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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, are thought to trigger cellular and molecular mechanisms that determine atherosclerotic plaque vulnerability to rupture. Magnetic resonance imaging (MRI) 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 (CFD) has allowed researchers to obtain time-resolved wall shear stress (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 (3D) 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

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)

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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, thin fibrous cap, or intra-plaque haemorrhage, that have been shown to be key determinants of plaque vulnerability (Naghavi *et al.*, 2003b; Naghavi *et al.*, 2003a), and these features can be identified by MRI (Saam *et al.*, 2007).

Due to the challenges of measuring wall shear stress 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 wall shear stress 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 wall shear stress 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 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 (0.625mm). 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 $0.0035 \text{ Pa}\cdot\text{s}$. Due to the lack of patient-specific flow information from the common, external, and internal carotid arteries, assumed flow conditions were defined at the inlet (common carotid artery) and outlets (internal and external carotid arteries) of the model: a fully-developed Womersley flow was assumed at the entrance with a cardiac period of 0.98 seconds, 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 lipid-rich necrotic core, calcification, loose matrix 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, lipid-rich necrotic core (LRNC) and intra-plaque haemorrhage (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 three-dimensional 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 W, Martin K, Lorensen B. The Visualization Toolkit: An Object-Oriented Approach To 3D Graphics. 4th ed. Clifton Park, NY: Kitware Inc; 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 and CCA respectively) were cut longitudinally by the planes P_{ICA} , P_{ECA} and P_{CCA} 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 in table 1. Note that in four of the eight arteries where a lipid-rich necrotic core was detected, intra-plaque haemorrhage 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 where calcification was detected, whereas higher values were commonly found for the regions with intra-plaque haemorrhage.

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. Intra-plaque haemorrhage (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 lipid-rich necrotic cores (LRNCs). The mean value of the peak wall shear stress 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 lipid-rich necrotic core (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 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 colour-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 colour-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 6 out of 8 cases. The Pearson coefficient calculated using data points of all 8 arteries is 0.302 ($P < 0.001$).

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 wall shear stress 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 wall shear stress to plaque vulnerability by co-registering the distribution of wall shear stresses along the lumen of atherosclerotic lesions and plaque features, including vulnerable features such as intra-plaque haemorrhage (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 10 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 loose matrix (a) is identified in regions with relatively low values of WSS at diastole (0.4 - 2.7 Pa, excluding case 6), whereas intra-plaque haemorrhage (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 intra-plaque haemorrhage, those with intra-plaque haemorrhage 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 wall shear stress field would be impacted by this assumption; however, the location and extent of wall shear stress 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 wall shear stress are minor in the carotid bifurcation (Perktold *et al.*, 1991a; Perktold *et al.*, 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.

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Abbreviations

CA	Calcification
CCA	Common Carotid Artery
CFD	Computational Fluid Dynamics
ECA	External Carotid Artery
ICA	Internal Carotid Artery
IPH	Intraplaque Hemorrhage
LM	Loose Matrix
LRNC	Lipid-Rich Necrotic Core
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
VIL	Vascular Imaging Laboratory

WSS Wall Shear Stress
2/3-D two/three-Dimensional

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Figure 1.
Wall shear stress (WSS) distribution at peak systole.

Figure 2. Schematic demonstrating how the size of plaque components is quantified. T_{IPH} denotes the thickness of intra-plaque haemorrhage (IPH), whereas T_{LRNC} denotes the thickness of lipid-rich necrotic core (LRNC).

Figure 3.
3D distribution of plaque components along an atherosclerotic carotid lesion.

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 colour-coded and superimposed on the 2D maps.

Figure 7. Wall shear stress variation with the cardiac cycle along the luminal surface overlying (a) loose matrix, (b) calcification, (c) lipid-rich necrotic core, and (d) intra-plaque haemorrhage, as detected in the ten carotid bifurcations considered in this study. Three cardiac cycles are included.

Figure 8.

Comparison of averaged peak systole wall shear stress (WSS) over the region overlying a lipid-rich necrotic core (LRNC) between cases with intra-plaque haemorrhage (IPH) and cases without. Mean and standard deviation WSS values are included for each group.

Figure 9.

2D WSS-Plaque Component maps for the cases with lipid-rich necrotic core (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 colour-coded and superimposed on the luminal surface.

Figure 10. MRI-CFD framework to determine the role of local hemodynamics in carotid plaque progression and future clinical events.

Table 1

Components of the atherosclerotic plaques used to build and test the framework.

Artery	Plaque components
1	LM, CA, LRNC, IPH
2	LM, LRNC, IPH
3	LM, CA, LRNC
4	LM, CA, LRNC
5	LM, CA, LRNC, IPH
6	LM, CA, LRNC
7	LRNC
8	LM, CA, LRNC, IPH
9	LM, CA
10	LM, CA

LM: loose matrix, CA: calcification, LRNC: lipid-rich necrotic core, IPH: intra-plaque haemorrhage.

Table 2

Pearson correlation coefficient between lipid-rich necrotic core thickness (T_{LRNC}) and wall shear stress (WSS) for each artery and the corresponding P value.

Case	Pearson Correlation	P value	n
1	0.24	<0.001	350
2	0.56	<0.001	642
3	0.30	<0.001	379
4	0.34	<0.001	1004
5	0.28	<0.001	306
6	0.47	0.008	31
7	0.06	0.72	36
8	-0.04	0.46	300