Mass Transport of Low Density Lipoprotein in Reconstructed Hemodynamic Environments of Human Carotid Arteries: The Role of Volume and Solute Flux Through the Endothelium

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The accumulation of low density lipoprotein (LDL) in the arterial intima is a critical step in the initiation and progression of atheromatous lesions. In this study we examine subject-specific LDL transport into the intima of carotid bifurcations in three human subjects using a three-pore model for LDL mass transfer. Subject-specific carotid artery computational models were derived using magnetic resonance imaging (MRI) to obtain the geometry and phase-contrast MRI (PC-MRI) to acquire pulsatile inflow and outflow boundary conditions for each subject. The subjects were selected to represent a wide range of anatomical configurations and different stages of atherosclerotic development from mild to moderate intimal thickening. A fluid–solid interaction (FSI) model was implemented in the computational fluid dynamics (CFD) approach in order to consider the effects of a compliant vessel on wall shear stress (WSS). The WSS-dependent response of the endothelium to LDL mass transfer was modeled by multiple pathways to include the contributions of leaky junctions, normal junctions, and transcytosis to LDL solute and plasma volume flux from the lumen into the intima. Time averaged WSS (TAWSS) over the cardiac cycle was computed to represent the spatial WSS distribution, and wall thickness (WTH) was determined from black blood MRI (BBMRI) so as to visualize intimal thickening patterns in the bifurcations. The regions which are exposed to low TAWSS correspond to elevated WTH and higher mass and volume flux via the leaky junctions. In all subjects, the maximum LDL solute flux was observed to be immediately downstream of the stenosis, supporting observations that existing atherosclerotic lesions tend to progress in the downstream direction of the stenosis. [DOI: 10.1115/1.4028969]

Keywords: atherosclerosis, LDL, carotid artery, FSI, three-pore model

Introduction

Atherosclerosis is a degenerative arterial disease characterized by atheromatous lesions that localize in specific sites of the vasculature. Initiation of these lesions is related to focal uptake of low density and very low density lipoproteins into the subendothelial intima, where they may become oxidized and attract monocytes to attack, through macrophagic phagocytosis, what is perceived to be an inflammatory process. The resulting engorged macrophages transform to foam cells and become trapped in the artery due to the failure of resolving this inflammation, leading to a cascade of pro-atherogenic cellular and molecular responses [1]. Arteries typically respond in the earlier stages of plaque development by employing adaptive processes that sequester the inflammatory region away from the endothelial layer, and the result is a localized intimal-medial thickening without lumen encroachment [2] and without effects on hemodynamics. However, as the disease progresses, these adaptive processes can no longer compensate for plaque growth, and focal luminal narrowing occurs. Plaques can progress in a fashion that leads to a stable but hemodynamically

significant flow reducing lesion; or they can progress as an unstable phenotype that may rupture, causing acute thrombosis and sudden myocardial infarction [3].

While atherosclerosis is a complex disease involving genetic, systemic, behavioral and environmental factors, its focal manifestation argues for the importance of localized biomechanical and biochemical components. Within this context, transport of LDL into the intima, coupled with inadequate clearance, is a critical pro-atherosclerotic process [4]. Various mechanisms and pathways influence transport within the lumen and from the lumen into the arterial wall, and fluid dynamics plays an important role both in terms of “passive” transport (convection and diffusion) and “active” transport whereby WSS elicits LDL and monocyte receptor expression on endothelial cells [5]. A three-pore model for LDL transport has been proposed [5,6] in which contributions to transport arise from transcytosis, flux through normal endothelial cell junctions, and flux through “leaky” junctions. While important in homeostasis, the well-studied vesicular pathway, where circulating LDL reaching the endothelial cell surface is engulfed and transported into the intima through transcytosis, contributes only modestly to transport across the endothelial layer [7]. Plasma is transported through endothelial cell junctions, but if these are tight, the large molecular size of LDL prohibits its passage into the intima. The most significant pathway, therefore, is the “leaky

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junction,” found at regions of arterial branching, bifurcations, and areas along the inner curvature of vessels, and elevated LDL concentration is present in the intima at these leaky sites [8]. Leaky junctions are formed by the detachment of adjacent endothelial cells due to apoptosis and mitosis of the cell. The role of leaky junctions has been demonstrated in in vitro experiments [9,10] where an endothelial cell layer was coated on a porous medial structure. When an increase of apoptosis and mitosis rate was induced, it was found that the volume flux of blood plasma and solute flux of LDL increased linearly with the rate of endothelial cell apoptosis and mitosis. Thus, even though the enhancement of LDL uptake by LDL-receptor expression has been observed at low WSS regions, the vesicular pathway makes a limited contribution by comparison to the leaky junction pathway, which contributes approximately 90% of the solute flux.

In efforts to provide more detailed descriptions of LDL transport in the circulation, computational approaches have been utilized with different assumptions relating to the mechanisms influencing LDL passage through the endothelium. Initial studies focused on particle transfer with flow characteristics in the lumen and the concentration change of solute on the luminal surface being correlated with local flow features. This has been termed a free-wall model because the arterial wall serves as the boundary condition and the physiological response of endothelium is ignored [11–14]. The vessel wall is treated as a fully saturated porous medium with interstitial flow due to structural features, consisting of fiber matrix structures, e.g., proteoglycans. The interstitial flow, which convects LDL particles into the subendothelial layer and within vessel wall, is calculated with Darcy’s model [15] or Brinkman’s model [13,16] to obtain detailed transport of the solute based on single-layer or multilayer models. In the single-layer model, the wall is treated as single porous medium with homogeneous parameters for mass transport [6,16,17], while in multilayer models, the vessel wall is treated as a complex structure consisting of the intima, internal elastic lamina (IEL), and the media [18–20]. Due to limitations of current medical imaging techniques to obtain detailed in vivo vessel structure, application of multilayered models has been limited primarily to 2D idealized vessel geometries with or without stenosis. However, a recent study [21] has employed a four layer model to image data from a human carotid bifurcation. This report differs from our current study in that flux through leaky junctions is not modeled for the endothelium layer and the WTH is taken to be constant. With increased understanding of the physiological response of endothelial cells to shear stress, shear-dependent transport properties have been employed at the endothelium as the interface condition between the lumen and arterial wall [11,13,15–17,19,22].

Several studies using the Kedem-Katchalsky model, which defines the coupling of transendothelial solute and volume flux through a single pathway of leaky junctions with shear-dependent hydraulic conductivity or permeability of the endothelium, showed an increase of LDL accumulation at low WSS regions by the enhancement of volume flux through leaky junctions [15,18,19]. The single pathway approach has been extended to multiple pathways, including vesicular transcytosis, normal junctions and leaky junctions, for implementing more accurate LDL and plasma flow movement through each pathway [6]. The multiple pathways approach reveals more detailed underlying mechanisms that explain elevated LDL accumulation at low WSS regions by the observation that total transendothelial infiltration flow is enhanced through greater formation of leaky junctions at these sites. A shear stress-dependent three-pore model has been applied to an example of LDL accumulation in a patient-specific left coronary artery [23]. The pathways modeled include blood plasma and LDL flux into the intima through transcytosis, normal junctions, and leaky junctions; and this was coupled to a convection-diffusion-reaction model of LDL transport within the wall media. The arterial anatomy was obtained from computerized tomography (CT) images of a specific patient, although the flow

waveform used in the model was taken from a generic coronary artery waveform. An interesting aspect of that study is that the CT image was utilized to virtually “remove” a heavily calcified region, leaving a geometry that represented the patient’s “healthy” state. The authors concluded that (i) the plaque that was imaged by CT developed at a site of predicted high LDL concentration and (ii) in the diseased geometry, the location of high LDL concentration shifted to the distal region of the plaque.

To further explore the relationship between fluid dynamics and sites of predicted LDL uptake in the artery wall, we have utilized the three-pore model for LDL transport [5,6,23] to investigate flow in carotid artery bifurcations of three human subjects with varying stages of WTH. The computational models were constructed from BBMRI from three patients which had shown distinctive geometrical characteristics from mild to moderate stenosis. In addition to the geometry being patient-specific, we obtained pulsatile blood velocity data for the inflow and outflow boundary conditions in each case using PC-MRI. Because the flow field can be affected by wall compliance, we also incorporated a FSI model in the investigation to account compliant vessel wall effects on WSS. TAWSS was calculated and incorporated into the three-pore model to account for LDL passage into the intima. The results are employed to investigate relationships between WSS, WTH, and predicted LDL uptake and to relate these to individual patient characteristics.

Methods

Construction of Hemodynamic Models. MRI data sets for the left carotid artery bifurcation for three subjects were selected from the EFFERVESCENT data base at Emory University and used to develop computational model geometries and supply velocity boundary conditions for CFD. Patients in that study, which was approved by the Emory University Institutional Review Board, were 50–75 yr old (mean = 58 yr) and were asymptomatic for carotid artery disease. All images were acquired on an MRI scanner (Achieva 3 T, Philips Medical Systems, Best, The Netherlands) using a 4-channel, bilateral carotid coil, and relevant parameters are provided in Table 1. From the bifurcation apex (referred to as the origin) one set of 10×2 mm contiguous, interleaved, axial slices was taken in the inferior direction covering the common carotid artery (CCA) and another set was acquired in the superior direction covering the internal carotid artery (ICA) and external carotid artery (ECA). The software package Segment (Cardiac MR group, at Lund University) in which the edge is detected by a fast algorithm for tracking moving interfaces in a level set-like manner [24] was used to segment images. The points of contour of the lumen and outer wall were imported to the CAD program, Geomagic (Geomagic, Inc., NC), in which the NURBS

Table 1 Pulse sequence parameters for the PCMR data and T2W MRI

	PCMR	T2W TSE
Sequence	2D cine GRE	T2 TSE
Flip angle	10	90
TR	8.3 ms	1700 ms
TE	4.9 ms	50 ms
FOV	112×160 mm	120×160 mm
Matrix	128×256	384×512
Pixel size	0.6×0.6 mm	0.3×0.3 mm
Phases	16	1
Slices number	2	20
Slice thickness	3 mm	2 mm
Fat-Sat	no	no
NSA (NEX)	2	2
VENC	100 cm/s	N/A
Prepulse	N/A	180–180 NS (black blood)

Fig. 1 (a) Reconstructed carotid artery from BBMRI. (b) BBMRI of subject 2 at CCA. (c) PCMR image at cross section taken 10 mm inferior from bifurcation apex (units (m/s)) and velocity distribution from FSI with rescaled method at the same location (units (m/s)) at peak acceleration in diastole (red circle in middle CCA flow rate profile).

(nonuniform rational B-spline) algorithm was used to make a 3D loft model.

The inner wall and outer wall of the blood vessel in each subject and 3D transparent models are shown in Fig. 1(a). Carotid arteries from the three subjects depicted the general features found in the human carotid artery. In all subjects, geometrical nonplanarity is observed between mother and daughter arteries. The tortuous curvature of the ICA varies among individuals but, in general, is more severe than the curvature of the ECA. There is a carotid bulb in the ICA and stenoses are observed around the beginning of the bifurcation at the outer wall, becoming more severe from subjects 1 to 3.

PC-MRI data consist of magnitude (anatomic) and phase (velocity) MR images. Magnitude PC-MR images were used to isolate the region of interest (ROI), and the segmented ROI was employed as the mask to isolate the same region of phase images for obtaining velocity information. PC-MRI at a slice 10 mm inferior from the apex was used to compute the CCA flow rate and at 10 mm above for the ICA/ECA flow rates. A total of 30 time points were measured in a cardiac cycle. A MATLAB in-house code was used to isolate the inlet and outlet areas from magnitude PC-MRI, and a region growing algorithm was utilized to implement the segmentation. PC-MRI data were rescaled to supply quantitative velocity information. The velocity data and lumen areas for the 30 time points were employed to compute points in the flow waveforms, and a 7-harmonics Fourier series was used to describe

the time variation over the cycle. Figure 2(a) presents the inflow and outflow waveforms for subject 2. Although the flow waveforms were similar among the three subjects, there were individual differences, especially in the time variation of the flow division into ICA and ECA beyond the bifurcation; and individual, subject-specific waveforms were employed for the computations. These PC-MRI-derived flow waveforms were imposed for outlet flow boundary conditions at the ICA and ECA. Because the FSI simulation requires an actual pressure and there were no intra-vascular pressure made in the subjects, a generic pressure waveform [25] was imposed at the CCA inlet as shown in Fig. 2(b).

Computational Methods. In order to consider the arterial wall influence on flow patterns, an FSI approach was employed with an external staggered iterative method, in which velocity and pressure of blood flow are calculated by the Navier–Stokes equations (N–S) and continuity equation on the current configuration in the fluid domain and then total stress is transferred to the vessel structure as an external force. The initial arterial geometry is then updated and serves as the updated flow domain at the next time step. For accurate calculation of blood flow in a moving domain, the arbitrary Lagrangian–Eulerian (ALE) algorithm has been utilized [26]. The incompressible Navier–Stokes equations in ALE coordinates with the assumption of Newtonian rheology and constant density are

Fig. 2 (a) Flow rate profiles of CCA, ICA/ECA for subject 2 in a cardiac period from PCMRI. (b) Generic pressure curve at CCA inlet for FSI simulation.

$$\rho_{\text{blood}} \left(\frac{\partial v}{\partial t} + (v - \hat{v}) \cdot \nabla v \right) = -\nabla p_{\text{lumen}} + \mu_{\text{blood}} \nabla^2 v + F \quad (1)$$

$$\nabla \cdot v = 0 \quad (2)$$

Because of the noninvasive nature of this study and the absence of knowledge of constituent wall components, the arterial wall was treated as an elastic homogeneous material with constant Young's modulus and density. Additionally, the local WTH as derived from MRI images was employed in the solid mechanics computations. Fully constrained boundary conditions were applied on the edge of the CCA and ICA/ECA to give stability to the structural calculation. To eliminate the extra volume formation which comes from the mismatch between the in vivo state and the beginning of the calculation with no stress state, a physiological pressure range (83 mmHg–152 mmHg) was scaled down to a reduced pressure range (5 mmHg–74 mmHg). The primary reason for choosing 5 mmHg as an initial diastolic pressure was that it was enough to prevent negative pressure developing at the outlets and, at the same time, does not cause geometrical deformation of the arterial wall. The arterial wall was modeled with a commercial FEM (finite element method) program, ANSYS MECHANICS 12.1 (Ansys, Canonsburg, PA). Interpolation between FVM and FEM codes was done by Ansys Multiphysics on the interface surface with an under-relaxation method. This prevents numerical divergence and is termed “artificial added mass instability,” [27,28] when FSI is implemented by the staggered iterative method with similar densities between fluid and structure such as is the case with blood and arterial wall. A full description of the FSI procedure and verification of flow patterns by comparing

subject-specific PC-MRI data with the computed results can be found elsewhere [29].

In pulsatile transient simulations, numerical calculations were performed for three cardiac cycles to ensure dynamic equilibrium and improve the accuracy of the computations by eliminating start-up effects. The time step was chosen as 1/1000 of a cardiac cycle, and the flow and solid domains were meshed with 3D tetrahedral and prismatic elements with the final grid sizes: subject 1—79,000 and 146,000 in fluid and solid domain; subject 2—255,000 and 292,000; and subject 3—191,000 and 209,000. These were selected after grid sensitivity studies using the criteria that each parameter variation in the fluid and solid domains was less than 1%.

Three-Pore Model for LDL Transport. The endothelial layer is a major barrier to solute transendothelial passage from the lumen to the intima because the gap between endothelial cells under normal conditions is less than the size of most of biomolecules, e.g., LDL and albumin. LDL particles, which are carried with blood flow in the lumen, may attach to the endothelial cell surface via LDL receptors and then can be transferred to the sub-endothelial layer by vesicles through the process of vesicular transcytosis. However, the portion of LDL passage via this mechanism is under 10%, in contrast to over 90% of LDL particles passing through cellular leakage which is formed by the detachment of endothelial cells [7,9,10]. Higher detachment rates are caused by elevated apoptosis and mitosis of cells under low or oscillatory WSS conditions, often referred to as “disturbed flow.” Thus, it is essential to include shear-dependent local transport parameters based on the occurrence of leaky junctions, which in turn leads to variations in volume and solute fluxes across the endothelial layer. A multiple pathway “three-pore model” has been suggested for describing LDL mass transport, and the model has been applied to an idealized stenosis geometry and an example of a subject-specific human coronary artery [6,23]. We briefly describe this model here, and further details may be found in Refs. [6,23]. To include the physiological response of endothelial cells to WSS, the model proposes the concept of the fraction of leaky junctions (ϕ), represented by the ratio of the area occupied by leaky junctions to the total area of cells. A mathematical model is formulated to link the local fraction of leaky junctions and local WSS as seen in Eq. (3), based on published biological experimental data, which connects several steps to construct a series of relationships

$$\begin{aligned} SI &= 0.380e^{-0.790WSS} + 0.225e^{-0.043WSS} \\ \#MC &= 0.003797e^{14.75SI} \\ \#LC &= 0.307 + 0.805 \times (\#MC) \\ \phi &= \frac{\#LC \times \pi R_{\text{Endo}}^2}{S_{\text{unit}}} \end{aligned} \quad (3)$$

Here SI is the shape index of endothelial cells, which represents the alignment of these cells under local WSS. #MC and #LC are the number of mitotic cells at the regions with specific shape index observed by Chien [30] and the number of leaky cells which is correlated with the number of mitotic cells, respectively. Finally, the local fraction of leaky junctions is determined based on the area occupied by leaky cells per unit area, in which R_{Endo} is the radius of an endothelial cell (15 μm) and S_{unit} is a periodic circular unit area, set to be 0.64 mm². Once obtaining the fraction of leaky junctions, local transport properties via normal junction and leaky junction, i.e., hydraulic conductivity (L_p), LDL diffusive permeability (P_e), the reflection coefficient of particles (σ_r), are computed using pore theory. The plasma flow (J_v) in the arterial wall is essential for calculating LDL mass flux because transendothelial passage of LDL into the intima depends on the amount of infiltration. An electrical circuit analogy [19,22] has been used to model flow dynamics in the arterial wall, in which the pressure

Fig. 3 (a) Streamlines and velocity distributions at four cross sections in subject 1 carotid artery at the middle of diastole (red dot in CCA flow rate profile). (b) TAWSS in anterior and posterior views (units (Pa)).

gradient between luminal surface (P_l^{end}) and the interface to the media-adventitia ($P_{\text{wall}}^{\text{adv}}$) acts the driving pressure force and the total resistance to fluid flow (R_T) is determined by the combination of endothelial resistance (R_{end}) and arterial wall resistance (R_{wall}). Hydraulic conductivity via normal junctions ($L_{p,Nj}$) is obtained from the resistance via the inverse relationship, and varies with WTH at specific sites; however, in the leaky junction ($L_{p,Lj}$), it depends on WSS mediated with φ and, as a consequence, the dynamic resistance of the endothelium through parallel coupling with the normal junction pathway can be implemented. Equation (4) models the approach to determining infiltration

$$\begin{aligned}
 J_{v,T} &= \frac{P_l^{\text{end}} - P_{\text{wall}}^{\text{adv}}}{R_T} \\
 R_T &= R_{\text{end}}^T + R_{\text{wall}} \\
 \frac{1}{R_{\text{end}}^T} &= \frac{1}{R_{\text{end}}^{Nj}} + \frac{1}{R_{\text{end}}^{Lj}} \\
 &= L_{p,Lj} + L_{p,Nj}
 \end{aligned} \quad (4)$$

The resistances of the intima, IEL and media are represented by a single wall resistance R_{wall} based on studies done by Simon et al. [31] in which a comparison of infiltration between de-endothelialized and intact arteries showed that the increase of the fluid flux with elevated luminal pressure varied linearly in the case of endothelial layer destruction, whereas a nonlinear relationship was observed in the intact artery. For this reason, it seems to be reasonable that other parts of artery except the endothelial cell layer may be treated as one structure. Darcy's law [6,15,17] was adopted to construct R_{wall} , which was expressed as $(\mu_{\text{plasma}} \cdot \text{WTH})/K_D$, where μ_{plasma} (7.2×10^{-4} Pa·s) [32], WTH and K_D (2.0×10^{-18} m²) [22] are the dynamic viscosity of the pore fluid, WTH, which was acquired from the patient-specific geometry, and Darcy's permeability, respectively. The contribution of each pathway to overall apparent permeability of LDL (Pe_{tot}) is determined based on biological observations by Cancel et al. [7], in which the permeability via transcytosis (Pe_T) is not affected by local WSS variation, so that the contribution of transcytosis is represented with a unique value, and the permeability of normal junctions (Pe_{Nj}) is negligible because LDL is too large to cross the intercellular tight connections between endothelial cells.

Fig. 4 (a) Streamlines and velocity distributions at four cross sections in subject 2 carotid artery at the middle of diastole. (b) TAWSS in anterior and posterior views (units (Pa)).

In contrast, the permeability of leaky junctions (Pe_{Lj}) responds dynamically to local WSS, as noted previously. These pathways can be represented by the following equation:

$$\begin{aligned} Pe_{tot} &= Pe_{Tr} + Pe_{Lj} \\ Pe_{Lj} &= Pd_{Lj} Z_{Lj} + J_{v,Lj} (1 - \sigma_{f,Lj}) \\ J_{v,Lj} &= J_{v,T} \frac{L_{p,Lj}}{L_{p,Lj} + L_{p,Nj}} \end{aligned} \quad (5)$$

where Pd_{Lj} , Z_{Lj} , and $\sigma_{f,Lj}$ are diffusive permeability, a fractional reduction factor in solute concentration gradient at the pore entrance, and the solvent drag coefficient of the leaky junction, respectively. These parameters were obtained from pore theory considering the physical size of LDL molecules and open gaps at leaky junctions [6]. Total permeability of the endothelium to LDL (Pe_{tot}) is used to produce solute flux of LDL on the luminal surface by the multiplication of LDL endothelial concentration on the luminal side. In the lumen, LDL concentration is influenced primarily by local flow patterns since the relatively large molecular size limits the effects of diffusion. Thus, convection forces are dominant in controlling particle movement, which leads to spatial

variations of concentration in the artery lumen, especially at low velocity regions. However, in studies using an idealized geometry [33] and a subject-specific carotid artery [29] in which convection-diffusion effects were incorporated into the governing equations along with an LDL surface reaction model, the increase of LDL concentration at the endothelial surface at these sites was found to be less than 3% of the lumen concentration.

Therefore, in our study, the spatial concentration of LDL on the luminal surface is treated as constant and set at the inlet concentration (C_0). The luminal pressure (P_1^{nd}) is set at 120 mmHg and 30 mmHg and is assigned as the boundary pressure at the media-adventitia interface (P_{wall}^{adv}) [22], which gives a 90 mmHg pressure gradient (ΔP) across the artery wall. While it would be interesting to model LDL transport through the arterial structure, detailed LDL concentration profiles in the blood vessel wall are not considered in this study. Current in vivo noninvasive imaging is limited in its ability to assess specific atherosclerotic components in arterial soft tissue, and material properties of each component are dependent on individual subjects, especially for lesion constituents. Multilayer models have the potential to reveal LDL concentration profiles in the arterial wall, however, and certain characteristics have been found to be in common

Fig. 5 (a) Streamlines and velocity distributions at four cross sections in subject 3 carotid artery at the middle of diastole. (b) TAWSS in anterior and posterior views (units (Pa)).

[16,18,21,22,32,33]. First, the resulting LDL concentrations in the vessel show similar patterns, where higher LDL accumulation has been shown in the intima and LDL concentration becomes reduced in the subsequent arterial structures. Second, LDL concentration or mass flux at the lumen side determines the resulting LDL distribution in the arterial wall. High mass flux to and across the endothelial surface leads to higher LDL accumulation in the intima and, sequentially, higher LDL in the media with a gradual decrease from the wall side of endothelium to the interface of media-adventitia [34].

Results

Flow Patterns. The characteristics of flow patterns in each subject are demonstrated in Figs. 3–5 using an instantaneous streamline visualization taken at mid-diastole, which usually shows more complex flow patterns than systole in human carotid arteries. The great variability in flow characteristics among individuals is clearly demonstrated. It is emphasized that not only geometry but also flow division into ICA and ECA are strong influences on the flow field. In subject 1, the flow is relatively unidirectional with little helical flow patterns present (Fig. 3(a)). In subject 2, out of

plane curvature in the ICA and local area expansion at the ICA side of the bifurcation lead to discernible helical flow patterns which persist well into the distal ICA (Fig. 4(a)). In contrast, the CCA and ECA show relatively uniform flow patterns except for a small region at the lateral ECA side of the bifurcation where a localized region of secondary flow exists. Subject 3 presents the most complex flow among the subjects, and strong secondary flows can be seen across the entire bifurcation region with helical patterns persisting distally into both ICA and ECA (Fig. 5(a)).

WSS. Instantaneous WSS magnitude values were averaged over the pulsatile cycle (TAWSS) and are presented in Figs. 3(b), 4(b), and 5(b) (note that TAWSS values at the CCA inlet are artificially high due to the assumption of a blunt entry velocity profile). Typically, low TAWSS is seen in the bifurcation for all subjects, but the spatial variation among individuals is significant. Interestingly, subject 1 has the lowest TAWSS at the ECA side of the bifurcation (Fig. 3(b)), likely reflecting a geometric change over time as a plaque developed in the carotid sinus (See increased WTH on ICA side of sinus, Fig. 6(a)). Subject 2 has a large area of low TAWSS at the bifurcation, with the ICA side of the sinus being prominently low, and also a region of low TAWSS

Fig. 6 WTH in subjects. (a) Subject 1, (b) subject 2, and (c) subject 3 (units (m)).

in the CCA along the posterior wall (Fig. 4(b)). Subject 3 presents low TAWSS in the sinus and also a fairly large zone of low TAWSS in the CCA, seen clearly in the proximal view (Fig. 5(b)).

WTH. WTH was derived from segmented MR image data as previously described and depicted in Figs. 6(a)–6(c) as “shadows” that are suggestive of local thickening. Figures 4(a) and 5(a) show WTH at several specific cross sections of the arteries for subjects 2 and 3, and it is seen that these individuals did not appear to have advanced focal WTH. The quantitative WTH data were employed in both FSI and LDL flux computations.

Volume and Mass Flux. To acquire volume flux via normal and leaky junctions, the fraction of leaky junctions (ϕ) is obtained from the local TAWSS via Eq. (3), and local transport parameters are acquired based on this value. The velocity of plasma infiltration through the endothelial surface and total LDL mass flux are presented in Figs. 7–9. Based on the model, the plasma volume flux through normal junctions depends upon WTH, but not TAWSS, whereas the plasma flux and LDL mass flux through leaky junctions depends largely on TAWSS. Thus, variations in volume and LDL mass flux seen in the figures can be interpreted through observations in WTH and TAWSS variations.

In subject 1, total volume flux ($J_{v,T} = J_{v,Lj} + J_{v,Nj}$, combination of Figs. 7(a) and 7(b)) is in the range between 1.0×10^{-8} and $2.0 \times 10^{-8} \text{ ms}^{-1}$ over the majority of the carotid artery, except for narrow regions of slight intima media thickness progression around the carotid bulb, because WTH is a factor in determining the resistance to interstitial flow in the arterial porous structure. The computed magnitude of total volume flux is similar to previous experimental and theoretical investigations. In the study of Meyer et al. [34], the filtration flow in a straight segment of rabbit thoracic aorta was measured and found to be $\sim 1.78 \times 10^{-8} \text{ ms}^{-1}$

Fig. 7 The volume and mass flux for subject 1. (a) The distribution of volume flux via leaky junctions ($J_{v,Lj}$) from anterior (left) and posterior view (right) and (b) the volume flux via normal junctions ($J_{v,Nj}$) (c) Total mass flux of LDL (J_s).

when the luminal surface was pressurized with 70 mmHg. The range of our computed values is also similar to the theoretical study of Prosi et al. [33] who applied a multilayered model to represent the blood vessel structure. The corresponding filtration flow was $1.76 \times 10^{-8} \text{ ms}^{-1}$ when 70 mmHg was applied as the pressure gradient between the endothelial surface and the interface of the media and adventitia. The area of high volume flux through leaky junctions ($J_{v,Lj}$) is limited to the connection of the CCA and ECA, which corresponds to an area of low TAWSS in this subject. The value of flow filtration at this region is approximately $0.3 \times 10^{-8} \text{ ms}^{-1}$ and is higher than most other regions by a factor of ten. At the outer wall of the beginning of the bifurcation a high volume flux through leaky junctions is observed; however, the filtration flow via normal junctions shows its lowest value at these regions. Figure 7(c) presents the distribution of total mass flux across the endothelium which demonstrates the dominance of LDL mass transfer by the convection of plasma infiltration via the leaky pathway. The range of these values is also dynamic as with $J_{v,Lj}$, and the difference between the proximal CCA and the beginning of the bifurcation is a factor of ten.

As noted previously, nonplanarity and curvature of the carotid arteries of subject 2 contribute to complex flow patterns in the carotid bulb region. For this reason, the distributions of mass and volume flux are more variable in subject 2 (Fig. 8). The maximum of $J_{v,Lj}$ is observed in the sinus and downstream of the stenosis, and a relatively elevated value is found around the junction of the CCA and ECA (Fig. 8(a)). In contrast, the minimum value of $J_{v,Nj}$ occurs at the stenosis and anterior side of the CCA/ECA junction, coinciding with high WTH regions. The maximum value of infiltration ($2.82 \times 10^{-8} \text{ ms}^{-1}$) in this subject is very similar to measurements in the rabbit aorta conducted by Tedgui and Lever [35], in which total interstitial flow was $2.8 \times 10^{-8} \text{ ms}^{-1}$ when the aorta was pressurized with 70 mmHg intraluminal pressure. $J_{v,Lj}$ is low

Fig. 8 The volume and mass flux of subject 2. (a) The distribution of volume flux via leaky junctions ($J_{v,Lj}$) from anterior (left) and posterior view (right) and (b) the volume flux via normal junctions ($J_{v,Nj}$) (c) Total mass flux of LDL (J_s).

in the ECA where a low occurrence of leaky junctions is expected due to relatively uniform flow patterns (Fig. 8(a)). The maximum in mass flux ($26.0 \times 10^{-13} \text{ mol/m}^2 \cdot \text{s}$) is present in the bulb downstream of the stenosis, where values are higher than those in most other regions ($3.0 \times 10^{-13} \text{ mol/m}^2 \cdot \text{s}$) by a factor of ~ 10 (Fig. 8(c)). In addition to the carotid bulb, mass flux is elevated at the anterior and posterior sides of the junction between CCA and ICA/ECA where high $J_{v,Lj}$ and WTH are colocalized.

Subject 3 presents a lower total filtration flow in the majority of the carotid artery by comparison to the other subjects (Fig. 9; $1.0 \times 10^{-8} - 1.5 \times 10^{-8} \text{ ms}^{-1}$). Lower flow filtration can be explained by the fact that WTH, which acts to increase resistance to interstitial flow in a porous vessel wall, is generally greater for this subject. As seen in Fig. 6(c), geometrical features of this subject, including out-of-plane curvature in the CCA and the development of a discernable stenosis in the outer wall around the beginning of ICA/ECA, cause highly complex flow patterns to be present; and this hemodynamic environment leads to large areas of low TAWSS. For this reason, elevated values of $J_{v,Lj}$ are observed at the carotid bulb downstream of the stenosis and at regions proximal to both the ICA and ECA entrances. Most notably, the posterior side of the CCA experiences high volume flux through leaky junctions, a situation not found in other subjects. As expected, the spatial pattern of mass flux follows that of leaky junction distribution.

Direct comparison of mass flux to experimental data is not available because the measurement of J_s in biological experiments is very challenging and, as a consequence, there is a lack of related literature. However, our findings can be compared with numerical results from other studies. Olgac et al. [6] showed LDL mass flux values in ideal recirculation regions that are very similar to ours. Sakellarios et al. [36] show somewhat lower values in the range of $3.6 - 4.4 \times 10^{-13} \text{ mol/m}^2 \cdot \text{s}$. This difference in J_s may be that in our

Fig. 9 The volume and mass flux of subject 3. (a) The distribution of volume flux via leaky junctions ($J_{v,Lj}$) from anterior (left) and posterior view (right), (b) the volume flux via normal junctions ($J_{v,Nj}$), and (c) total mass flux of LDL (J_s).

current study J_s is determined by $J_{v,Lj}$, which is responsive to LDL particle passage via leaky junction, whereas there is no separation via normal and leaky junctions in their investigation.

Discussion

Although atherosclerosis is a complex inflammatory disease with many contributing factors, the focal accumulation of LDL is a necessary condition for development of atheromatous lesions. Such accumulation involves both physical and active biological mechanisms, including convective and diffusive LDL transport in flowing blood, interaction of blood and endothelial cells through mechanical forces that affect endothelial cell shape and function, inflammatory responses within the artery wall, and LDL clearance mechanisms that are inadequate. Convective and diffusive mass transfer alone cannot explain focal LDL accumulation. In fact, reliance on LDL wall distribution computed through such models can lead to erroneous conclusions. In this study we adopt a shear-dependent three-pore model [6] for LDL transport to and across the endothelium and consider the contribution of normal and leaky junctions to volume flux of blood plasma, mass flux of LDL, and their coupled and parallel interactions. Because evidence points to a close relationship between leaky junctions and WSS, the three-pore model must be combined with the fluid dynamic equations of motion. Since flow fields are highly dependent upon individual, subject-specific geometry and flow rates, image-based CFD approaches offer a methodology to elucidate atherosclerotic plaque localization and subsequent progression. Thus, it is critical to reconstruct the hemodynamic environment of subject-specific models to obtain WSS on the surface of the endothelium since the distribution and magnitude of WSS is used to assign the fraction of leaky junction (ϕ) which is a basis to gain

local mass transport parameters. Three left carotid arteries from human subjects were selected for study, representing a range of geometrical features: a simple artery with little curvature (subject 1); a more tortuous curvature in the ICA with mild stenosis (subject 2); and severe out-of-plane curvature in the CCA with a more advanced stenosis in the ICA/ECA around the carotid bulb (subject 3). Geometric models were constructed from BBMRI. Based on these individual models, an FSI method has been used to compute the hemodynamic environment with patient-specific boundary conditions obtained from PC-MRI to reflect compliant effects of the arterial wall and therefore avoid the rigid body limitation, which has been adapted in many previous hemodynamic investigations [29].

The computed results for flow patterns and WSS distributions highlight the importance of the role of subject-specific vascular geometry in determining focal sites of LDL accumulation in the intima. In subject 1 (Fig. 3), it is revealed that relatively uniform streamlines are present over most of the region, and accordingly the low TAWSS region is limited to a relatively small area in the proximal region of the bifurcation. Interestingly, based on the LDL mass transfer model, one would predict that development of a plaque on the ECA side of the bifurcation is more likely than at the ICA side in this individual (Fig. 7(c)). In subject 2 (Fig. 4), nonplanar curvature is present and a mild stenosis is localized at the outer wall of the bifurcation on the ICA side, leading to helical flow patterns with a single vortex in the carotid bulb. The predictions for locations of higher levels of LDL in the wall strongly suggest that further plaque progression in this subject will occur in the distal direction along the outer wall of the bulb (Fig. 8(c)). The high LDL values in the CCA at the entrance to the ECA may also imply that this may be a future site of a developing plaque. Finally, subject 3 presents the most complex flow patterns and largest zones of disturbed flow among the three subjects studied. Strong helical flows exist in both ICA and ECA lateral regions of the sinus, and there is a large zone of low TAWSS in the CCA as flow approaches the bifurcation (Figs. 5(a) and 5(b)). High levels of LDL mass transfer are predicted at three areas in the bifurcation: the anterior wall of the sinus on the ICA side; the lateral wall of the sinus at the ECA orifice; and the posterior side of the CCA as it approaches the entrance to the ICA (Fig. 9(c)).

This study reinforces the fact that lumen geometry alone is insufficient for predicting LDL mass transfer. Lumen geometry, coupled with inflow and outflow boundary conditions, does dictate WSS, and this strongly affects the fraction of leaky junctions. However, WTH is also a factor that controls plasma infiltration and hence LDL transport, and a larger WTH can act to inhibit LDL entry into the wall, even in the presence of low TAWSS and enhanced leaky junctions.

The methodology employed in this study is based on noninvasive imaging, although it could also be applied to intravascular imaging using ultrasound (IVUS) in a subject-specific manner. This could have the added value of providing information on wall and plaque components that could be used to improve FSI modeling, which is limited to a simple elastic model in our study. We also did not consider the LDL concentration profile across the blood vessel wall. To include this would be interesting although a thorough model for this would be a multicomponent approach that includes a geometric distribution of structures such as fibrotic tissue, calcium, necrotic core, and lipid pool in addition to elastin and collagen. Our available image information could not provide this. Intramural filtration of plasma in the arterial wall may be influenced by the deformation of vascular soft tissue via the interaction between void space for plasma fluid and mechanical strain of porous structures. Major arterial microstructures including intima, IEL, media and adventitia, can be expected to affect the mechanical stress distribution in the vessel wall and as a consequence, the change of plasma filtration. In the study by Ayyalasamayajula et al. [37], the filtration flow has been alternated in magnitude and direction in a cardiac cycle due to variation of arterial soft tissues, although the effect of leaky junctions was not

considered. However, this dynamic response is minimized when it is averaged over a cardiac cycle, resulting in an overall transfer of intramural filtration on endothelial surface into arterial wall. It was beyond the scope of our study to implement fully coupled FSI considering porous materials based on detailed anatomical arterial structures and subject-specific tissues. However, the current methodology does capture critical interactions between the blood and vessel wall that are essential to lesion development and progression. A major shortcoming is, of course, that the study has no biological data for these subjects with which the LDL mass transfer computations can be compared directly. Finally, while we have explored effects of very different carotid geometries, this is a study of only three subjects.

We hypothesize that one application of the work is to employ the methodology to investigate atherosclerotic plaque localization mechanisms in animal models where harvesting of biological tissue can be done so as to provide data for connecting predictions with experimental findings. The methodology could also be employed in longitudinal studies of plaque progression in human subjects as a model for predicting future events. Finally, the opportunity to employ IVUS studies in human coronary arteries, perhaps combined with infrared detection of intravascular lipid, could be an intriguing application in situations where catheterization is required for clinical evaluation of coronary artery disease.

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Nomenclature

F	= body forces
J_v	= volume flux
$J_{v,T}$	= total volume flux
$J_{v,Nj}$	= the volume flux via normal junction
$J_{v,Lj}$	= volume flux via leaky junction
K_D	= Darcy's permeability
L_p	= hydraulic conductivity
$L_{p,Lj}$	= hydraulic conductivity via leaky junction
$L_{p,Nj}$	= hydraulic conductivity via normal junction
p	= pressure
p_{l}^{end}	= pressure at luminal surface
p_{wall}^{adv}	= pressure on interface to the media-adventitia
Pd_{Lj}	= diffusive permeability
Pe	= LDL diffusive permeability
Pe_{Lj}	= permeability via leaky junction
Pe_{Nj}	= permeability via normal junction
Pe_{tot}	= total apparent permeability of LDL
Pe_{Tr}	= permeability via transcytosis
R_{end}	= endothelial resistance to fluid flow
R_{end}^{Nj}	= endothelial resistance to fluid flow via normal junction
R_{end}^{Lj}	= endothelial resistance to fluid flow via leaky junction
R_{Endo}	= radius of endothelial cell
R_T	= total resistance to fluid flow
R_{wall}	= arterial wall resistance to fluid flow
S_{unit}	= a periodic circular unit area
SI	= shape index of endothelial cell
v	= fluid velocity
$\hat{v}$	= computational grid motion in the spatial domain
Z_{Lj}	= fraction reduction factor in solute concentration gradient at the pore entrance
μ_{blood}	= dynamic viscosity of blood, 0.00345 (Pa.s)
μ_{plasma}	= dynamic viscosity of the pore fluid
ρ_{blood}	= density of blood, 1050 (kg/m ³)
σ_r	= reflection coefficient of particles

$\sigma_{f,L,j}$ = solvent drag coefficient of the leaky junction
 ϕ = fraction of leaky junction
 #MC = number of mitotic cell
 #LC = number of leaky cell

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