effectively “collapsing” multiple data points into a single summary measure, it has the advantages that data are reproducible, that small errors in registration have a negligible impact on relationships between WSS and IMT, and that results are easily subjected to statistical analysis. The accuracy and reproducibility of the whole technique from scan to reconstruction to simulation has been assessed previously using a carotid bifurcation phantom (3) and by comparison with in vivo MRI data (2).

**Computational details.** Time-integrated parameters such as the oscillatory shear index (OSI), time-averaged wall shear stress (WSSav) over the cardiac cycle, and the wall shear stress angle gradient (WSSAG) were calculated. These were defined as

\[
OSI = 0.5 \times \left( 1 - \frac{\int_0^{t_p} \tau_w \, dt}{\int_0^{t_p} \tau_w \, | \, dt} \right) \tag{2}
\]

\[
WSS_{av} = \frac{1}{t_p} \int_0^{t_p} |\tau_w| \, dt \tag{3}
\]

\[
WSSAG = \frac{1}{T} \int_0^{T} \left( \frac{1}{A_i} \int_0^{A_i} \frac{\partial \phi}{\partial x} \, dA_j \right) + \frac{1}{A_i} \int_0^{A_i} \frac{\partial \phi}{\partial y} \, dA_j \tag{4}
\]

where \( \tau_w \) is the WSS vector, \( t \) is time, \( t_p \) is the cycle period, \( \phi \) is the scalar field of the shear stress angle deviation, \( A_i \) is the control volume surface area, and \( S \) is the entire surface of the carotid wall. The WSSAG is calculated in an arbitrary coordinate system, \( ijk \) or \( xyz \). The scalar field of angular differences is defined as follows. Here, \( \tau_i \) refers to the stress vector at the location of interest, and \( \tau_j \) represents the surrounding stress vectors: shear stress and normal stress. WSSAG is a measure of the angle between adjacent wall shear vectors and has been proposed as an alternative to the WSS angle deviation as a marker for sites possibly at risk for dysfunctional endothelial cells. The WSSAG has the advantage of being a mesh-independent parameter (10).

**Fig. 2.** Instantaneous wall shear stress (WSS) patterns in a representative subject during systolic acceleration (A), systolic deceleration (B), and diastole (C). The flow waveform and the time point in the cardiac cycle are shown at bottom.
Statistical analysis. Data are presented as means ± SD. Data analysis was performed using Stata 9.2 (StataCorp, College Station, TX), and statistical power calculations were performed using GPower (16). P < 0.05 was considered significant.

RESULTS

Spatial patterns of flow and instantaneous WSS patterns in the carotid bifurcation were complex and varied during the cardiac cycle (Figs. 2 and 3). Similarly, patterns of WSSav, OSI, and WSSAG were also complex. Overall, the magnitude of WSSav was significantly lower in the bulb than the CCA, whereas IMT, OSI, and WSSAG were significantly higher in the bulb than the CCA (Table 1). WSS estimated by the Poiseuille equation was on average higher than that calculated by CFD in the CCA [1.14 (0.07) vs. 0.49 (0.07) Pa; mean (SE), P < 0.01], but there was a moderate correlation between the two estimates of WSS [β-coefficient (SE) = 0.61 (0.21), r² = 0.42, P = 0.01] in the CCA. In contrast, there was no significant correlation between WSS measured by CFD and that estimated by the Poiseuille equation in the bulb [β-coefficient (SE) = 0.14 (0.10), r² = 0.16, P = 0.16].

In the CCA, there was a highly significant inverse relationship between WSSav measured by CFD and IMT, but the relationship in the bulb was less evident and was not statistically significant (Table 2; Fig. 4). OSI was not related to IMT in either the CCA or the bulb (Table 2; Fig. 4), and WSSAG showed a significant relationship with IMT in the CCA but not in the bulb (Table 2; Fig. 4). In contrast, SBP and cSBP were highly significantly related to IMT in both the CCA and bulb (Table 2; Fig. 5). Weaker relationships between DBP and IMT were also seen (Table 2).

DISCUSSION

This study uses 3D ultrasound and CFD to determine patterns of flow in the carotid artery. The complex flow patterns seen result in marked spatial and temporal disparities in the distribution of WSS and related parameters, especially in the region of the bulb throughout the cardiac cycle. Our observations are similar to those made previously by us and others (6, 29, 32, 37, 43) in a limited number of subjects using MRI to define carotid geometry and flow in combination with CFD techniques. WSS values estimated on the basis of the Poiseuille relationship (11, 21, 24) are higher than those measured by CFD and show moderate agreement only in the CCA. Our observations are important in emphasizing the difficulty of determining WSS using Poiseuille assumptions in complex arterial geometries in vivo and question the validity of associations previously seen using this approach in clinical studies. The use of ultrasound rather than MRI has several advantages: it is noninvasive and relatively cheap; has good time resolution.

Table 2. Association of measured parameters with IMT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β-Coefficient (SE)</th>
<th>r²</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSSav</td>
<td>−0.004 (0.08)</td>
<td>0.62</td>
<td>0.001</td>
</tr>
<tr>
<td>OSI</td>
<td>0.32 (0.61)</td>
<td>0.02</td>
<td>0.6</td>
</tr>
<tr>
<td>WSSAG</td>
<td>0.16 (0.06)</td>
<td>0.39</td>
<td>0.02</td>
</tr>
<tr>
<td>SBP</td>
<td>0.004 (0.001)</td>
<td>0.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP</td>
<td>0.005 (0.001)</td>
<td>0.53</td>
<td>0.003</td>
</tr>
<tr>
<td>cSBP</td>
<td>0.004 (0.001)</td>
<td>0.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDsys−LDdia/</td>
<td>2.36 (1.27)</td>
<td>0.22</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Bulb</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSSav</td>
<td>−0.35 (0.33)</td>
<td>0.08</td>
<td>0.3</td>
</tr>
<tr>
<td>OSI</td>
<td>−0.16 (0.32)</td>
<td>0.02</td>
<td>0.6</td>
</tr>
<tr>
<td>WSSAG</td>
<td>−0.04 (0.04)</td>
<td>0.07</td>
<td>0.4</td>
</tr>
<tr>
<td>SBP</td>
<td>0.003 (0.001)</td>
<td>0.47</td>
<td>0.007</td>
</tr>
<tr>
<td>DBP</td>
<td>0.003 (0.002)</td>
<td>0.15</td>
<td>0.17</td>
</tr>
<tr>
<td>cSBP</td>
<td>0.003 (0.001)</td>
<td>0.38</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data are linear regression coefficients (SE), r², and P values. Statistically significant correlations are shown in bold.
for measurement of flow; and allows measurement of flow, arterial geometry, and IMT in a single examination. However, this approach has limitations in that the 3D boundary flow profile cannot be measured directly, and the carotid bifurcation cannot be fully visualized in all subjects because of the proximity of the bifurcation to the angle of the jaw in some cases.

This study confirmed previous observations in the CCA (34) showing a positive relationship between SBP and IMT (7, 23, 36) and an inverse relationship between WSSav and IMT (21). However, SBP was the strongest predictor of IMT in the carotid bulb, and there was no significant relationship with WSSav or other WSS-related parameters at this location. Although our ability to detect a weak relationship between WSS and IMT in the bulb may be limited by the relatively narrow range of WSS measured in the bulb, these findings imply that SBP rather than WSSav is the major determinant of IMT in healthy subjects without evidence of plaque or focal thickening. This observation is consistent with another study that employed MRI and CFD to estimate WSS in the carotid artery of two individuals and failed to find a relationship between WSS and carotid wall thickness measured by black blood MRI (37). It is also in keeping with observations of a population-based study of 1,715 subjects in the Rotterdam study that suggested that modest increases in IMT, similar to those seen in our study, were related to the effects of pressure on the arterial wall, whereas only larger increases in IMT represented atherosclerosis. The increase in arterial wall thickness seen in association with elevated BP can be viewed as an adaptive response that tends to normalize wall circumferential tensile stress (8, 18). In our study, we observed a weak inverse relationship between distension of the CCA and IMT. It has been suggested that cyclic distension of the vessel (stretch) in response to the pressure pulse may influence atheroma formation. Decreased endothelial distension in vitro is associated with impaired endothelial function (28), and sites of atheroma formation in the carotid bifurcation correspond well with regions where circumferential tension and WSS are most out of phase (38).

Although our findings suggest an important role for BP in increasing IMT, our observations should not be taken to imply that WSS is not involved in the development of atherosclerosis. IMT in the bulb progresses more rapidly than IMT in the CCA (35), and the focal distribution of low or oscillating WSS and its correspondence with sites of development of atherosclerotic plaques have long been a powerful argument underpinning the
proposed relationship between disturbed flow patterns and atherogenesis (10, 13, 41, 42). The sample size of our study was too small to permit multivariate analysis of the data and to identify possible interactions between WSS and BP. We consider it plausible that low WSS acts in conjunction with increased BP to accelerate intimal thickening and the development of atherosclerosis. Clearly, further work is required to clarify this question.

Our data also do not imply that blood flow or WSS has no role in adaptation of arterial structure in response to changes in flow. Work in animals in vivo (9, 27) has convincingly demonstrated an important role for blood flow in the regulation of arterial diameter. It is likely that this effect is mediated by the ability of the endothelium to act as a mechanotransducer (14) sensing long-term changes in flow and signaling this to the underlying smooth muscle. However, our data do suggest that the regulation of arterial structure in vivo is complex and is likely to depend on a number of factors, including BP, possibly acting via circumferential tensile stress on the arterial wall.

In conclusion, increased IMT in the CCA and bulb is closely related to increased BP. This suggests that the early increase in IMT seen in healthy subjects without evidence of plaques or focal thickening in the carotid artery is likely to be a response to elevated pressure rather than to low shear stress.

GRANTS

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REFERENCES


Fig. 5. Regression plots of carotid IMT vs. systolic blood pressure (SBP; A) and carotid SBP (cSBP; B) in the CCA and bulb.

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