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A framework for the co-registration of hemodynamic forces and atherosclerotic plaque components

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Abstract

Local hemodynamic forces, such as wall shear stress (WSS), are thought to trigger cellular and molecular mechanisms that determine atherosclerotic plaque vulnerability to rupture. Magnetic resonance imaging has emerged as a powerful tool to characterize human carotid atherosclerotic plaque composition and morphology, and to identify plaque features shown to be key determinants of plaque vulnerability. Image-based computational fluid dynamics has allowed researchers to obtain time-resolved WSS information of atherosclerotic carotid arteries. A deeper understanding of the mechanisms of initiation and progression of atherosclerosis can be obtained through the comparison of WSS and plaque composition and morphology. To date, however, advance in knowledge has been limited greatly due to the lack of a reliable infrastructure to perform such analysis. The aim of this study is to establish a framework that will allow for the co-registration and analysis of the three-dimensional distribution of WSS and plaque components and morphology. The use of this framework will lead to future studies targeted to determining the role of WSS in atherosclerotic plaque progression and vulnerability.

Keywords: hemodynamics, wall shear stress, atherosclerosis, carotid

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1. Introduction

Cells present in the arterial vessel wall keep the values of hemodynamic forces within their physiological range by adjusting their structure and function at the cellular, molecular, and genetic levels (Davies 2009, Lee et al 1996, Chiu et al 2009, Cheng et al 2006, Davies and Tripathi 1993, Davies et al 2001, Malek et al 1999). However, under certain circumstances, these responses to abnormal hemodynamics may lead to pathologies, such as atherosclerosis. Indeed, low shear stress exerted on the wall by the blood flow (WSS) induces atherogenic endothelial gene expression, whereas high and unidirectional WSS stimulates the expression of an atheroprotective phenotype (Malek et al 1999). Furthermore, recent studies have suggested that endothelial cells may modify the balance between cap-reinforcing extracellular matrix synthesis by smooth-muscle cells and extracellular matrix degradation by metalloproteinases secreted by infiltrating macrophages as a response to shear stress (Cheng et al 2006, Clowes and Berceli 2000). These studies suggest that there might be a link between plaque distribution and composition and shear stress patterns.

Magnetic resonance imaging (MRI) has emerged as a powerful tool to characterize human atherosclerotic plaque composition and morphology (Cai et al 2005, Saam et al 2005). This information is vital since the plaque’s vulnerability to cause cardio- and cerebrovascular complications is not determined accurately by the luminal diameter information alone. There are certain plaque features, such as large lipid-rich necrotic core (LRNC), thin fibrous cap, or intra-plaque haemorrhage (IPH), that have been shown to be key determinants of plaque vulnerability (Naghavi et al 2003a, 2003b), and these features can be identified by MRI (Saam et al 2007).

Due to the challenges of measuring wall shear stress (WSS) in vivo and its distribution along the arterial wall (Marshall et al 2004), time-resolved wall shear information is obtained by solving the Navier–Stokes equations that govern the flow with computational fluid dynamics (CFD) packages (Marshall et al 2004, Steinman 2002, Xue et al 2008, Zhao et al 2002). The geometries used in these numerical models are commonly the result of the 3D rendering of the MRI segmentation. Even though different groups have successfully estimated WSS patterns in carotid atherosclerotic plaques, a technique that correlates these force patterns with plaque composition is still lacking.

In the present work, we propose an MRI-based framework that co-registers plaque morphological and compositional features with the corresponding WSS distribution. This framework will use a multi-sequence MRI protocol to characterize human carotid atherosclerotic plaques three-dimensionally, and MRI-based CFD models to obtain the three-dimensional (3D) distribution of shear stress along the luminal surface of the lesions.

2. Methods

MR images of ten subjects with carotid atherosclerosis were extracted from the University of Washington’s Vascular Imaging Laboratory (VIL) extensive database. The segmentation had been performed by experienced reviewers from the VIL prior to the initiation of this study, using a custom designed analysis software (CASCADE) (Kerwin et al 2007). Reviewers followed imaging interpretation criteria specifically developed for carotid atherosclerotic plaque detection and characterization and validated against histology (Saam et al 2005, Cai et al 2005). CASCADE has been specifically designed to register and segment axial images acquired at different locations along the carotid bifurcation with a multi-contrast MR protocol (Yuan et al 2006). The MR protocol had been approved by the local ethics committee and informed consent was obtained prior to patient enrolment.
2.1. Computational fluid dynamics (CFD) model

An unstructured tetrahedral mesh was constructed for each carotid artery after outlining the lumen boundaries for each imaged slice using a customized version of the MATLAB code, DistMesh, developed by Persson and Strang (2004). Briefly, the lumen surface was first reconstructed by using volume interpolation and an isosurface routine (Kerwin and Yuan 2002). Then, the tetrahedral mesh was generated using the Matlab Delaunay triangulation routine with the node position optimized by a distance-function-based smoothing procedure. The length of the tetrahedron edge was chosen to be the in-plane resolution of original MR image (0.625 mm).

Once the computational mesh had been built, it was imported into a CFD software package (COMSOL Multiphysics, Stockholm, Sweden) in which the Navier–Stokes equations were solved using finite element analysis. Blood was treated as a Newtonian, viscous fluid with a density of 1045 kg m$^{-3}$ and dynamic viscosity of 0.0035 Pa s. Due to the lack of patient-specific flow information from the common, external, and internal carotid arteries (CCA, ECA and ICA respectively), assumed flow conditions were defined at the inlet (CCA) and outlets (ICA and ECA) of the model: a fully-developed Womersley flow was assumed at the entrance with a cardiac period of 0.98 s, peak Reynolds number of 609.63; traction free was imposed at the outlets. A no-slip boundary condition was applied along the luminal surface. The computational time step was set at 100 ms. Three cycles were computed in order to generate a reproducible solution. Post-processing of the resulting velocity field yielded a 3D distribution of the shear stress along the luminal surface (figure 1).

2.2. 3D distribution of lesion composition and morphology

In addition to the lumen, the wall boundaries as well as LRNC, calcification (CA), loose matrix (LM) and haemorrhage boundaries were outlined for each imaged slice, if those plaque
components were present. The wall and plaque component surfaces were reconstructed using the same algorithm used to reconstruct the lumen surface in section 2.1 (Kerwin and Yuan 2002). These surfaces were then resliced in 0.5 mm interslice intervals, resulting in transverse contours. The lumen, wall and plaque component boundaries were first reconstructed and then resliced in order to estimate the component thickness.

Figure 2 shows a transverse section that was resliced from an internal carotid artery with lumen, outer wall, LRNC and IPH boundaries. Each point on the lumen boundary was paired with a corresponding point from the outer wall boundary. This relationship was established by using the modified symmetric correspondence algorithm (Papademetris et al. 2002). The point-by-point arterial wall thickness was defined as the distance between each pair of corresponding points on the wall and lumen. The distance between the first encountered interface of a plaque component (LRNC or IPH) and the second encountered interface of that same plaque component was computed and superimposed on the lumen boundary (e.g., the distance $T_{IPH}$ in figure 2 is superimposed on point p of the lumen boundary). This procedure mapped the size and position information of each plaque component and the arterial thickness distribution along a lesion on the luminal surface. Figures 3 and 4 exemplify this mapping:
the 3D distribution of plaque features shown in figure 3 is mapped on the luminal surface as depicted in figure 4. This method was implemented using C++ and the Visualization Toolkit (Schroeder et al 2006).

Therefore, each point on the lumen surface is now equipped with WSS at each time point, the wall thickness and the thicknesses of various plaque components. We refer to this 3D map as the WSS–plaque component map hereafter.

### 2.3. 2D flattening maps

In order to facilitate the visual interpretation and comparison of the 3D WSS–plaque component maps, the 3D maps were flattened onto 2D planes so that each transverse contour of the 3D surface was mapped to a 2D line with the arc-length of the contour preserved. The arc-length preserving mapping algorithm has been described in detailed in Chiu et al (2008) and is briefly summarized here. The internal, external and common carotid arteries (ICA, ECA

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**Figure 4.** Projection of the 3D distribution of plaque components size and wall thickness (all measured in mm) onto the luminal surface. T: thickness, LRNC: lipid-rich necrotic core, IPH: intra-plaque haemorrhage, and LM: loose matrix.
Figure 5. Schematic of the arc-length preserving map. The ECA and ICA contours immediately distal to the bifurcation, and the CCA contour immediately proximal to the bifurcation were mapped to the 2D arc-length preserving map with arc-length preserved as indicated by the arrows.

Figure 6. 2D arc-length preserving maps are used to visualize the distribution of plaque components and morphology. The thickness distributions of various plaque components (LRNC: lipid-rich necrotic core, IPH: intra-plaque haemorrhage, LM: loose matrix) were color-coded and superimposed on the 2D maps.

and CCA respectively) were cut longitudinally by the planes PICA, PECA and PCCA respectively as shown in figure 5. The contours are mapped to straight lines on the 2D flattened map with arc-length preserved. Figure 5 provides several examples demonstrating how ECA, ICA and CCA contours were mapped to the 2D arc-length preserving map. Figure 6 shows the 2D arc-length preserving map representation of the 3D thickness distribution maps displayed in figure 4.

3. Results

Ten human carotid atherosclerotic arteries extracted from the VIL’s database were used to build and test the proposed framework. The components identified for each artery are summarized
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Table 1. Components of the atherosclerotic plaques used to build and test the framework.

<table>
<thead>
<tr>
<th>Artery</th>
<th>Plaque components</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LM, CA, LRNC, IPH</td>
</tr>
<tr>
<td>2</td>
<td>LM, LRNC, IPH</td>
</tr>
<tr>
<td>3</td>
<td>LM, CA, LRNC</td>
</tr>
<tr>
<td>4</td>
<td>LM, CA, LRNC</td>
</tr>
<tr>
<td>5</td>
<td>LM, CA, LRNC, IPH</td>
</tr>
<tr>
<td>6</td>
<td>LM, CA, LRNC</td>
</tr>
<tr>
<td>7</td>
<td>LRNC</td>
</tr>
<tr>
<td>8</td>
<td>LM, CA, LRNC, IPH</td>
</tr>
<tr>
<td>9</td>
<td>LM, CA</td>
</tr>
<tr>
<td>10</td>
<td>LM, CA</td>
</tr>
</tbody>
</table>


In table 1. Note that in four of the eight arteries where a LRNC was detected, IPH was also present.

In the following, we first performed a region-based analysis of the WSS–plaque component map for each component to identify (1) the temporal variation of the WSS averaged over the region where each type of plaque components exists (section 3.1) and (2) whether there is any statistically significant difference between the regional WSS average computed for different plaque components at peak systole (section 3.2). The novelty of the proposed WSS–plaque component map is that each point is equipped with the WSS values and the thickness of various plaque components. With this map, we can perform local analyses on how the size of a certain type of plaque component is correlated with the WSS values on a point-by-point basis. Vulnerable plaques are usually characterized by a large pool of LRNC. In this study, we performed local evaluation of the correlation between LRNC thickness with WSS and the results are presented in section 3.3.

3.1. WSS temporal variation and plaque components

WSS can be averaged along the region of the luminal surface overlying each plaque component to detect WSS thresholds associated with the presence of specific plaque components. Figure 7 summarizes the temporal variation of WSS for plaque components identified in the analyzed arteries.

Note that the WSS values at diastole varied among the different plaque components, being generally lowest for the regions were CA was detected, whereas higher values were commonly found for the regions with IPH.

3.2. WSS distribution and presence of high-risk plaque components

WSS levels corresponding to plaque features known to be associated to adverse outcomes and plaque progression and destabilization can be measured and analyzed to detect vulnerable thresholds. IPH has been identified as a high-risk feature. Peak-systolic WSS can be extracted from the results of the numerical simulation for the regions underlying LRNCs. The mean value of the peak WSS across the region with LRNC was computed and levels were compared between the LRNCs with haemorrhage with those LRNCs without IPH, as illustrated in figure 8. A LRNC was identified in eight of the analyzed arteries; four of these LRNCs contained IPH (table 1). Lower WSS was measured in the LRNCs containing haemorrhage.
3.3. WSS distribution and lipid-rich necrotic core size distribution

The severity of atherosclerosis can be assessed by characterizing plaque composition using MRI. In particular, a large LRNC has shown to be a feature of vulnerable plaques that can be successfully evaluated using MR (Cai et al 2005, Takaya et al 2006). Thus, the thicknesses
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Figure 9. 2D WSS–plaque component maps for the cases with LRNC. Two maps are displayed for each artery and each row shows the maps generated for a single artery. The left column shows the maps with the LRNC thickness. The right column shows the WSS maps. Both LRNC and WSS distribution maps are color-coded and superimposed on the luminal surface.

of the MR-identified LRNCs were measured and the resulting size distribution flattened maps are shown in figure 9. The left column of figure 9 shows the flattened map with the thickness of LRNC color-coded and superimposed. Black represents that no LRNC is present in the
region. The right column of figure 9 shows the flattened map with WSS color-coded and superimposed, in which LRNC regions were outlined by the white lines. Pearson correlation coefficients between LRNC thickness and WSS values at regions with LRNC present were tabulated in table 2. There is a statistically significant positive correlation between WSS and $T_{LRNC}$ for six out of eight cases. The Pearson coefficient calculated using data points of all eight arteries is 0.302 ($P < 0.001$).
Table 2. Pearson correlation coefficient between lipid-rich necrotic core thickness ($T_{LRNC}$) and WSS for each artery and the corresponding $P$ value.

<table>
<thead>
<tr>
<th>Case</th>
<th>Pearson correlation</th>
<th>$P$ value</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.24</td>
<td>&lt;0.001</td>
<td>350</td>
</tr>
<tr>
<td>2</td>
<td>0.56</td>
<td>&lt;0.001</td>
<td>642</td>
</tr>
<tr>
<td>3</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>379</td>
</tr>
<tr>
<td>4</td>
<td>0.34</td>
<td>&lt;0.001</td>
<td>1004</td>
</tr>
<tr>
<td>5</td>
<td>0.28</td>
<td>&lt;0.001</td>
<td>306</td>
</tr>
<tr>
<td>6</td>
<td>0.47</td>
<td>0.008</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>0.06</td>
<td>0.72</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>0.06</td>
<td>0.46</td>
<td>300</td>
</tr>
</tbody>
</table>

4. Discussion

Vascular endothelial cells respond to the shear stress exerted on them by the flowing blood by modifying their signal transduction, gene expression, structure and function. In fact, there is increasing evidence that lower values of shear stress are responsible for the development of endothelial phenotypic changes associated with atherogenesis, whereas high shear stress induces phenotypic changes that are atheroprotective (Chiu et al. 2009). It has been suggested that advanced lesions might lead to WSS levels conducive to increased plaque growth and instability (Davies 2009); however, a consensus regarding the levels triggering instability is still lacking (Stone et al. 2012, Groen et al. 2007). In this study we have developed a framework that allows the analysis of the potential contribution of WSS to plaque vulnerability by co-registering the distribution of WSS along the lumen of atherosclerotic lesions and plaque features, including vulnerable features such as IPH (Takaya et al. 2005). This framework may be used in serial studies to detect thresholds of WSS triggering the cellular and molecular processes leading to vulnerable plaque features.

Though over the last decade MR-based CFD models have been used to identify flow patterns in healthy or early-stage atherosclerotic arteries (Thomas et al. 2005, Lee et al. 2008), as well as in advanced lesions with surface disruption (Groen et al. 2007), there has not been any systematic study to determine how the distribution of WSS may contribute to plaque progression and vulnerability; thus, a consensus regarding vulnerable WSS values has not been reached. The purpose of the proposed framework is to provide the appropriate tool to precisely perform such study. We applied this framework to investigate ten carotid atherosclerotic arteries. We used a histologically validated MRI multi-contrast protocol (Yuan and Kerwin 2004) to characterize and quantify carotid lesions since MRI has proved to be an established technique for this purpose (Underhill et al. 2010). The results of the segmentation rendered 3D maps of the plaques’ burden and components. Furthermore, the resulting 3D luminal reconstruction was used to build CFD models to solve for the blood flow and the corresponding distribution of WSS. Preliminary analysis of the WSS–plaque component map suggests that the presence of plaque components may be associated to certain values of WSS: figure 7 suggests that LM (a) is identified in regions with relatively low values of WSS at diastole (0.4–2.7 Pa, excluding case 6), whereas IPH (d) seems to be located in regions with relatively higher values of diastolic WSS (2.6–4.72 Pa, excluding case 4). Note that these WSS values were held during a third of one cardiac cycle. Furthermore, comparing among LRNCs with and without IPH, those with IPH were associated with a lower WSS (figure 8), suggesting that low WSS may be promoting the presence of this high-risk plaque feature that is associated with accelerating plaque growth and adverse outcomes (Takaya et al. 2005, Takaya et al. 2006).
Local low WSS have also been identified as predictors of plaque growth and worsening of clinically relevant luminal obstructions in coronary arteries (Chatzizisis et al 2008, Stone et al 2012).

The preliminary results obtained with the developed framework are constrained by the small sample size used in the development, as well as by the limitations of the CFD modeling assumptions. (1) A fully-developed pulsatile flow with a fixed Womersley and Reynolds numbers was used for all the bifurcations due to the lack of patient-specific flow data for the boundary conditions. The absolute values of the WSS field would be impacted by this assumption; however, the location and extent of WSS patterns have been shown to remain fairly constant when using non-specific inlet conditions (Hoi et al 2010). This limitation can be overcome by improving the CFD models with the use of patient-specific flow data for the boundary conditions as measured with MR. A phase-contrast MR sequence can be added to the current MR protocol to measure the flow at the model’s inlet and outlets (figure 10). (2) The imaging coverage, however, represents a major limitation, since the geometrical features are not allowed to completely exert their influence into the flow (Ford et al 2008). This limitation should be considered in the design of future serial studies, where a larger coverage could be included. (3) Finally, blood was assumed to behave as a Newtonian fluid, and the vessel wall as a rigid tissue; however, independent studies have shown that the effects of non-Newtonian fluid behavior and wall distensibility on the distribution of WSS are minor in the carotid bifurcation (Perktold et al 1991a, 1991b, Younis et al 2004).

5. Conclusion

Although different groups have successfully estimated WSS patterns in carotid atherosclerotic plaques, there has not been any attempt before to correlate WSS distribution patterns with the location and size of specific components of the atherosclerotic plaque. In this work, we have developed 2D and 3D WSS–plaque component maps and demonstrated their potential as a tool...
for identifying WSS patterns that may be linked to vulnerable plaque features. The preliminary results reported suggest that there might be a link between the presence of haemorrhage, a critical factor in plaque progression and destabilization, and low WSS acting on the luminal surface. If further serial studies bear out this association, WSS might be used as a marker for the risk of intra-plaque hemorrhage and subsequent adverse events.

Acknowledgments

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