The transport of LDL across the deformable arterial wall: the effect of endothelial cell turnover and intimal deformation under hypertension

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Dabagh M, Jalali P, Tarbell JM. The transport of LDL across the deformable arterial wall: the effect of endothelial cell turnover and intimal deformation under hypertension. Am J Physiol Heart Circ Physiol 297: H983–H996, 2009. First published July 10, 2009; doi:10.1152/ajpheart.00324.2009.—A multilayered model of the aortic wall is introduced to investigate the transport of low-density lipoprotein (LDL) under hypertension, taking into account the influences of increased endothelial cell turnover and deformation of the intima at higher pressure. Meanwhile, the thickness and properties of the endothelium, intima, internal elastic lamina (IEL), and media are affected by the transmural pressure. The LDL macromolecules enter the intima through leaky junctions over the endothelium, which are created by dying or dividing cells. Water molecules enter the intima via the paracellular pathway through breaks in tight junctions after passing the glyocalyx as well as through leaky junctions. The glyocalyx is modeled as a Brinkman porous medium to describe the fluid filtration associated with its structure. Combined Navier-Stokes and Brinkman equations are solved for the transmural flow, and the convective-diffusion equation is employed for LDL transport. The permeation of LDL over the surface of smooth muscle cells is modeled through a uniform reaction evenly distributed in the macroscopically homogeneous media layer. Simulations are performed in an axisymmetric plane centered at a leaky cell. The overriding issue addressed is that LDL fluxes across the leaky junction, the intima, fenestral pores in the IEL, and the media layer are highly affected by the transmural pressure, which affects the endothelial cell turnover rate and the compaction of intima. The present model, for the first time and with no adjustable parameters, is capable of making many realistic predictions including the proper magnitudes for the permeability of endothelium and intimal layers and the hydraulic conductivity of all layers as well as their trends with pressure. Results for the volume flux through the wall and the hydraulic conductivity of the entire arterial wall, the endothelium, and subendothelial layers at 70 and 180 mmHg are in good agreement with previous experimental studies.

lipoprotein transport; computational fluid dynamics; convection-diffusion model; atherosclerosis

ATHEROSCLEROSIS IS A DISEASE of large arteries, where the pressure is high, but not veins, where the pressure is low (24). Vessels may differ in wall thickness, wall composition, transmural pressure, and other characteristics, but it is not clear which parameters have the highest impact on arterial disease susceptibility (2, 19, 23, 24, 34). On the other hand, the penetration of macromolecules such as low-density lipoprotein (LDL) into the arterial wall with accumulation in the intima and media is widely accepted as a precursor to atherosclerotic disease (2, 17, 19, 23, 24, 34). Therefore, a full description of LDL transport across the arterial wall in association with wall structure and transmural pressure is essential (23, 24, 34).

Previous experimental studies have shown that vesicles (21, 29) and leaky junctions (14, 15, 31) are two pathways for LDL to cross the endothelium. Vesicles take up LDL from extracellular fluid by receptor-mediated endocytosis, whereas leaky junctions are associated with endothelial cells in a state of turnover or death (apoptosis). It was recently shown in vitro (2) that LDL fluxes mainly through leaky junctions (>90%) and is rarely transported by vesicles (<10%), when transmural convection is present. This is consistent with other in vivo studies (24). On the other hand, it is well known that hypertension accelerates atherogenesis by increasing the turnover and apoptosis of endothelial cells, the opening of endothelial junctions, and, hence, an enhancement of transendothelial macromolecular transport (33). Moreover, Huang et al. (9) suggested that the size and frequency of the leakage sites correlates with the formation and growth of macromolecular leakage spots in the arterial intima. It has also been shown (3, 10, 11, 13, 25) that the growth of these spots is altered by transmural pressure.

Curmi et al. (3) showed in excised arteries that the LDL concentration distribution across the arterial wall could change significantly under elevated pressure. The effect of pressure on LDL transport within the rigid arterial wall has been studied through single layer or multilayer models (19, 23, 34). Yang and Vafai (34) and Sun et al. (23) treated different wall layers as rigid and homogeneous porous media and the endothelium as a single-pore model. Olgac et al. (19) modeled the endothelium using a three-pore model, including a leaky junction, where the wall was taken as a single layer porous medium without internal elastic lamina (IEL). The influence of hypertension on LDL transport and accumulation within a multilayered-deformable arterial wall with a leaky junction endothelial transport model has not been studied yet.

In the present study, the dependence of LDL transport on the transmural pressure is investigated using a deformable multilayer model, in which the penetration of water and LDL through leaky and tight junctions into the wall is described by a pore model applied to the endothelium. The fraction of leaky junctions is correlated to the transmural pressure with the help of experimental studies available in literature. In our model, the aortic wall comprises the endothelium, intima, IEL, and media layers. Such a multilayer model provides more details about the transport phenomena than a single layer model. The intima layer is modeled as a deformable porous medium, which leads to a pressure-dependent Darcy permeability (10). The IEL is modeled as an impermeable barrier to both fluid and LDL...
except at the fenestral pores distributed over the IEL (4, 5). Fenestral pores are filled with a porous structure that is a continuation of the intimal matrix (9, 10). The media layer is introduced as a homogeneous porous medium in which the rate of disappearance of LDL by surface reaction or cell permeation over the smooth muscle cells (SMCs) is described through a first-order reaction. The thickness and transport properties of each layer including the hydraulic permeability, the diffusivity, the lag coefficient, and the porosity are calculated locally as a function of transmural pressure. The model has no adjustable parameters and is able to predict the proper magnitude of the LDL permeability and the hydraulic conductivity of wall layers.

**METHODS**

**Geometric model.** The choice of a geometric model for the endothelium, pathways through endothelium, and subsequent layers of arterial wall is very important in the study of LDL and water transport. In principle, a three-dimensional (3D) geometry would provide the most accurate results, but a two-dimensional (2D) geometry can be used to save computational expense. Such simplified models have been considered earlier in Weinbaum et al. (31) and recently in Olgac et al. (19).

In these models, the arrangement of leaky cells is assumed to be locally symmetric so that a periodic cylindrical unit can be found that is centered around a leaky cell, as shown in Fig. 1A. Figure 1B sketches the array of periodic units from the top in which leaky cells (black dots) are separated by 2Δ with a hexagonal distribution over the endothelial surface. Each periodic unit has a 3D cylindrical shape, which can be reduced to a 2D axisymmetric geometry with the following assumptions: 1) endothelial clefts are distributed as concentric rings over the endothelium and 2) fenestral pores are also assumed to be concentric rings (fenestral rings) over the IEL.

The anatomy of the periodic unit including the rings for clefts and fenestral pores is illustrated in Fig. 1A. The axisymmetric plane contains the cross-sectional view of all layers of the arterial wall, which are depicted with more details in Fig. 2. An example of the entire computational domain can be seen in Fig. 2A in which the media layer covers the major portion of the domain. Above the media layer, a part of the computational domain is zoomed in to show the other parts included in the model. Figure 2B demonstrates the zoomed region containing the leaky junction, the fenestral ring, and the cleft, which are all connected to the intima. Closer views of the three aforementioned parts are displayed in Fig. 2C. Note that there is a layer of glyocalyx with 500 nm thickness at the top of the cleft (30). The presence of the break (length of 315 nm) through the tight junction (length of 3,590 nm) is modeled in our 2D axisymmetric geometry as a porous medium of thickness 15 nm located 67 nm below the bottom of the glyocalyx layer (32).

The effective permeability of the porous medium is explained later in Calculation of model parameters. Note that the incoming flow to the computational domain is let through the top edges of leaky junction and clefts, indicated by inflow in Fig. 2C. The depth of leaky junction and clefts are 2 μm, and the depth of fenestral rings are equal to the thickness of the IEL, which is 1 μm.

**Governing equations.** Despite the pulsatilic nature of blood flow, the steady state condition has been considered in this study to model the time-averaged conditions. Under the assumption of steady-state conditions and an incompressible fluid with Newtonian rheology, interstitial flow through the clefts and leaky junction is governed by the Navier-Stokes and continuity equations

\[ \nabla \cdot \mathbf{u} = 0 \]  
\[ \mathbf{u} \cdot \nabla \mathbf{u} = -\nabla P + \mu \nabla^2 \mathbf{u} \]  

where \( u \) and \( P \) are the velocity vector and pressure in the corresponding endothelial cleft or junction, respectively, \( \rho \) is the density of blood plasma taken as 1,000 kg/m³, and \( \mu \) is the dynamic viscosity of blood plasma equal to 7.2 × 10⁻³ Pa.s. The thickness of the porous glyocalyx layer, based on several electron microscopy studies, is estimated to be less than 500 nm (30). This layer covers the top of clefts within which the Brinkman equation is employed to describe the transmural flow. In addition to the glyocalyx layer, the transmural flow through the porous medium, which accounts for the tight junction and breaks, intima, fenestral pores, and the media layer is modeled using the Brinkman equation,

\[ (\mu/K_p)\mathbf{u} = -\nabla P + (\mu/\epsilon) \nabla^2 \mathbf{u} \]  
\[ \nabla \cdot \mathbf{u} = 0 \]  

where \( \epsilon \) and \( K_p \) are the porosity and the hydraulic permeability of the corresponding layer, \( \mathbf{u} \) is the superficial velocity vector of the corresponding layer, and \( P \) is the pressure. Darcy’s law was applied in previous studies of flow through arterial wall layers, whereas by applying the Brinkman model no-slip boundary conditions along the
surfaces of the endothelial junctions and the fenestral pores will be satisfied.

The LDL transport in the leaky junctions of the endothelium is coupled with the transmural flow. It is modeled by the convection-diffusion equation:

$$\nabla \cdot (-D_{ij} \nabla C_i) + u_{ij} \nabla C_i = 0$$  \hspace{1cm} (5)$$

where $C_i$ is the LDL concentration and $D_{ij}$ is the diffusion coefficient of LDL through the leaky junction. The transport of LDL in the intima and fenestral pores is modeled by:

$$\nabla \cdot (-D_{i,n} \nabla C_i) + K_{c,n} u_{n} \cdot \nabla C_i = 0$$  \hspace{1cm} (6)$$

$$\nabla \cdot (-D_{i,IEL} \nabla C_i) + K_{c,IEL} u_{IEL} \cdot \nabla C_{IEL} = 0$$  \hspace{1cm} (7)$$

where $K_{c,n}$, $K_{c,IEL}$, $D_{i,n}$, and $D_{i,IEL}$ are the solute lag coefficients and the diffusion coefficients of the intima and the fenestral pores in the IEL. The LDL transport through the media layer is modeled by the convection-diffusion equation with reaction as:

$$\nabla \cdot (-D_{i,m} \nabla C_i) + K_{c,m} u_{m} \cdot \nabla C_m = k_m C_m$$  \hspace{1cm} (8)$$

where $k_m$ is the consumption rate constant in the media layer. The consumption encompasses all the processes accounting for loss of LDL within the media layer including consumption by the SMCs (19, 23).

Boundary conditions. For calculation of the transmural flow, a constant pressure boundary condition is applied at the inlet of clefts for LDL. At the media-adventitia interface, we choose for simplicity the condition: $n \cdot (D V C) = 0$. Here, $n$ represents the unit vector normal to the interface. It has been shown (34) that the effect of several different types of media-adventitia boundary condition on the species distribution within the intima, IEL, and inner media layers is negligible. At the left edge of the computational domain ($r = 0$), a symmetry boundary condition is also applied for the convection-diffusion equation. For the right edge ($r = \xi$) of the domain and the solid surfaces of leaky and interendothelial junctions as well as fenestral pores, the insulation boundary condition is applied

$$n \cdot (D V C + u V n) = 0$$  \hspace{1cm} (9)$$

Calculation of model parameters. The endothelium is treated as a thin layer of normal cells and leaky cells with intercellular junctions. Leaky cells, the cells either dying or dividing, with radius $R_{cell}$ are regularly distributed and spaced apart by $2k$ (Fig. 1B). As shown in Fig. 1A, leaky cells are located at the center of the periodic unit of radius $\xi$. The leaky junction is a hollow cylindrical shell surrounding the leaky cell with width $2w$. Similarly, interendothelial junctions are considered as parallel cylindrical openings between two adjacent endothelial cells (adopting the approach in Refs. 9 and 19). The glycocalyx covering the plasma membrane of endothelial cells is believed to fill the entrance of the intercellular junctions. The major molecular components of the glycocalyx are proteoglycans with their glycosaminoglycan side chains and glycoproteins (24). However, recent observations from autocorrelation imaging techniques have suggested a structural model for the glycocalyx, which is composed of bush-like clusters of core proteins (22, 32). Based on these images, we model the glycocalyx as a fiber matrix characterized by a (Darcy) hydraulic permeability coefficient, $K_{pg}$, given by (32):

$$K_{pg} = 0.0572 \alpha \left( \frac{\Delta}{\delta} \right)^{2.377}$$  \hspace{1cm} (10)$$

where $\delta$ is the fiber radius (6 nm) and $\Delta$ is the spacing between fibers (20 nm). $K_{pg}$ is calculated as $3.6 \times 10^{-17}$ m$^2$. It is assumed that LDL does not enter the glycocalyx because of its size (22 nm) relative to the fiber spacing.

Weinbaum et al. (32) proposed an idealized mathematical model for the glycocalyx layer as the hexagonal arrangement of core proteins.
and cluster foci. We have employed this model to determine the porosity of glyocalyx as \( \varepsilon_{pg} = \sqrt{\frac{3}{2}} \pi (a/\Delta)^2 \) where \( \varepsilon_{pg} \) is computed to be 0.49.

The tight junctions form lines of contact between the adjacent cells and act as barrier for water and solute to flow within the cleft (22). The dominant pathway for water through tight junctions in clefts is large, infrequent, widely spaced breaks (22, 32). The detailed structural morphology measurements for rat mesentery venules show that the clefts between adjacent endothelial cells have uniform width of 18–21 nm on average and there are tight junction strands with discontinuous leakages, or breaks, of mean length 2\( \Delta = 315 \) nm and mean spacing of 2\( \Delta = 3,590 \) nm. The tight junction with periodic breaks is modeled as a homogeneous porous medium having an effective hydraulic permeability. This porous medium accounts for tight regions that do not allow water flow and breaks that do allow water flow. The effective hydraulic permeability is calculated by

\[
K_{eff} = K_{bc} \frac{A_{bc}}{A_{r}}
\]

where \( K_{bc} \) is the hydraulic permeability of the break with area \( A_{bc} \) through the tight junction having area \( A_{r} \). Here, \( K_{bc} \) is determined by 16/3 \( A_{bc}^3/P_{bc}^2 \), where \( P_{bc} \) is the perimeter of the open channel representing the break (6). \( K_{bc} \) and \( K_{eff} \) are obtained as 4.72 \( \times 10^{-16} \) m\(^2\) and 4.14 \( \times 10^{-17} \) m\(^2\), respectively. The effective porosity of the porous medium accounting for tight regions and breaks is calculated using fiber matrix theory (9):

\[
K_{eff} = K_{bc} \frac{A_{bc}}{A_{r}}
\]

where \( A_{eff} = A_{r}/A_{rs} = 0.088 \).

The fraction of leaky junctions, \( \Phi \), is defined as the ratio of the area of leaky cells to the total area of cells:

\[
\Phi = \frac{R_{cell}^3}{\varepsilon^3}
\]

where \( R_{cell} \) is the radius of the endothelial cell taken as 10 \( \mu \)m for rabbit thoracic aorta (9). Experiments with the aortas of rats (9, 14, 15) and rabbits (27) have shown that leaky cells constitute less than 0.05% of the population. On the other hand, Wu et al. (33) determined that hypertension exacerbates the development of atherogenesis by increasing the turnover rate of endothelial cells and, hence, the macro-molecular permeability of endothelium in the rat aorta. They found that the frequencies of both endothelial cell mitosis and death increase in hypertensive rats. In the present study, the influence of higher values of \( \Phi \) on the LDL transport through the rabbit thoracic aorta wall has been investigated by taking \( \Phi \) as 1 \( \times 10^{-3}, 2 \times 10^{-3}, 10^{-2} \), and 4 \( \times 10^{-2} \) at 180 mmHg (33), whereas \( \Phi \) is taken as 5 \( \times 10^{-4} \) at 70 mmHg (9, 14, 15, 27). Another important consideration in the formulation of the model is the resistance of the leaky junction to the transport of LDL. We assume that the dimensions of the leaky junction are much larger than the LDL diameter (about 20 nm) and that there is no glyocalyx over the leaky junction. Therefore, the diffusion coefficient of LDL through the leaky junction, \( D_{bc} \), is taken equal to the LDL diffusivity in the plasma (2.5 \( \times 10^{-11} \) m\(^2\)/s).

The pressure-dependent transport properties of the intima, i.e., the porosity, the diffusion coefficient, the permeability, and the lag coefficient are calculated by using a heterogeneous fiber matrix theory, which includes the proteoglycan and collagen components of the intima (9). The proteoglycan matrix comprises proteoglycan core proteins \((r_{CP} \approx 2 \text{ nm})\) with glycosaminoglycan \((r_{CG} \approx 0.6 \text{ nm})\) fibers attached that are bound to a long central filament of hyaluronic \((r_{CF} \approx 2 \text{ nm})\). The collagen \((r_{CG} \approx 20 \text{ nm})\) is much thicker than any of the proteoglycan components and its length per unit volume is much smaller. Therefore, the presence of the collagen is treated separately from that of the proteoglycan components (9). The porosity of intima layer is estimated as:

\[
\varepsilon_{i} = \frac{\varepsilon_{CG} \varepsilon_{PG}}{1 - \varepsilon_{CG} - \varepsilon_{PG}}
\]

where \( \varepsilon_{CG} \) and \( \varepsilon_{PG} \) are the porosities of proteoglycan matrix and collagen fibers, respectively. These porosities are functions of intima thickness, which is pressure dependent, defined as:

\[
\varepsilon_{CG} = 1 - \frac{L_{0}}{L_{i}} \varepsilon_{c}
\]

\[
\varepsilon_{PG} = 1 - \frac{L_{0}}{L_{i}} \varepsilon_{c}
\]

where \( \varepsilon_{c} \) is the thickness of the intima at zero luminal pressure; \( L_{i} \) is its thickness at a given pressure. \( \varepsilon_{CG} \) and \( \varepsilon_{PG} \) are porosities at zero luminal pressure. \( L_{0} \) is adopted as 0.5 \( \mu \)m from the literature (10). \( \varepsilon_{CG} \) is estimated as 0.95 based on experimental studies suggesting that collagen only occupies about 5% of the intimal volume at zero pressure (11, 27). \( \varepsilon_{PG} \) is determined by (9):

\[
1 - \varepsilon_{PG} = \frac{3}{n} \left( \beta_{CG}^2 + r_{CG}^2 + r_{CP}^2 / \alpha \right)
\]

where \( n = \ell / \delta \) and \( \delta \) is the average fiber spacing taken as 40 nm, \( \beta \) is the ratio of glycosaminoglycans fibers to protein core lengths taken as 5, and \( \alpha \) is the ratio of proteoglycan monomers to central filament lengths taken as 3 (9, 10). Thus \( \varepsilon_{PG} \) is calculated as 0.9866. The intima thickness at 70 and 180 mmHg are adopted from the study by Huang et al. (10) as 0.155 and 0.0575 \( \mu \)m, respectively. Therefore, \( \ell \) is calculated as 0.8025 at 70 mmHg and 0.4994 at 180 mmHg.

The diffusion coefficient of LDL within the intima layer is calculated using fiber matrix theory (9):

\[
D_{i} = D_{0} \exp \left[ -\left( 1 - \varepsilon_{CG} \right)^{1/2} \left( 1 + \frac{r_{i}}{r_{*}} \right) \right]
\]

where \( r_{i} \) is the radius of LDL and \( r_{*} \) is an effective radius for the entire proteoglycan matrix.

\[
r_{*} = \left( \frac{\alpha r_{M}^2 + r_{CP}^2}{\alpha + 1} \right)^{1/2}
\]

\[
r_{M} \text{ is an effective monomer radius of proteoglycan core protein and}
\]

\[
\text{glycosaminoglycans fibers, calculated by:}
\]

\[
r_{M} = \left( \beta_{CG}^2 + r_{CG}^2 \right)^{1/2}
\]

\[
D_{0} \text{ takes into account the presence of the collagen}
\]

\[
D_{i} = D_{0} \left( \varepsilon_{PG} + \varepsilon_{CG} - 1 \right) \exp \left[ -\left( 1 - \varepsilon_{CG} \right)^{1/2} \left( 1 + \frac{r_{i}}{r_{CG}} \right) \right]
\]

where \( D_{0} \) is the LDL diffusion coefficient in free media (5 \( \times 10^{-10} \) m\(^2\)/s). Therefore, \( D_{i} \) is calculated as 2.13 \( \times 10^{-12} \) m\(^2\)/s at 70 mmHg and 3.25 \( \times 10^{-13} \) m\(^2\)/s at 180 mmHg. The pressure-dependent permeability of the intima layer is adopted from the model of Huang et al. (10) as \( K_{p} = 0.42 \times 10^{-16} \) m\(^2\) at 70 mmHg and 0.07 \( \times 10^{-16} \) m\(^2\) at 180 mmHg. The lag coefficient for LDL transport in the intima, \( K_{l} \), is given by

\[
K_{l} = 2 - \Phi_{l}
\]

where \( \Phi_{l} \) is the partition coefficient

\[
\Phi_{l} = \exp \left[ -\left( 1 - \varepsilon_{PG} \right) \left( 2 - \frac{r_{i}}{r_{l}} \right) \right] \left( \varepsilon_{CG} + \varepsilon_{PG} - 1 \right)
\]

\[
\times \exp \left[ -\left( 1 - \varepsilon_{CG} \right)^{1/2} \left( 1 + \frac{r_{i}}{r_{CG}} \right) \right]
\]

\( r_{l} \) is assumed to be equal to \( r_{*} \). \( K_{p} \) is computed as 1.915 and 1.997 at 70 and 180 mmHg, respectively.

The IEL is treated as an impermeable layer with fenestral pores, which are uniformly distributed over the IEL. Huang et al. (9–11) found that
fenestral pores have a porous structure that appears to be a continuation of the intimal, rather than medial, matrix. Thus we have taken the same properties of the intima for the IEL. On the other hand, the area fraction and the size of fenestral pores are recognized as crucial parameters in solute transport through the arterial wall. Experimental data in various animals show the area fraction of fenestral pores, \( f \), ranging from 0.002 to 0.02 and the diameter of fenestral pores, \( d_{i} \), ranging from 0.4 to 2.1 \( \mu m \). The equivalent diameter of fenestral rings, \( d \), in our axisymmetric model is obtained from the relationship:

\[
f = \frac{A_{0}}{A_{int}} = \sum 2\pi r_{i}d_{i}
\]

where \( r_{i} \) is the distance of the \( i \)-th fenestral ring from the axis of symmetry. The value of \( f \) is set to 3.49 \times 10^{-3} (4, 5, 10). Therefore, \( d \) is determined as 0.083 \( \mu m \) at 70 mmHg. Huang et al. (10) showed that fenestral pores experience a minor enlargement due to hoop tension under pressure. Based on their experiment, we have taken \( d \) as 0.091 \( \mu m \) at 180 mmHg, which is about 10% larger than that at 70 mmHg.

The media layer is modeled as a homogeneous porous media with a hydraulic permeability of \( K_{pm} \), given as (8):

\[
K_{pm} = K_{ref}/(1 + F)
\]

where \( F \) is the volume fraction of SMCs embedded in a continuous porous medium assumed as a Darcy medium with the permeability of \( K_{ref} \) equal to \( 1.43 \times 10^{-18} \text{ m}^2 \). This porous medium is composed of interstitial proteoglycan and collagen fiber matrix. \( K_{pm} \) is determined as \( 6.09 \times 10^{-19} \text{ m}^2 \) after taking \( F \) as 0.4. The influence of SMCs on the diffusion and the lag coefficient of LDL in the media layer has been considered separately. The diffusion coefficient of LDL in the media layer is expressed as:

\[
D_{tm} = D_{im}/[1 - F(f(F))]
\]

where \( D_{tm} \) is

\[
D_{im} = D_{i} \exp \left[ -\left( 1 - \epsilon_{im} \right)^{1/3} \left( 1 + r_{i}/r_{i0} \right) \right]
\]

\( D_{i} \) is the LDL diffusivity in the free media (\( 5 \times 10^{-10} \text{ m}^2/\text{s} \)), \( a_{i} \) is the radius of fibers in the extracellular matrix phase of the media layer (3.22 nm), \( \epsilon_{im} \) is the porosity of the extracellular matrix phase (0.43), and \( f(F) \) is a function introduced in Ref. 8 as:

\[
f(F) = 1 - 2 \frac{1 - \frac{1}{\sqrt{1 + \frac{4}{\pi} \left( \frac{1}{\sqrt{1 - \frac{4}{\pi}} + \frac{1}{\sqrt{1 - \frac{4}{\pi}} - \frac{1}{\sqrt{1 - \frac{4}{\pi}}}} \right)}}}{\pi / 2 + 1 - \frac{4}{\pi} F}
\]

\( \rho \), density of blood plasma; \( \mu \), dynamic viscosity of blood plasma; \( R_{cell} \), radius of endothelial cell; \( W \), half-width of a leaky junction; \( \phi \), fraction of leaky junctions; \( D_{i} \), diffusion coefficient of low-density lipoprotein (LDL) through the leaky junction; \( \xi_{i} \), thickness of leaky junction; \( K_{pm} \), hydraulic permeability of the glycolcylx; \( \epsilon_{flj} \), porosity of glycolcylx; \( L_{p} \), thickness of glycolcylx; \( K_{eff} \), effective hydraulic permeability of the porous medium, which accounts for tight regions and breaks; \( K_{i} \), hydraulic permeability of the break; \( K_{pm} \), pressure-dependent permeability of intima; \( K_{ref} \), lag coefficient for LDL transport in the intima; \( D_{i} \), diffusion coefficient of LDL within the intima layer; \( \epsilon_{i} \), porosity of intima layer; \( L_{i} \), thickness of intima; \( K_{ref} \), lag coefficient for LDL transport in the fenestral pores; \( D_{im} \), diffusion coefficient of LDL within the fenestral pores; \( f \), area fraction of fenestral pores; \( d \), diameter of fenestral pore; \( K_{pm} \), hydraulic permeability of media layer; \( D_{tm} \), diffusion coefficient of LDL in the media layer; \( K_{cen} \), lag coefficient of the media layer; \( r_{im} \), consumption rate constant within the media layer; \( L_{m} \), thickness of media layer.

Table 1. Summary of parameters used for modeling the multilayer, deformable thoracic aorta wall

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \rho ), Kg/m(^3)</td>
<td>1.000</td>
<td>2–4, 19, 20</td>
</tr>
<tr>
<td>( \mu ), Pa(\cdot)s</td>
<td>7.2\times 10^{-4}</td>
<td>2–4, 19, 20</td>
</tr>
<tr>
<td>( R_{cell} ), ( \mu )m</td>
<td>10</td>
<td>13, 14</td>
</tr>
<tr>
<td>( \phi )</td>
<td>0.0005 (70 mmHg), 0.0005, 0.01, 0.02, 0.01, 0.04 (180 mmHg)</td>
<td>12, 13</td>
</tr>
<tr>
<td>( \xi_{i} ), ( \mu )m</td>
<td>447 (70 mmHg), 447, 316, 223, 100, 50 (180 mmHg)</td>
<td>16</td>
</tr>
<tr>
<td>( H_{i} ), ( \mu )m</td>
<td>125 (70 mmHg), 100 (180 mmHg)</td>
<td>21</td>
</tr>
<tr>
<td>( D_{ij} ), ( m^2)/s</td>
<td>2.5\times 10^{-11}</td>
<td>2, 13</td>
</tr>
<tr>
<td>( L_{ij} ), ( \mu )m</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>( K_{ij} ), ( m^2)/s</td>
<td>3.6\times 10^{-17}</td>
<td>21</td>
</tr>
<tr>
<td>( \epsilon_{ij} )</td>
<td>0.49</td>
<td>21</td>
</tr>
<tr>
<td>( L_{ij} ), mm</td>
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<td>21</td>
</tr>
<tr>
<td>( K_{eff} ), ( m^2)</td>
<td>4.14\times 10^{-17}</td>
<td>21</td>
</tr>
<tr>
<td>( K_{Bt} ), ( m^2)</td>
<td>4.72\times 10^{-16}</td>
<td>21</td>
</tr>
<tr>
<td>( \epsilon_{eff} )</td>
<td>0.088</td>
<td>21</td>
</tr>
<tr>
<td>( K_{pm} ), ( m^2)</td>
<td>0.42\times 10^{-16} (70 mmHg), 0.07\times 10^{-16} (180 mmHg)</td>
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</tr>
<tr>
<td>( K_{ref} )</td>
<td>1.915 (70 mmHg), 1.997 (180 mmHg)</td>
<td>14</td>
</tr>
<tr>
<td>( D_{i} ), ( m^2)/s</td>
<td>2.13\times 10^{-12} (70 mmHg), 3.25\times 10^{-13} (180 mmHg)</td>
<td>14</td>
</tr>
<tr>
<td>( \epsilon_{i} )</td>
<td>0.8025(70 mmHg), 0.4994 (180 mmHg)</td>
<td>14</td>
</tr>
<tr>
<td>( L_{i} ), ( \mu )m</td>
<td>0.155 (70 mmHg), 0.0575 (180 mmHg)</td>
<td>14</td>
</tr>
<tr>
<td>( K_{cen} )</td>
<td>1.915 (70 mmHg), 1.997 (180 mmHg)</td>
<td>14</td>
</tr>
<tr>
<td>( D_{ref} ), ( m^2)/s</td>
<td>2.13\times 10^{-13} (70 mmHg), 3.25\times 10^{-13} (180 mmHg)</td>
<td>14</td>
</tr>
<tr>
<td>( f )</td>
<td>( 3.49\times 10^{-3} )</td>
<td>14</td>
</tr>
<tr>
<td>( d ), ( \mu )m</td>
<td>0.083 (70 mmHg), 0.091 (180 mmHg)</td>
<td>14</td>
</tr>
<tr>
<td>( K_{pm} ), ( m^2)</td>
<td>6.09\times 10^{-19}</td>
<td>1, 19, 20</td>
</tr>
<tr>
<td>( D_{im} ), ( m^2)/s</td>
<td>4.3012\times 10^{-14}</td>
<td>27</td>
</tr>
<tr>
<td>( K_{cen} )</td>
<td>3.33</td>
<td>27</td>
</tr>
<tr>
<td>( r_{im} ), ( \text{m}^2)/s</td>
<td>1.2\times 10^{-2}</td>
<td>27</td>
</tr>
<tr>
<td>( L_{m} ), ( \mu )m</td>
<td>12.1845 (70 mmHg), 96.94 (180 mmHg)</td>
<td>16</td>
</tr>
</tbody>
</table>
Thus \( D_{\text{mm}} \) is calculated as \( 4.3012 \times 10^{-14} \text{ m}^2/\text{s} \) from Eq. 25. The lag coefficient of the media layer, \( K_{\text{cfm}} \), is defined as:

\[
K_{\text{cfm}}^{*} = \frac{1}{1 - F}
\]

where \( K_{\text{cfm}}^{*} \) is the lag coefficient for convective transport in the extracellular matrix phase (\( K_{\text{cfm}}^{*} = 2 \) for LDL). Thus \( K_{\text{cfm}} \) is calculated as 3.33 for LDL in the media layer. The uptake of LDL by SMCs is modeled as a first-order reaction evenly distributed throughout the entire media layer. The assumption of a first-order reaction for the uptake of LDL by SMCs was proposed by Truskey et al. (28) and later applied to the media layer by Huang and Tarbell (8). The effective reaction rate, \( k_{\text{m}} \), of LDL uptake within the media layer is:

\[
k_{\text{m}} = \frac{2F}{1 - F} \frac{1}{1 + Da/R} (r_{\text{m}}/R)
\]

where \( R \) is the radius of one SMC (2 \text{ \mu m}), \( r_{\text{m}} \) is the first-order reaction rate over the surface of the SMC given in literature as \( 2.2 \times 10^{-8} \text{ m}^2/\text{s} \) (9). \( Da \) is the Damkohler number, and \( Sh \) is the Sherwood number representing the dimensionless mass flux at the surface of an SMC

\[
Sh = \frac{K_{\text{L}} R}{D_{\text{mm}}}
\]

where \( K_{\text{L}} \) is the mass transfer coefficient. The Damkohler number represents the dimensionless reaction rate

\[
Da = \frac{k_{\text{m}} R}{D_{\text{m}}}
\]

\( Da \) and \( Sh \) are determined as 0.88 and 4 for LDL, respectively. Then, \( k_{\text{m}} \) is \( 1.2 \times 10^{-2} \text{ s}^{-1} \) for LDL.

There are no experimental data available that indicate a dependence of \( k_{\text{m}} \) on pressure, shear stress, or stretch although these forces are known to affect proliferation, apoptosis, and migration of SMC (29).

**Computational method.** The axisymmetric illustration of the computational domain in Fig. 1A represents the local environment around a leaky cell in the arterial wall. It is a transverse section of the wall consisting of the endothelium, intima, IEL, and media layers. The width of computational domain is \( \xi \) in the \( r \) direction. As discussed earlier, hypertension increases the cell turnover rate (d), which in turn affects on \( \xi \). The width and the depth of leaky junctions are taken as 40 nm and 2 \text{ \mu m}, respectively. The number of clefts within the periodic unit varies as \( \xi \) changes under hypertension. The study of Huang et al. (10) for rabbit thoracic aorta revealed that the thin intimal layer compresses from 0.5 \text{ \mu m} at 0 mmHg to 0.155 \text{ \mu m} at 70 mmHg and then to 0.0575 \text{ \mu m} at 180 mmHg. In the present study, the intimal thickening in chronic hypertension is not accounted for. Tedgui and Lever (25) presented data for the thickness of the rabbit thoracic aorta as 125 \text{ \mu m} at 70 mmHg and 100 \text{ \mu m} at 180 mmHg. According to the aforementioned data, we set the thicknesses of intima and media to 0.155 \text{ \mu m} and 121.845 \text{ \mu m} at 70 mmHg and 0.0575 \text{ \mu m} and 96.945 \text{ \mu m} at 180 mmHg, respectively. The lengths of different layers of aortic wall at 70 and 180 mmHg along with all of the other model parameters are presented in Table 1.

The set of governing equations (Eqs. 1–8) were solved by means of the finite element method provided in Comsol Multiphysics, Version 3.4 (Comsol). The flow calculations were performed first to obtain the pressure and velocity fields, which were used in the mass transport calculations for LDL. In any given geometry, the numerical results for the flow and LDL transport were determined to be independent of mesh density. At 70 mmHg, a computational mesh was employed consisting of 600 quadratic elements in each leaky and interendothelial junction, 5,600 quadratic elements in the intima, 200 quadratic elements in each fenestral pore, and 13,000 quadratic elements in the media layer. The same numbers of mesh elements were taken in all subdomains at 180 mmHg, except for the intima and media that contained 4,000 and 9,500 quadratic elements, respectively. Linear elements were defined throughout the entire system.

**RESULTS**

Figure 3 demonstrates the spatial distribution of LDL concentration within the intima, IEL, and media layers, where the distance between the leaky junction and the first fenestral pore (\( a \)) is 10 \text{ \mu m}. Here, \( a \) is defined as \( a = r_{\text{LJ}} - r_{\text{FP}} \), where \( r_{\text{LJ}} \) and \( r_{\text{FP}} \) are the radial positions of leaky junction and the closest fenestral pore to the axis of symmetry, respectively. Figure 3A shows the distribution of normalized concentration, \( C' = C/C_{0} \), versus the normalized radial position (\( r' \)) and the normalized axial position (\( z' \)) at 70 mmHg. Note that \( C \) is the local
concentration and \( C_0 \) is the concentration at the inlet of the leaky junction. Figure 3B represents a similar concentration distribution at 180 mmHg. The radial position is normalized by the radius of the periodic unit \( r^* = r/H \), whereas the axial position is normalized by the thickness of arterial wall at any given pressure, that is \( z = zH \). In the present study, the value of \( H \) is taken as 125 \( \mu m \) at 70 mmHg, and 100 \( \mu m \) at 180 mmHg (11).

The location of \( z = 0 \) represents the lumen-endothelium interface, while \( z = 1 \) represents the media-adventitia interface. A deeper insight into the behavior of LDL transport may be obtained by presenting the radial concentration profiles at various depths in the medial layer (Fig. 4). The distributions of LDL concentration within the media layer are displayed in Fig. 4, A and B, corresponding to 70 and 180 mmHg. Here, \( z = (z - z_m)/H \), where \( z \) is the dimensionless depth in the media and \( z_m \) is the axial position of the media-IEL interface. The distance between the leaky junction and the nearest fenestral pore to the axis of symmetry (\( a \)) is 10 \( \mu m \). A comparison between Fig. 4, A and B, reveals that the LDL concentration calculated at 180 mmHg within the media is lower than at 70 mmHg. This reflects the reduction in thickness and hydraulic permeability of the intima and IEL at 180 mmHg relative to 70 mmHg. Figure 4, A and B, also shows that there is a maximum concentration at any depth within the media layer, which occurs at the radial position of the nearest fenestral pore to the leaky junction. The existence of this distinct maximum reflects the high resistance of the intima to the transport of LDL. In fact, the transport of LDL through the intima takes the nearest fenestral pore to leave the intima to the media, where it faces less transport resistance.

It is obvious from Fig. 3 that the LDL concentration drops across the thickness (\( z \)) of the medial layer. Figure 4 also demonstrates the medial local concentration profile versus the radial coordinate, \( r^* \), (\( r^* = r/\xi \)). A noticeable feature of the concentration profiles in Fig. 4, A and B, is that at \( z^* = 0.3 \), the LDL concentration is nearly same in both panels. However, in the regions corresponding to \( z^* > 0.3 \), \( C^* \) is about twice as large at 70 mmHg than that at 180 mmHg. At the midsection of the media (\( z^* = 0.5 \)), the radial concentration profile becomes essentially flat. As sections move further toward the media-adventitia interface (\( z^* > 0.5 \)), the profiles are nearly one-dimensional. Thus results show that the region of nonuniform concentration in the radial direction has the same thickness at both 70 and 180 mmHg, whereas within this region the LDL concentration is higher for 70 mmHg. Here, the value of the dimensionless concentration at \( z^* = 0.50 \) is \(-0.01 \), which is independent of transmural pressure.

Leaky endothelial junctions occurring during cell turnover and death have been postulated to be major pathways for enhanced lipoprotein transport across the vascular endothelial layer. Based on the study by Wu et al. (33), it is assumed that the cell turnover fraction (\( \phi \)) increases under chronic hypertension by up to a factor of 100. Figure 5 presents the axial distribution of LDL concentration within the medial layer at 70 mmHg with \( \phi = 0.005 \) and at 180 mmHg with five different values of \( \phi \) up to 0.04. In Fig. 5, \( (C^*) \) represents the normalized...
medial concentration \((C') = \langle C \rangle / C_0\), where \(C\) is the mean value of concentration calculated over all the elements in a circular slice with radius \(\xi\) having the thickness of 0.5 \(\mu\)m along the \(z\)-axis. \(\langle C \rangle\) is defined as:

\[
\langle C \rangle = \frac{2 \sum_k C(r_k, z_k) h(r_k, z_k) r_k}{\xi \sum_k h(r_k, z_k)}
\]

where \(h(z_k, r_k)\) is the local element size, \(C(z_k, r_k)\) is the local concentration, and \(z_k, r_k\) are the radial and axial positions of element \(K\) located inside the slice. It is worth mentioning that in Fig. 5, the concentration reaches a plateau at about the dimensionless position of 0.15, then rises slightly and continues to decline afterward. The noise and large variations close to the intima (diminished farther into the media) may come from the discrete spacing of the clefts and the fenestral pores. Figure 5 indicates that the rate of cell turnover affects significantly the LDL concentration distribution within the medial layer. This shows that the ratio of the radial distance required to disperse LDL to the radius of periodic unit, \(\xi\), increases as \(\phi\) is raised due to hypertension. This ratio is responsible for raising the average concentration over the periodic unit within the media.

Figure 6 presents the LDL flux in the \(z\) direction, \(J_S\), at four different sites: across the inlet of leaky junction (Fig. 6A), across the outlet of leaky junction (Fig. 6B), across the inlet of fenestral pore (Fig. 6C), and across the outlet of fenestral pore (Fig. 6D). In Fig. 6, the results of LDL flux are plotted for \(\phi = 0.0005\) at 70 and 180 mmHg and \(\phi = 0.04\) at 180 mmHg. The LDL fluxes corresponding to \(\phi = 0.001, 0.002\), and 0.01 at 180 mmHg are not shown in Fig. 6 since they overlay on the results for \(\phi = 0.0005\). The solute flux can be described (26) as a combination of convection, \(J_C\), due to bulk flow and diffusion, \(J_D\), due to diffusion. The convection and diffusion fluxes of tracer within the wall can be expressed at any point in a differential form as (26):

\[
J_D = -D \frac{dC}{dz}\]

Fig. 6. LDL flux as a function of the radial position. A: inlet of leaky junction (LJen; lumen-endothelium interface). B: outlet of leaky junction (LJex; endothelium-intima interface). C: inlet of the nearest fenestral pore to leaky junction (FPen; intima-IEL interface). D: outlet of fenestral pore (FPex; IEL-media interface). \(J_S\), LDL flux in the \(z\) direction.
where $C$ and $dC/dz$ are the concentration and the concentration gradient at a point in the wall, $D$ is an effective diffusion coefficient for the solute within the tissue, $u$ is the transmural velocity, and $K_{cf}$ is the lag coefficient. Figure 6A demonstrates that the LDL flux is larger at the inlet of leaky junction in 70 mmHg than that in 180 mmHg. As shown in Fig. 6B, the flow field becomes very nonuniform at 180 mmHg since the flux profile at the outlet of the leaky junction is highly asymmetric so that more flux is leaving from the outer edge. The asymmetry of the outgoing flux from the leaky junction reveals the strong influence of the compact structure and the small thickness of intima on the transport phenomena at higher pressure. For the same reason, the flux profile corresponding to 180 mmHg at the inlet of fenestral pore is considerably more asymmetric than at 70 mmHg (Fig. 6C). In contrast, the profile of flux at the outlet of fenestral pore entering the media has a fairly symmetric shape even at 180 mmHg, which can be related to the notable thickness of media layer. Although not shown in Fig. 6A–D, the flux profile abruptly rises once the cell turnover parameter increases from 0.01 to 0.04 for the pressure of 180 mmHg, whereas it is almost unchanged up to $\phi = 0.01$. This is why the flux profiles are only shown for $\phi = 0.0005$ and 0.04 at 180 mmHg.

Figure 7 demonstrates the axial distribution of LDL concentration within the media layer at 180 mmHg with $\phi = 0.002$ for different values of the parameter $a$, which is defined as $a = r_{LJ} - r_{FP}$. The local oscillations appearing in Fig. 7 (especially the case with triangular symbols) have numerical origins associated with the mesh size relative to spacing of fenestral pores and intercellular clefts and averaging. Note that the parameter $a$ is exclusively defined in axisymmetric geometry because fenestral pores are represented as fenestral rings. Therefore, one may consider a number of simulations through which $a$ varies with a uniform distribution. Here, the value of $a$ is chosen as 10, 5, 0, and $-5 \mu m$. The highest value for medial dimensionless concentration ($C^*$) is observed when a fenestral ring is located right beneath the leaky junction ($a = 0$). For the other values of $a$, the medial concentration distributions are similar and substantially lower. It should be noted that in a more realistic 3D model, $a = 0$ would imply that all fenestral pores are aligned with a leaky junction. This is unlikely to occur in a real endothelial monolayer. There will be a distribution of $a$ values associated with the many leaky junctions, and the results will be characterized by a mean value of $a$ that is nonzero. Thus the results for $a = \pm 5 \mu m$ are expected to be more realistic.

Figure 8 presents the local LDL flux profile versus axial position in the intima at a distance of 40 nm from the leaky junction where a fully developed flow is achieved. Figure 8A shows the LDL flux at 70 mmHg with $\phi = 0.0005$ and at 180 mmHg with $\phi = 0.0005$ and 0.04. The noticeable feature of Fig. 8A is the higher values of LDL flux in the region close to the leaky junction at 180 mmHg, which are the result of decreased values for the thickness, porosity, and hydraulic permeability of the intima under higher pressure. This is
interesting since it shows that the intimal flux of LDL increases locally near the leaky junction under elevated pressure. In other words, the convective mass transport of LDL is boosted in the region close to the leaky junction. Figure 8B shows the LDL flux across the intima for different values of \(a\), assigned as 10, 5, 0, and \(-5\ \mu m\) at 180 mmHg. As expected, the flux is lowest when the fenestral pore is right beneath the leaky junction because the outgoing flux from the leaky junction substantially enters the fenestral pore and only a small portion of the LDL flux is diverted into intima. Figure 8B indicates that the maximum intimal LDL flux occurs when \(a = 5\ \mu m\). It may be explained based on the definition of the solute flux, Eqs. 33 and 34, which show flux depends on both \(C\) and \(J\). To get a better understanding of the observations in Fig. 8B, the average velocities across the leaky junction and clefts are presented in Fig. 9A for the same geometries shown in Fig. 8B. The superficial velocity, \(U\), is defined as the mean velocity across the leaky junction or clefts, calculated by

\[
U = \frac{\int_1^2 ru(r)dr}{rd_1} \quad (35)
\]

where \(d_1 = r_2 - r_1\) is the width of junction (leaky or interendothelial), \(u(r)\) is the local velocity in the junction, and \(r\) is the radial position in the middle of the junction. As shown in Fig. 9A, for the case of \(a = 0\ \mu m\), the velocity is higher than other cases at the outlet of the leaky junction, which in turn increases the LDL flux within the intima (Eqs. 33 and 34). The velocity in the leaky junction and clefts are shown for 70 and 180 mmHg in Fig. 9B, where \(a = 0.0005\) and \(a = 10\ \mu m\). The value of velocity in the leaky junction is higher at the lower pressure, whereas it is the opposite for clefts. Differences between the velocities are associated with different resistances (inverse of permeability) to flow in the intima due to pressure differences and different distances between junctions and fenestral pores. The hydraulic permeability of intima also decreases at 180 mmHg, which forces the flow to pass through the nearest fenestral pore. However, the flow distributes more uniformly at 70 mmHg as the resistance against flow imposed by the intima is lower.

Figure 10 shows the radial distribution of LDL concentration within the intimal layer. The set of lines, in Fig. 10A, represents the case of \(\phi = 0.002\) for different values of \(a\). These lines demonstrate how the value of \(\phi\) controls the region containing detectable tracer concentration. The first fenestral ring in our model represents a relatively large opening from the intima layer to the media, which allows the transport of water and significant amount of LDL into the media. Thus the concentration of LDL falls sharply to very low values at the position of the fenestral ring. The surprising results in Fig. 10A are from the cases with \(a = 0\) and \(-5\ \mu m\), where the region with high LDL concentration extends to the vicinity of the next cleft (at \(r/R_{cell} = 3\)). In the geometry with \(a = -5\ \mu m\), the flow out from leaky junction is divided into two branches toward the first and second nearest fenestral pores to the leaky junction. However, the cleft plays an important role when \(a = 0\). This role is even more important when the IEL is modeled as a porous layer with an effective hydraulic permeability, \(K_{PEL}\), obtained from our simulations based on the Darcy’s law as \(1.2 \times 10^{-20} \ m^2\) at 70 mmHg and \(4.1 \times 10^{-21} \ m^2\) at 180 mmHg. In fact, \(K_{PEL}\) is the hydraulic permeability for the IEL if it is assumed as a homogeneous porous medium. The LDL concentration within the intima is shown for this case in Fig. 10B by solid lines marked by square (for 180 mmHg) and circular symbols (for 70 mmHg). The dashed lines marked by square (for 180 mmHg) and circular symbols (for 70 mmHg) demonstrate the LDL concentration through intima where fenestral pores are present over the IEL. Here, \(\phi\) and \(a\) are set to 0.0005 and 10 \(\mu m\), respectively. The region with high LDL concentration, in this case, is spread within a radius smaller than 3\(R_{cell}\), which is the location of the first cleft next to the leaky junction. The mean LDL concentration within intima, \(C_{in}\), is calculated by:

\[
\tilde{C}_{in} = \frac{C_i \cdot dV}{A_{int} \cdot L_i} \quad (36)
\]

where \(V_i\) is the volume of intima. Figure 11 displays the variation of \(\tilde{C}_{in}\) versus \(\phi\). These results indicate that the average LDL concentration in the intima would not change.
with pressure if the fraction of leaky junctions was constant. As \( \phi \) increases under hypertension, \( C_{in} \) rises proportionally.

Table 2 displays the values of apparent permeability of the endothelium (\( P_e \)) and the hydraulic conductivity (\( L_p \)) of the endothelium, intima, media, and the whole arterial wall. The volume flux (\( J_V \)) through the aorta wall has also been shown in Table 2. The apparent permeability of the endothelium (\( P_e \)) is calculated by:

\[
P_e = \frac{J_{Se} A_{lj}}{\Delta C A_{tot}}
\]

where \( J_{Se} \) is the mean LDL flux across the leaky junction, \( A_{lj} \) is the area of the leaky junction \(-2\pi r dr\), \( r \) is the radial position of leaky junction, \( A_{tot} \) is the total area of domain \(-\pi \phi^2\), and \( \Delta C \) is defined as \( C_0 - C \), where \( C \) is the average concentration over the radius of the domain at the endothelial-intimal interface. The apparent permeability of the intima (\( P_{in} \)) is calculated by

\[
P_{in} = \frac{J_{Se} A_{lj}}{\Delta C A_{tot}}
\]

where \( \Delta C \) is \( C - \bar{C}_1 \), and \( \bar{C} \) is the average concentration over the radius of the domain at the IEL-media interface. The hydraulic conductivity is defined as:

\[
L_p = \frac{J_V}{\Delta P}
\]

where \( j \) stands for one of the wall layers or the whole vessel wall and \( \Delta P \) is the corresponding pressure drop. \( J_V \) is calculated by:

\[
J_V = u_{lj} A_{lj} + \sum_j u_{lj} A_{lj}
\]

where \( u_{lj} \) and \( u_{lj} \) are the velocity in the leaky junction and cleft, respectively. The hydraulic conductivity (\( L_p \)) of the aorta wall is given by:

\[
1/L_p = 1/L_{pe} + 1/L_{pin} + 1/L_{pm}
\]

where \( e, in, \) and \( m \) stand for endothelium, intima, and media layers, respectively. Note that the hydraulic conductivity of the intima includes the hydraulic permeability of the IEL. Here, \( L_p \) is first calculated from Eq. 39, and then it is checked whether Eq. 40 is satisfied. Tedgui and Lever (25) showed that the hydraulic conductivity of the total wall, calculated from the filtration data, is \( 4.00 \pm 1.31 \) cm/(s.mmHg) at 70 mmHg, and \( 2.44 \pm 0.80 \times 10^{-8} \) cm/(s.mmHg) at 180 mmHg. The values of hydraulic conductivity given in Table 2 are in good agreement with the values measured by Tedgui and Lever (25). Note that the value of \( L_{pe} \) at 70 mmHg (\( 2.3 \times 10^{-7} \) cm·s⁻¹·mmHg⁻¹) is very close to the in vitro results (24). This suggests that the in vitro endothelial cell monolayer model is a good physiological model. Tedgui and Lever (25) also presented the values of \( J_V \) as \( 2.8 \times 10^{-6} \) cm/s and \( 4.4 \times 10^{-6} \) cm/s for 70 and 180.
The calculated values for $J_V$ here, the sum over clefts and leaky junction, are in good agreement with the experimental results of Tedgui and Lever (25). Moreover, we calculated the fraction of water flow that goes through the leaky junction and the clefts. According to previous studies (2, 24), clefts are the major pathways for water. This is also confirmed by our results in which the fraction of water flow passing through the leaky junction varies from 2% to 23% for $\phi$ in the range of 0.0005 to 0.04. The most important quantity given in Table 2 is the apparent permeability of the endothelium which increases with the rate of cell turnover and death. This observation has also been reported in several experiments (3, 13, 18, 25, 27). The value of $P_e$ decreases from $1.2 \times 10^{-8}$ cm/s at 70 mmHg to $0.7 \times 10^{-8}$ cm/s at 180 mmHg and increases with larger values of $\phi$ above the normal physiological levels of order 0.001. Truskey et al. (27) reported the value of $P_e$ as $1.9 \pm 0.8 \times 10^{-8}$ cm/s at 100 mmHg in their in vivo study of endothelial permeability to LDL. Curmi et al. (3) estimated $P_e$ as $2 \times 10^{-8}$ cm/s at 70 mmHg and $8 \times 10^{-8}$ cm/s at 160 mmHg. Our predicted results are consistent with these in vivo values. The results of present study for $P_e$ imply that the endothelial permeability is influenced by the fraction of leaky cells, the positioning of fenestral pores, the compaction of subendothelial layers, and the pressure-driven convection under high pressure. We have examined the influence of the intimal compaction on $P_e$ by generating the geometry at 180 mmHg with the same fraction of leaky cells, intimal thickness, and transport properties of the wall as was performed in 70 mmHg. We observed that in this geometry $P_e$ increases from $1.19 \times 10^{-8}$ cm/s at 70 mmHg to $3.1 \times 10^{-8}$ cm/s at 180 mmHg, which reveals the important role of the wall compaction on $P_e$.

The apparent permeability of the intima, given in Table 2, is dramatically reduced at 180 mmHg relative to 70 mmHg as the thickness and hydraulic permeability of intima are decreased at 180 mmHg. It can also be observed that $P_{in}$ is significantly affected by the value of $\phi$ and the displacement of fenestral pores.

**DISCUSSION**

It has been demonstrated that hypertension affects the development of atherosclerotic lesions in both human beings and experimental animals (1, 3, 11, 13, 16, 25, 33). The penetration of LDL into the arterial wall with accumulation in the intima and media layers has been also recognized as an initiating factor in atherosclerotic disease (2, 17, 19, 23, 24, 34). Some earlier studies on hypertensive animals have reported increased transendothelial LDL permeability in arteries (1, 33). It has also been indicated that hypertension may lead to an enhancement of LDL entry to the intima by altering the permeability of the endothelium (indirect effect) rather than by increasing the filtration velocity (direct effect) (1, 3, 16, 33). The mechanism of the enhancement of endothelial permeability under hypertension has been described by Wu et al. (33). They found that increased mitosis and apoptosis of endothelial cells and associated transient leaky junctions could increase the endothelial permeability to macromolecules in the rat aorta. The present numerical study was designed to examine these mechanisms quantitatively and to assess the significance of the various arterial wall structures in modulating transport. The physiological parameters used in the model are taken from data of rabbit thoracic aorta.

Endothelial deformation over fenestral pores have been theoretically predicted and subsequently revealed by light and electron microscopic observations of transendothelial sections at high lumen pressure (11). If the subendothelial intima undergoes a large volumetric strain, and if the local intimal deformation is proportional to the local transendothelial pressure difference, then endothelial indentations appear over the fenestral pores at higher lumen pressures due to the large pressure drop near the fenestral pores. Therefore, the present study also focused on intimal compaction and its influence on LDL transport within the aortic wall.

A multilayered model was used to study the transport of LDL locally through the aortic wall, including the endothelium, intima, IEL, with fenestral pores, and media. The presence of leaky and normal interendothelial junctions distributed through the endothelium was taken into account. The pressure-dependent thicknesses and transport properties of the intima, IEL, and media layers were calculated separately. We have not used adjustable parameters in the model. Most of the parameters come from first principles, whereas several come from reported experimental values that do have ranges. In view of these limits on the assignment of parameters, it is reassuring that many of the predictions in Table 2 are in accord with experimental observations. Numerical results reveal that LDL concentration within the media layer decreases under acute elevation of pressure, whereas it increases with the rising pressure.
fraction of leaky junctions under hypertension. Curmi et al. (3) investigated, ex vivo, the effect of high pressure on LDL transport in an arterial wall after 5, 30, 60, and 120 min. They concluded that synergy between increased endothelial permeability and compaction of the media together with enhanced pressure-driven convection might account for the marked increase in LDL concentration observed in the inner wall at high pressure. On the other hand, Meyer et al. (16) studied, ex vivo, the effect of pressure-driven convection and vessel wall stretching on the pressure-related changes in LDL and albumin transport across the rabbit thoracic aorta wall pressurized at 70, 120, and 160 mmHg for 30 min. The variation of endothelial permeability was not investigated in Ref. 16. Meyer et al. (16) also showed that pressure-induced stretching of the vessel wall is a major determinant of albumin and LDL transport across the arterial wall, and pressure-driven convection specifically enhances the accumulation of LDL in the inner media. By studying the effect of blood pressure levels on transendothelial macromolecular transport, Huttner (12) demonstrated that the passage of protein tracers (horseradish peroxidase and ferritin) through rat arterial endothelium is influenced by sudden changes of arterial blood pressure. On the other hand, Bretheron et al. (1) indicated, in vivo, that hypertension increases the influx of LDL into the aortic intima in rabbits. However, they reported that the reversal of hypertension did not result in an immediate reduction in the rate of LDL influx and concluded that the increased LDL flux under hypertension was caused by an indirect effect on the aortic wall permeability rather than a direct effect of the increased filtration pressure. In the present study, Figs. 3 and 4 reveal that even though the aortic wall is compressed under hypertension, the LDL concentration decreases within the media layer. However, Fig. 5 shows that LDL concentration rises significantly by increasing the fraction of leaky junctions, which is associated with the enhancement of endothelial permeability under hypertension. These results, particularly at the higher rate of cell turnover, are in good agreement with the results of Curmi et al. (3) obtained from aortas incubated at 160 mmHg for 2 h. Curmi et al. (3) also showed (Fig. 5B of Ref. 3) that the relative concentration of LDL increases significantly with the incubation time of aortas at 160 mmHg. We have examined the effect of endothelial permeability by generating the geometry at 180 mmHg aortas at 160 mmHg. We have examined the effect of endothelial permeability by generating the geometry at 180 mmHg with the same fraction of leaky cells as at 70 mmHg. Results of LDL concentration are in good agreement with those of Ref. 16. They are also in close agreement with the results for 5 and 30 min in Ref. 3. However, after 1 h of incubation of aorta under a high pressure the LDL concentration increases significantly due to increase of endothelial permeability. This also has been confirmed by the results from the present study (Fig. 5). Figure 8A shows that the local intimal flux of LDL near to a leaky junction increases with pressure. However, the local LDL concentration in the region close to the leaky junction remains constant as pressure rises, as shown in Fig. 10B. Therefore, the mean LDL concentration within the intima, shown in Fig. 11, is not affected by pressure if the fraction of leaky junctions remains constant. The mean LDL concentration is expected to rise as the fraction of leaky junction increases. This is evident from Fig. 11, which indicates the significant contribution of enhanced endothelial permeability to the accumulation of LDL in the intimal layer.

In conclusion, the present multilayered model of the deformable aortic wall revealed important details about the influence of hypertension on the transport of LDL and its accumulation in the subendothelial zone, which might explain increased atherosclerosis susceptibility in hypertension. The model considers for the first time the roles played by the increase of endothelial cell turnover and the compaction of arterial wall layers in modulating the apparent permeability of the endothelium and intima, the hydraulic conductivity of the artery wall and wall layers, and the transport of LDL through the wall layers under changes in pressure. The model makes many realistic predictions without adjustable parameters and aids in our understanding of the factors that initiate atherogenesis. First, the results show that the accumulation of LDL through subendothelial layers is caused by the indirect effect of hypertension increasing the endothelial permeability to LDL through its influence on cell turnover. Second, we have demonstrated that intimal compaction and the enhancement of endothelial cell turnover are effects of hypertension, which may gradually cause the accumulation of LDL within the intima. The LDL concentration also increases dramatically throughout the media layer under hypertension, particularly in the region near the IEL. This region of the artery wall is important due to the development of intimal hyperplasia and the migration of SMCs from the media to the intima. The transport and accumulation of LDL within the intima and its subsequent oxidation appear to be critical processes in the formation of the early foam cell lesions. Finally, results for the relative change of hydraulic conductivity with pressure are in good agreement with experimental measurements. This supports our assumption of intimal compaction and increased endothelial cell turnover rate under hypertension. Our computational model can also be advanced in the future with 3D features to further enhance our understanding of the transport phenomena in arterial wall.

REFERENCES

EFFECT OF HYPERTENSION ON ARTERIAL WALL


