Effects of transmural pressure and wall shear stress on LDL accumulation in the arterial wall: a numerical study using a multilayered model

Nanfeng Sun,1 Nigel B. Wood,1 Alun D. Hughes,2 Simon A. M. Thom,2 and X. Yun Xu1
1Department of Chemical Engineering and 2National Heart and Lung Institute, International Centre for Circulatory Health, Imperial College London, London, United Kingdom

Submitted 22 November 2006; accepted in final form 31 January 2007

Sun N, Wood NB, Hughes AD, Thom SA, Xu XY. Effects of transmural pressure and wall shear stress on LDL accumulation in the arterial wall: a numerical study using a multilayered model. Am J Physiol Heart Circ Physiol 292: H3148–H3157, 2007. First published February 23, 2007; doi:10.1152/ajpheart.01281.2006.—The accumulation of low-density lipoprotein (LDL) is recognized as one of the main contributors in atherogenesis. Mathematical models have been constructed to simulate mass transport in large arteries and the consequent lipid accumulation in the arterial wall. The objective of this study was to investigate the influences of wall shear stress and transmural pressure on LDL accumulation in the arterial wall by a multilayered, coupled lumen-wall model. The model employs the Navier-Stokes equations and Darcy’s Law for fluid dynamics, convection-diffusion-reaction equations for mass balance, and Kedem-Katchalsky equations for interfacial coupling. To determine physiologically realistic model parameters, an optimization approach that searches optimal parameters based on experimental data was developed. Two sets of model parameters corresponding to different transmural pressures were found by the optimization approach using experimental data in the literature. Furthermore, a shear-dependent hydraulic conductivity relation reported previously was adopted. The integrated multilayered model was applied to an axisymmetric stenosis simulating an idealized, mildly stenosed coronary artery. The results show that low wall shear stress leads to focal LDL accumulation by weakening the convective clearance effect of transmural flow, whereas high transmural pressure, associated with hypertension, leads to global elevation of LDL concentration in the arterial wall by facilitating the passage of LDL through wall layers.

low-density lipoprotein transport; lipid accumulation; atherosclerosis; hypertension

atherosclerosis is predominantly a disease of the large arteries that involves a characteristic accumulation of lipoproteins in the arterial wall (7, 28). It is suggested that arterial mass transport of atherogenic molecules such as low-density lipoprotein (LDL) mediates the focal lipid accumulation in the arterial wall and hence plays an essential role in atherogenesis.

Arterial mass transport refers to the mass transport process of solute molecules from the bulk blood flow to and through the arterial wall, and it has been investigated both theoretically and experimentally. Depending on the treatment of the arterial wall, we can classify computational models into three groups: wall-free models, single-layered models, and multilayered models. The wall-free models are the simplest and have been used to model the solute dynamics in the blood lumen for oxygen (11, 12, 17, 24, 25, 27), albumin (26), and LDL (4, 5, 35–37). In these cases, the arterial wall was treated as a boundary condition; thus the transport process therein was not included in the models. The single-layered models assume that the arterial wall behaves as one layer of porous medium with homogeneous transport properties, and this approach has been employed to model oxygen and LDL transport (22, 29, 30, 32). However, the single-layered models do not account for the heterogeneous transport properties through different layers of the wall, thereby compromising the model complexity as well as accuracy. Multilayered models are so far the most comprehensive models, which treat the arterial wall as a number of layers of porous medium with different transport properties. However, the application of a multilayered model is usually limited to two-dimensional idealized geometries due to its high computational cost (13, 14, 23).

The complexity of model inputs, i.e., transport properties, of these three model classes also depends on the description of the arterial wall. In the wall-free models, the model parameters, which are mainly transport properties of solute molecules in the blood plasma, are relatively easy to measure in experiments and to apply to computations thereafter. In models that include wall-side transport, the effective transport properties of solute molecules in the porous wall are far more difficult to measure. Furthermore, it is almost impossible to obtain directly the heterogeneous transport properties corresponding to different layers of the wall using current experimental techniques. To circumvent these difficulties, two ways of determining model parameters have been proposed: one is by means of theoretical modeling, and another is by analyzing experimental data. However, unrecognized transport mechanisms might be omitted in the theoretical models with consequent derivation of inaccurate parameters. For instance, the endothelial permeability of LDL was underestimated by the pore theory and needed to be scaled before being used in the mass transfer calculation (14, 23). An electrical analogy approach was exploited to obtain the transport parameters based on the reported experimental data (19), but the zero-dimension method did not account for the distribution in the arterial wall (23).

In the present study, the arterial mass transport of LDL was investigated using a multilayered model, taking into account the effects of transmural pressure and shear-dependent hydraulic conductivity of the endothelium. A new approach based on optimization theory and experimental data reported by Meyer et al. (19) was used to determine the transport properties of LDL in both the intima and media. The model dimensions and
simulated flow conditions were typical of the epicardial coronary arteries with mild stenoses.

**Model Settings**

**Governing Equations**

Similar to the single-layered model used in a previous study (32), the multilayered model includes fluid dynamics and solute dynamics in the blood lumen and the arterial wall. As shown in Fig. 1, the model accounts for fluid dynamics and mass transfer in the blood lumen, intima, and media. Navier-Stokes equations were employed to model bulk blood flow in the lumen, whereas Darcy’s Law was used to model transmural flow in the intima and media. As for modeling of mass balance, the convection-diffusion equation was employed in the lumen, and an additional reaction term was added to form a convection-diffusion-reaction equation in the intima and media. Furthermore, to couple the fluid dynamics and mass balance at membranes, i.e., endothelium and internal elastic lamina (IEL), the Kedem-Katchalsky equations were employed (15).

**Fluid dynamics.** Blood flow was assumed to be steady, incompressible, laminar, Newtonian, and, hence, described by the Navier-Stokes equations:

\[
-\mu \nabla \mathbf{u} + \rho (\mathbf{u} \cdot \nabla) \mathbf{u} + \nabla p = 0
\]

\[
\nabla \cdot \mathbf{u} = 0
\]

in the fluid domain, where \( \mathbf{u} \) is blood velocity in the lumen, \( p \) is pressure, \( \mu \) is dynamic viscosity of the blood, and \( \rho \) is density of the blood.

The transmural flow in the intima was modeled by Darcy’s Law in the following:

\[
\mathbf{u}_i - \nabla \left( \frac{k_i}{\mu_p} p_i \right) = 0
\]

\[
\nabla \mathbf{u}_i = 0
\]

where \( \mathbf{u}_i \) is the velocity of the transmural flow in the intima, \( p_i \) is pressure in the intima, \( \mu_p \) is viscosity of the blood plasma, and \( k_i \) is the Darcian permeability coefficient of the intima. Similarly, transmural flow in the media was modeled by the following:

\[
\mathbf{u}_m - \nabla \left( \frac{k_m}{\mu_p} p_m \right) = 0
\]

\[
\nabla \mathbf{u}_m = 0
\]

where \( \mathbf{u}_m \) is the velocity of transmural flow in the media, \( p_m \) is pressure in the media, and \( k_m \) is the Darcian permeability coefficient of the media.

**Solute dynamics.** Mass transfer in the blood lumen is coupled with the blood flow and modeled by the convection-diffusion equation as follows:

\[
\nabla \cdot (-D_l \nabla c_l + c_l \mathbf{u}_l) = 0
\]

in the fluid domain, where \( c_l \) is the solute concentration in the blood lumen, and \( D_l \) is the solute diffusivity in the lumen.

Mass transfer in the arterial wall is coupled with the transmural flow and modeled by the convection-diffusion-reaction equations in the intima and media as follows:

\[
\nabla \cdot (-D_m \nabla c_m + K_{lag,m} \mathbf{u}_m) = r c_m
\]

\[
\nabla \cdot (-D_m \nabla c_m + K_{lag,i} \mathbf{u}_i) = r c_i
\]

where \( c \) is the solute concentration in the arterial wall, \( D \) is the effective solute diffusivity in the arterial wall, \( K_{lag} \) is the solute lag coefficient, \( r \) is the consumption rate constant, subscripts \( i \) and \( m \) stand for intima and media, respectively. The consumption encompasses all the processes accounting for loss of LDL within the arterial wall including consumption by the cells in the wall. Similar first-order reaction has been applied in many arterial wall models (9, 13, 14, 23) and previously in our single-layered model (32).

**Computational Geometry and Boundary Conditions**

An axisymmetric stenosis with 49% area reduction was adopted to test the model. This idealized geometry was assumed for convenience, but the degree of area reduction is fairly typical of the more modest degree of stenosis seen in clinical studies and indicative of relatively early atherosclerotic plaque (1). As shown in Fig. 2, the total length (z-axis) of the geometry is 25 \( D \), where \( D \) is the diameter of the nonstenosed region of the artery. The length of the stenosis was 1 \( D \), leaving the region of the artery. The length of the stenosis was 1 \( D \), leaving...
4D upstream and 20D downstream of the stenosis to minimize the effects of boundary conditions.

The endothelium geometry, at the interface between the lumen and the intima of the axisymmetric stenosis, was modeled by the following cosine expression:

\[
\frac{r_{\text{end}}(z)}{D} = \frac{\alpha_{\text{end}}}{D} \cos\left(\frac{2\pi(z - z_1 - z_2)}{z_2 - z_1}\right) + \frac{\beta_{\text{end}}}{D}
\]  

(10)

for 4D < z < 5D. On the other hand, the IEL that divides the intima layer and media layer was modeled by another cosine expression as follows:

\[
\frac{r_{\text{iel}}(z)}{D} = \frac{\alpha_{\text{iel}}}{D} \cos\left(\frac{2\pi(z - z_1 - z_2)}{z_2 - z_1}\right) + \frac{\beta_{\text{iel}}}{D}
\]  

(11)

for 4D < z < 5D. The intima and media thicknesses at unstenosed sections were assumed to be 0.0025D and 0.0725D, respectively. This is consistent with the single-layered model (32) and with assumptions made in other studies (13, 14). In Eqs. 10 and 11, \(r_{\text{end}}(z)\) and \(r_{\text{iel}}(z)\) are the radial positions of endothelium and IEL at location \(z\) in the stenosis, \(R\) is the radial position of the endothelium in the nonstenosed region, \(\alpha_{\text{end}} = 0.15D\) and \(\beta_{\text{end}} = 0.85D\) are the parameters for lumen constriction, \(\alpha_{\text{iel}} = 0.14D\) and \(\beta_{\text{iel}} = 0.865D\) are arbitrarily assigned parameters for intima thickening, \(z_1 = 4D\) is the start point of the stenosed region, and \(z_2 = 5D\) is the end point of the stenosed region.

To solve the system of equations in the described computational domain, adequate boundary conditions need to be applied. For steady flow, a fully developed parabolic velocity profile was assumed at the inlet, whereas normal flow conditions were prescribed at the outlet. To specify a pressure drop across the arterial wall, a constant pressure padv was assumed across the arterial wall, a constant pressure padv was assumed.

The momentum transport properties used in a previous study (32) were validated against measured transmural velocity reported (19). The transmural velocity given by one-dimensional simulations and experimental data reported by Meyer et al. (19), who provided the LDL concentration distribution in the rabbit aorta with respect to the distance from the lumen in the arterial wall under different transmural pressures.

The momentum transport properties used in a previous study (32) were validated against measured transmural velocity reported (19). The transmural velocity given by one-dimensional single- and multilayered models with constant momentum transport properties was compared with experimental data under transmural pressures of 70, 120, and 160 mmHg in Fig. 3. It is shown that both single- and multilayered models were able to predict transmural velocity in a reasonable range with constant momentum transport parameters under different transmural pressures. Thus it could be assumed that the elevation of transmural velocity, corresponding to increase in transmural pressure, is primarily due to the increased driving force rather than a change in resistance within the arterial wall, and this assumption was adopted in the computations.

To derive the mass transport properties, an optimization approach that minimizes the difference between one-dimensional simulation results, and experimental data was developed. The mass transport properties were denoted by vector \(\mathbf{x}\).

The simulated concentration distribution samples at predefined...
locations according to experimental data were denoted by vector \( c \). The relationship between \( x \) and \( c \) was described by a one-dimensional convection-diffusion-reaction transport model \( c = f(x) \) with appropriate boundary conditions. The optimization problem was formulated using the least squares method as follows:

\[
\min \sum_{j=1}^{n} W_j (c_j - c) \]

s.t. \( c_j = f(x_1, x_2, \ldots, x_m) \), \( j = 1, 2, \ldots, n \)

\( lb_k \leq x_k \leq ub_k \), \( k = 1, 2, \ldots, m \)

where \( c_j \) is the experimental value of LDL concentration at jth sampling point, \( c \) is the simulation result of LDL concentration at jth sampling point, \( W_j \) is the weighting coefficient of the jth sampling point, \( lb \) is the vector of lower bounds of \( x \), \( ub \) is the vector of upper bounds of \( x \). In this formulation, all the sampling points in the experimental data were taken into account, and, hence, the algorithm preserved the concentration distribution in the arterial wall, whereas zero-dimensional methods, such as the one based on electrical analogy, only retained boundary values but not the entire distribution.

To solve this optimization problem, the weighted accumulated error (sum of the difference between the simulation result and the experimental data at each data point) is minimized by finding the optimal vector \( x \) subject to physiological bounds \( lb \) and \( ub \). In the present study, the optimization problem was solved by a compass search routine.

For the single-layered model (see Ref. 32 for details), optimal values of some sensitive parameters, such as \( P_{end} \), \( D_m \), \( K_{lag} \), and \( r_{in} \), were obtained by solving the corresponding optimization problem. Because the media occupies more than 95% of the total thickness of the arterial wall (from endothelium to media-adventitia interface) in the model, it was assumed that the mass transport properties of media in the multilayered model were the same as the mass transport properties of the arterial wall in the single-layered model. It was also assumed that the endothelial permeability to LDL was the same in single- and multilayered models to ensure the consistency of transendothelial flux. Based on these assumptions, the optimal \( P_{end} \) was found by solving the optimization problem with a multilayered model.

By solving the optimization problem using two sets of experimental data corresponding to transmural pressures of 70 and 120 mmHg, respectively, two sets of mass transport properties were found and summarized in Table 1. Comparison with parameter values in other studies show that, although the optimal values derived in this study differ from data in the literature, they are generally within the range of literature values. The one-dimensional simulation results obtained by the single- and multilayered models using optimal parameters were compared with experimental data in Fig. 4. Both models adequately predicted the medial LDL distribution seen in the experimental data.

**RESULTS**

The computational model was implemented using a commercial finite element code, Comsol Multiphysics, Version 3.2 (Comsol). For solution of the Navier-Stokes equations, 20,774 computational nodes were used. For solution of the Darcy’s Law in both intima and media, 8,789 computational nodes were used. To model the mass transfer, the convection-diffusion equation was solved with 293,820 computational nodes. The convection-diffusion-reaction equations in the intima and media were solved with 52,290 computational nodes. A mesh sensitivity test was carried out on mass transport simulations to ensure grid independence of the obtained concentration field.

The simulation parameters for fluid dynamics were chosen to approximate physiological conditions in the human coronary artery. The diameter of the nonstenosed region of the artery was \( D = 0.004 \) m, the mean velocity \( u_0 = 0.24 \) m/s, dynamic viscosity \( \mu = 0.0035 \) Pa·s, density \( \rho = 1.050 \) kg/m³, and so the resulting Reynolds number was 288. Shear-dependent hydraulic conductivity was assumed as derived from experiment.

**Table 1. Summary of mass transfer model parameters estimated for the multilayered model using the proposed optimization approach based on experimental data of Meyer et al. (19)**

<table>
<thead>
<tr>
<th>Transmural Pressures</th>
<th>70 mmHg</th>
<th>120 mmHg</th>
<th>Literature Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_m ) (m²/s)</td>
<td>1.42 × 10⁻¹²</td>
<td>3.5 × 10⁻¹²</td>
<td>8.14 × 10⁻¹³ (38)</td>
</tr>
<tr>
<td>( P_{end} ) (m/s)</td>
<td>5.21 × 10⁻⁶</td>
<td>4.84 × 10⁻⁹</td>
<td>2 × 10⁻¹⁰ (22)</td>
</tr>
<tr>
<td>( r_{in} ) (lb⁻¹)</td>
<td>−6.05 × 10⁻⁴</td>
<td>−6.05 × 10⁻⁴</td>
<td>−1.4 × 10⁻⁴ (38)</td>
</tr>
<tr>
<td>( K_{lag} ) (lb⁻¹)</td>
<td>1.59 × 10⁻⁹ (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( K_{lag} ) (lb⁻¹)</td>
<td>0.1486</td>
<td>1.05</td>
<td>0.686 (22)</td>
</tr>
</tbody>
</table>

\( D_m \), LDL effective diffusivity in the media; \( P_{end} \), endothelial permeability to LDL; \( r_{in} \), consumption rate constants in the intima and media; \( P_{ph} \), internal elastic lamina permeability to LDL; \( K_{lag} \), solute lag coefficient of LDL in the arterial wall. In the present parameter estimation procedure, consumption rates and solute lag coefficients were assumed to have the same values in the intima and media because the intima layer is very thin and the concentration distribution therein could not be recorded in experimental data. For the same reason, LDL diffusivity in the intima layer cannot be estimated, and the value 1.2 × 10⁻¹¹ m²/s reported in the literature was used (see Ref. 38). Numbers in parentheses are reference citations (see REFERENCES).
tal data in our previously published analysis (32), which allowed hydraulic conductivity of the endothelium to increase with shear stress. Simulations were performed with both single- and multilayered model for comparison.

The LDL transport was modeled at two different transmural pressures using the corresponding model parameters determined by the optimization approach. First, LDL transport under a relatively low transmural pressure of 70 mmHg was investigated. From the fluid dynamics, variations of wall shear stress (WSS) magnitude in the axial direction of the stenosis model are shown in Fig. 5. The two points where WSS values are zero correspond to the separation point ($z = 4.673 D$) and reattachment point ($z = 5.865 D$), respectively. The area between these two points is the flow recirculation region. The transmural velocity and transendothelial LDL flux profiles in the immediate vicinity of the stenosis predicted by single- and multilayered models are compared in Fig. 6. Besides two minima of transmural velocity corresponding to the separation point and the reattachment point, a lower transmural velocity in the poststenotic region can be found in both cases. However, local discrepancies exist between the two sets of computational results. This is because the multilayered model is very sensitive to local geometry, especially in the very thin intimal layer, the thickness of which varies dramatically near the stenosis (31). In Fig. 6B, it is shown that although the transendothelial LDL flux given by the single- and multilayered model is dissimilar locally, the magnitudes of the flux agree well (both between 51 and 54), confirming that similar LDL flux across the endothelium was maintained. Thus there is no significant difference in transendothelial LDL flux between the single- and multilayered models, and a fair comparison between the two models can be made. The local differences were caused by the different patterns of transmural flow mentioned above, which drives the convective component of the LDL flux across the endothelium.

Figure 7 shows the averaged LDL concentration in the intima and LDL concentration at the IEL on the medial side. It is shown that the multilayered model, compared with the single-layered model, generally predicted a higher LDL concentration in the intima but a lower LDL concentration on the medial side of the IEL. The multilayered model also predicted more marked local accumulation of LDL in the intima at the reattachment point where WSS is zero. In the multilayered model, the IEL, which is a complex structure consisting of a fenestrated membrane of elastin lined on the intimal side by a fibrous network, was modeled as a membrane that acts as a molecular sieve, across which the convective flux plays an important role. Thus, in the poststenosis region where WSS is low, there are fewer LDL particles passing through the IEL due to a weaker convective driving force, resulting in a higher LDL concentration in the intima and lower LDL concentration in the media. This finding supports the hypothesis that local LDL accumulation in the arterial wall is caused by weaker convective clearance (32, 33).

LDL concentration profiles within the wall at different axial locations are shown in Fig. 8. A similar concentration distribution of LDL in the media can be found by using single- and multilayered models, although the multilayered model predicted much higher intimal LDL concentration. In fact, the intima, which is more porous than the media in structure (8, 9, 14), was lumped with the media by assuming constant transport parameters in the single-layered model. In the multilayered model, the more porous intima was treated individually, resulting in a higher intimal LDL concentration. Furthermore,
by comparing the intimal LDL concentration at different axial locations, it can be found that the intimal LDL concentration at the reattachment point was considerably higher than that up-stream and downstream of the stenosis, demonstrating the local accumulation of LDL in the low WSS region.

A mean transmural pressure of 120 mmHg, which in vivo is relatively high, was chosen to investigate the effect of hypertension on arterial LDL transport. Given that the transmural flow is several orders of magnitude smaller than the bulk flow, transmural pressure has a negligible effect on fluid dynamics in the blood lumen. Thus the WSS distribution under transmural pressure of 120 mmHg is the same as the WSS distribution shown in Fig. 5.

Averaged intimal LDL concentration and LDL concentration at the IEL on the medial side are shown in Fig. 9 for transmural pressure of 120 mmHg. There are remarkable differences from the results seen with a transmural pressure of 70 mmHg (Fig. 7). First, the global concentration of LDL is greatly increased when Δp_w = 120 mmHg because of the pressure-related variations of transport properties. Second, a number of local differences exist: 1) The multilayered model revealed variations of LDL concentration in the axial direction around the throat of the stenosis. Again, this can be explained by the fact that the multilayered model is more sensitive to local geometry than the single-layered model in terms of transmural flow. Especially under a higher transmural pressure, where the convective component of the transport process becomes more prominent, the transport process varies with respect to the local geometry. 2) Unlike the situation with a transmural pressure of 70 mmHg, the single-layered model predicted a noticeable peak in intimal concentration of LDL at the attachment point, because the convective clearance effect becomes more important at higher transmural pressure. 3) A local minimum at the reattachment point in the concentration profiles at the IEL on the medial side can be found with the multilayered model when Δp_w = 70 mmHg, whereas when Δp_w = 120 mmHg, a local maximum was observed with both single- and multilayered models. The reason for this phenomenon is complicated; that is, in addition to greater amount of LDL particles passing through the IEL due to a higher permeability when Δp_w = 120 mmHg, the convective clearance effect in the media is not strong enough to flush out the...
accumulation of LDL particles near the IEL, especially at the reattachment point where transmural flow is minimal. 

LDL concentration profiles within the wall at different axial locations are shown in Fig. 10. The medial concentration profiles given by single- and multilayered models agree well, and both single- and multilayered models predict a higher intimal concentration at the reattachment point due to a weaker convective clearance effect there.

DISCUSSION

A multilayered model was employed to study the transport of LDL in an idealized stenosis. Based on experimental data, two sets of model parameters corresponding to different transmural pressures were found using a newly proposed optimization approach. The numerical results showed that, under a higher transmural pressure, not only the endothelium allows more LDL but also outer layers of the arterial wall become more permeable, leading to global LDL accumulation in the intima and inner media. In fact, hypertension, especially when associated with hypercholesterolemia, accelerates the complications of atherosclerosis (3). Changes of macromolecular transport across the arterial wall under high transmural pressure might be one of the mechanisms through which hypertension contributes to atherogenesis (6). The results reported in this study support this hypothesis. A significantly higher intimal LDL concentration (>2.5-fold) was found when Δp_w = 120 mmHg compared with the concentration level at Δp_w = 70 mmHg. This is mainly due to a significant increase in the accumulation of LDL particles near the IEL, especially at the reattachment point where transmural flow is minimal.

LDL concentration profiles within the wall at different axial locations are shown in Fig. 10. The medial concentration profiles given by single- and multilayered models agree well,

Figure 8: Comparison between simulation results given by single- (solid lines) and multilayered (dashed lines) models at upstream (A), reattachment point (B), and downstream (C) of an axisymmetric stenosis under transmural pressure of 70 mmHg. c_w, LDL concentration in the arterial wall; r, radial position at the cross section.

Figure 9: Comparison of LDL concentration values in the intima (A) and at medial side of IEL (B) with single- (solid lines) and multilayered (dashed lines) models under transmural pressure of 120 mmHg.
overall LDL flux into the arterial wall due to larger endothelial permeability to LDL at high transmural pressure. Although high transmural pressure also induces elevated transmural flow that leads to stronger convective clearance of LDL, the effect of an increase in LDL transendothelial flux is far more dominating than the effect of stronger convective clearance; hence, the overall effect of high transmural pressure leads to global elevation of LDL concentration in the arterial wall as seen in the experimental data (19). The significant increase in endothelial permeability to LDL at higher transmural pressure indicates that convection driven by the transmural flow may not be the only transport pathway that is pressure dependent. Vesicular transport may also be accelerated by the pressure-thinning effect on the endothelium that shortens the transit time of LDL across the endothelium (20).

The pressure-driven distension of the arterial wall also alters transport properties of the outer wall layers as well as those of the endothelium. For instance, IEL permeability to LDL increased considerably when the transmural pressure was raised from 70 to 120 mmHg, whereas the effective diffusivity of LDL in media presented a smaller change. These uneven changes of transport properties possibly affect the local balance of influx and efflux in the inner media and contribute to LDL accumulation in the inner media when $\Delta p_t = 120$ mmHg.

Because the transport properties were found by applying an optimization approach to the experimental data reported by Meyer et al. (19), it is worth pointing out the possible uncertainties involved in parameter determination based on the experiments. First of all, the measurements were taken after only 30 min, which might be too short for LDL transport to reach equilibrium (2). Second, the rabbit aorta could distend freely without being limited by surrounding tissue in the experiments. Particularly, when transmural pressure was raised from 70 to 120 mmHg, the diameter of the aortic segments displayed a 22.4% increase from 5.22 ± 0.08 to 6.39 ± 0.14 mm, which is much greater than the distension that occurs in vivo. Consequently, the in vivo effect of hypertension on arterial wall transport properties is likely to be somewhat less than the difference estimated here.

As for transendothelial transport, which is the most important subprocess in arterial mass transport, Kemdem-Katchalsky equations were employed, which implicitly assumed the transport of water and LDL through a single pathway. It is generally believed that water and LDL pass the endothelium through different pathways (33). However, the assumption was acceptable in this macroscale model as long as a proper LDL flux across the endothelium was predicted because the mixing in the outer layers of the arterial wall will “wash out” these pathway effects. A shear-dependent hydraulic conductivity was employed in the present study, but shear dependence of endothelial permeability was not taken into account. The shear-dependent hydraulic conductivity, which determines the transmural flow, controls the LDL accumulation in the arterial wall through the convective clearance effect of transmural flow (32, 33). Therefore, focal LDL accumulation in the intima was found to colocalize with low WSS due to the contribution of transmural flow to the WSS regulation on LDL transport in the intima. However, to investigate the shear dependence of LDL transport across the endothelium and its consequences, one needs to employ a shear-dependent permeability. Although the endothelial permeability to LDL was suggested to be shear dependent (21), detailed experimental data that are ready to be adopted in computational studies do not exist. On the other hand, there are a number of studies providing detailed experimental data on shear-dependent endothelial permeability to albumin (10, 16, 34). Thus, by assuming the endothelial permeabilities to

![Fig. 10. Comparison between simulation results given by single- (solid lines) and multilayered (dashed lines) models at upstream (A), reattachment point (B), and downstream (C) of an axisymmmetric stenosis under transmural pressure of 120 mmHg.](http://ajpheart.physiology.org/)
albumin and LDL react similarly to shear stress, some insights can be gained about LDL transendothelial transport and its consequences. Tanishita and coworkers reported a dual response of albumin uptake by cultured endothelial cells to shear stress (16, 34). It was found that the albumin uptake increased with increasing WSS at lower shear stress (<1 Pa) and decreased with increasing WSS at higher shear stress (>2 Pa). If this finding is also applicable to LDL uptake by the endothelium, it can be inferred that more pronouncedly elevated concentration profiles would be found in the low WSS regions with computational simulations. Their finding also provided an explanation on atheroprotective effects associated with WSS higher than 1.5 Pa in the context of lipid transport and accumulation (18).

To evaluate the single- and multilayered model and to determine their appropriate usage, these two models were compared using two different sets of model parameters in the present study. Although the single-layered model was able to predict similar transendothelial LDL flux and medial LDL distribution as the multilayered model, it could not provide a separate and accurate description of the intima. However, the same tendency of LDL accumulation was found with the two models, especially using the second set of model parameters corresponding to $\Delta P_{\text{w}} = 120 \text{ mmHg}$. Because the multilayered model is computationally expensive, it can be suggested that the multilayered model should be applied to ideal computational geometries for theoretical investigation, whereas the single-layered model is satisfactory for the application to realistic and complicated computational geometries, when the computational resource is limited.

Same as most of the computational studies on arterial LDL transport (4, 5, 13, 14, 23), steady flow conditions were assumed in the present study. Since LDL accumulation in the arterial wall is a long-term process that takes many years to reach a critical level that becomes hemodynamically significant, the steady flow assumption seems to be reasonable and a good starting point. However, LDL transport from the blood lumen to and through the arterial wall is coupled with the pulsatile blood flow, indicating that LDL transport process is influenced by two dramatically different time scales. Therefore, the influence of pulsatile flow on LDL accumulation in the arterial wall needs to be investigated, and the steady flow assumption needs to be validated in future research.

In conclusion, by using a multilayered, coupled lumen-wall model together with optimized mass transfer parameters corresponding to two different transmural pressures, we have demonstrated that the convective clearance effect of transmural flow contributes to the WSS regulation of LDL accumulation in the intima. There is a global LDL accumulation in the intima and inner media at higher transmural pressure due to more LDL passage through the endothelium as well as more permeable outer layers of the arterial wall.

**GRANTS**

This work was supported by the Leverhulme Trust (F07 058/AA).

**REFERENCES**


