Fluid–structure interactions (FSI) based study of low-density lipoproteins (LDL) uptake in the left coronary artery

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The purpose of this study is to compare the effect of the different physical factors on low-density lipoproteins (LDL) accumulation from flowing blood to the arterial wall of the left coronary arteries. The three-dimensional (3D) computational model of the left coronary arterial tree is reconstructed from a patient-specific computed tomography angiography (CTA) image. The endothelium of the coronary artery is represented by a shear stress dependent three-pore model. Fluid–structure interaction (FSI) based numerical method is used to study the LDL transport from vascular lumen into the arterial wall. The results show that the high elastic property of the arterial wall decreases the complexity of the local flow field in the coronary bifurcation system. The places of high levels of LDL uptake coincide with the regions of low wall shear stress. In addition, hypertension promotes LDL uptake from flowing blood in the arterial wall, while the thickened arterial wall decreases this process. The present computer strategy combining the methods of coronary CTA image 3D reconstruction, FSI simulation, and three-pore modeling was illustrated to be effective on the simulation of the distribution and the uptake of LDL. This may have great potential for the early prediction of the local atherosclerosis lesion in the human left coronary artery.

According to the report from the American Heart Association (AHA), coronary atherosclerosis accounts for over 30% of cardiovascular diseases¹. Previous studies suggested that atherosclerosis lesion regions usually held local complex hemodynamic forces, such as vortex and oscillatory shear². Hemodynamic studies found that the blood flow is always complex around the arterial bifurcations where atherosclerosis lesions usually occur³. Many pieces of evidence suggested that the initiation and progression of the atherosclerotic disease involves a significant accumulation of low-density lipoproteins (LDL) in the arterial wall⁴,⁵. Due to the high clinical incidence of coronary atherosclerosis, it is of great clinical significance to study the distribution of hemodynamic parameters and the accumulation of LDL in the coronary artery.

Previous studies revealed that atherosclerotic plaque predisposed area coincides with the regions of high LDL concentration distribution⁶,⁷. However, concentration distribution alone cannot explain the focal accumulation of LDL within the arterial wall. Endothelium is a major barrier of the LDL transport from the artery lumen into the vessel wall⁸. There are two pathways for LDL via the endothelium: (1) vesicles absorb LDL from plasma by receptor-mediated endocytosis; (2) LDL directly pass through endothelium by leaky junctions⁹. Early experimental studies have shown that more than 90% of LDL transport into the arterial wall while only less than 10% of LDL flux via vesicular pathway¹⁰. However, the leaky junctions-based pathway is associated with endothelial cells in the state of mitosis or apoptosis¹¹. Researches showed that the fraction of leaky junction on endothelium is influenced by the shear stress on the luminal surface¹².

The arterial wall included multi-layers in physiologically. It was widely known that the distribution of the flow filed in arteries is co-regulated by all layers of the wall. Moreover, the LDL transport in the flowing blood is controlled by the convection–diffusion equation. To study the LDL transport to the arterial wall, previous researchers proposed many models for the representation of the multi-layer arterial wall, such as the four-layer model and the single-layered model¹³–¹⁷. However, these studies were based on the CAD-generated models that

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were unphysiological. In the current work, we want to go further than the existing literature on predicting the distribution and the uptake of LDL in the coronary arterial wall. To predict the LDL accumulation in the arterial wall, we introduced a three-pore model to represent the endothelium\textsuperscript{11,18}. This model is fully taking account of the contribution of the vesicular pathway, normal junctions, and leaky junctions to the transport of LDL from lumen to the arterial wall. According to the three-pore model, LDL transport was greatly governed by the local wall shear stress (WSS)\textsuperscript{12}, therefore, it was of great clinical significance to figure out which factors may be the key cause of disturbing the blood flow. Moreover, the numerical model was generated from a patient-specific CTA image, which made the study model closer to physiological conditions. Complex vascular geometric structure and pulsatile could lead to a spatial and temporal alterations of blood flow in the human arterial system\textsuperscript{19}. This made WSS difficult to measure in vivo. Fortunately, fluid–structure interactions (FSI) technique is capable of capturing arterial wall move and flow change with high time and spatial resolution. In this study, two-way fully coupled FSI simulations were carried out to capture the real-time changes of the intravascular flow field. The numerical simulations were performed with ANSYS 14.0 software. Hemodynamic parameters such as time-averaged wall shear stress (TAWSS), oscillatory shear index (OSI), relative residence time (RRT) and time-averaged wall shear stress gradient (TAWSSG) were analyzed in the present study\textsuperscript{20–22}.

Methods

Reconstruction of left coronary artery models. The CTA image used in this study came from a patient by medical examination in the Guangdong General Hospital. The voxel size of the coronary CTA image was 0.5 × 0.5 × 0.5 mm. This study was approved by the Research Ethics Committee of the Guangdong General Hospital, Guangdong Academy of Medical Sciences and conformed to the principles outlined in the Declaration of Helsinki.

Many good results were analyzed with the use of Computer-Aided Design (CAD)-generated arteries in the previous studies\textsuperscript{23,24}. However, these geometric models deviated from the physiological characteristics to a certain extent. In this study, the 3D fluid domain, as shown in Fig. 1a, was generated from the CTA image of a patient-specific left coronary artery. The first step was to extract and refine the centerline of the human left coronary arteries with the use of MIMICS software. The centerlines were formed by a series of center points that are located at the center of the cross-sectional plane of the 3D coronary artery. Then proceed as follows, dividing along the centerline to obtain circle borders of the human left coronary arteries on the vertical plane of the centerline, sweeping the circle borders, guided by the centerlines, to obtain the 3D model of the human left coronary artery. Lastly, we meshed the reconstructed model with the use of ANSYS ICEM-CFD software.

Figure 1. Reconstruction of 3D human left coronary artery. (a) Reconstructed human left coronary artery from the original CT coronary data of a 54-year-old male patient. LMA left main coronary artery, LAD left anterior descending artery, LCX left circumflex artery, D1 first diagonal branch of the LAD, OM left obtuse marginal branch. (b) Meshes of blood-phase & arterial wall of human left coronary artery.
A typical structure of an arterial wall includes six layers. These layers are glycocalyx, endothelium, intima, internal elastic lamina, media, and adventitia, respectively. To simplify the numerical model in this study, the arterial wall was regarded as a single-layer with constant thickness. In our present study, the coronary arterial wall was given the thickness of \(W_{TH} = 0.53\) mm and \(W_{TH} = 0.77\) mm for the normal and thickened wall cases, respectively.

Fluid and solid mesh was generated in ANSYS ICEM-CFD and ANSYS WORKBENCH-MESH, respectively. The mesh independence was considered achieved when the variation of TAWSS, OSI, and RRT were less than 3% between two successive simulations (see Supplementary materials). The fluid mesh consisted of 2,474,927 elements with 10 prismatic layers near the wall, and the solid mesh for the arterial wall thickness of 0.53 mm and 0.77 mm contained 61,432 elements and 79,252 elements, respectively (Fig. 1b). The pulsatile transient simulations were carried out for three full cardiac cycles with the uniform time step of 0.01 s. The data for analysis were obtained at the third cardiac cycle.

**Governing equations.** It was well known that blood flow is a non-Newtonian fluid in physical, especially for the blood flow in micro-vessels. Many numerical studies on LDL transport problems were based on non-Newtonian assumption by previous researchers. Moreover, previous studies suggested that the shear-thinning and viscoelastic of blood are essential factors that affect the blood flow under various flow rates. The non-Newtonian models such as sPTT model, Giesekus model, and Carreau model can obtain relatively accurate results than using Newtonian model, however, they are not convenient to study the effect of a specific viscosity on the flow. Hence, to study the effect of different viscosity on the LDL uptake, the blood flow here is assumption as homogeneous and incompressible blood with Newtonian rheology, the fluid dynamics in the artery lumen can be described by the Navier–Stokes equation. The governing equations of mass, momentum, and species were as follows,

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

\[
\rho \left( \frac{\partial \mathbf{u}}{\partial t} + \mathbf{u} \cdot \nabla \mathbf{u} \right) - \mu \nabla^2 \mathbf{u} + \nabla p = \mathbf{F} = 0
\]

\[
\frac{\partial C}{\partial t} + \mathbf{u} \cdot \nabla C = D \nabla^2 C = 0
\]

where \(\mathbf{u}\) and \(p\) are the fluid velocity vector and pressure, \(\rho (1,050 \text{ kg/m}^3)\) and \(\mu (0.0035 \text{ Pa} \cdot \text{s} \text{ and} 0.0040 \text{ Pa} \cdot \text{s})\) for normal and hyper-viscosity cases, respectively) are the blood density and viscosity, \(F\) is the fluid domain body force (in our present study, \(F\) is zero), \(C\) is the LDL concentration, and \(D\) is the free diffusivity coefficient of LDL which could be set as \(5.983 \times 10^{-12} \text{ m}^2 \text{s}^{-1}\).

The mechanism of the LDL transport into the vessel wall is in large measure determined by the endothelium. In this study, a three-pore model was introduced to describe LDL uptake on the left coronary arterial wall (see Supplementary materials), which was taking account of the contribution of the vesicular pathway, normal junctions, and leaky junctions as well as employing the local WSS to obtain the total LDL mass flux.

The arterial wall was considered as an elastic homogeneous material with a density of 1075 kg/m\(^3\), a Poisson’s ratio of 0.45, and an isotropic Young’s modulus (\(E\)) of 3 MPa. The conservation equation of the solid part can be derived from Newton’s second law of motion. The elastic–dynamic equation can be represented by

\[
\rho_s \ddot{d}_s - \nabla \sigma_s - f_s = 0
\]

where \(\rho_s\) is the density of arterial wall, \(\ddot{d}_s\) is the acceleration within the solid region, \(\sigma_s\) is the Cauchy stress tensor, and \(f_s\) is the solid domain body force.

**Boundary conditions and computation procedures.** A pulsatile flat inlet flow profile in the left main coronary artery (LMA) was set based on a previous study (Fig. 2a). Pressure-outlet boundary conditions were used at the four inferior ends of the fluid domain, and non-slip boundary condition was specified at the luminal wall. Fully constrained boundary conditions were applied on the edge of the LMA, left anterior descending artery (LAD), first diagonal branch of the LAD (D1), left circumflex artery (LCX) and left obtuse marginal branch (OM) to give stability to the structural calculation. \(P_{adv} = 17.5\) mmHg and \(P_{adv} = 30\) mmHg were applied at the wall for normal and hypertensive cases, respectively. A constant LDL concentration profile \(C_0\) equal to 2.86 \(\times 10^{-7}\) mmol/mm\(^3\), corresponding to the physiological LDL concentration in whole blood (bulk fluid concentration)\(^{13,34}\), was prescribed at the LMA inflow section. At each outflow section of the left coronary artery, \(\frac{\partial C}{\partial n} = 0\) were applied. At the luminal surface, the boundary conditions of LDL lumen-to-wall transfer were referred to previous studies.

To study the effect of the different factors on the LDL transport via endothelium, five cases were performed. The Control case represented a healthy individual. To study the effect of the elastic property of the arterial wall, a Case with a rigid wall was studied. The numerical simulations were performed with ANSYS 14.0 software. The details of five numerical calculations were as follows.

**Control:** wall thickness = 0.53 mm, viscosity = 0.0035 Pa \cdot s, blood pressures = 70 mmHg

**Case 1:** rigid wall, viscosity = 0.0035 Pa \cdot s, blood pressures = 70 mmHg

**Case 2:** wall thickness = 0.53 mm, viscosity = 0.0040 Pa \cdot s, blood pressures = 70 mmHg

**Case 3:** wall thickness = 0.53 mm, viscosity = 0.0035 Pa \cdot s, blood pressures = 120 mmHg
Case 4: wall thickness = 0.77 mm, viscosity = 0.0035 Pa · s, blood pressures = 70 mmHg.

Hemodynamic parameters. The characteristic time of endothelial cell response to shear stress in terms of mitosis or apoptosis was much longer than that of shear oscillation. Therefore, the following time-averaged hemodynamic parameters were used to characterizing the response of endothelial cells to the blood flow:

\[
TAWSS = \frac{1}{T} \int_{0}^{T} |WSS| \cdot dt \tag{5}
\]

\[
OSI = 0.5 \left[ 1 - \frac{\int_{0}^{T} |WSS| \cdot dt}{\int_{0}^{T} |WSS| \cdot dt} \right] \tag{6}
\]

\[
RRT = \frac{1}{TAWSS \cdot (1 - 2 \cdot OSI)} \tag{7}
\]

\[
TAWSSG = \frac{1}{T} \int_{0}^{T} \sqrt{ \left( \frac{\partial WSS}{\partial x} \right)^2 + \left( \frac{\partial WSS}{\partial y} \right)^2 + \left( \frac{\partial WSS}{\partial z} \right)^2 } \cdot dt \tag{8}
\]

where \(T\) is the duration of the cardiac cycle. \(WSS\) is the WSS vector which is defined as the scalar dot product of the unit normal vector to a surface and the viscous stress tensor. \(\partial /\partial x, \partial /\partial y,\) and \(\partial /\partial z\) are the partial derivatives with respect to the \(x, y\) and \(z\) coordinates, respectively. \(TAWSS\) represented the time-averaged magnitude of the WSS during the cardiac cycle(s). If \(TAWSS\) is less than 1 Pa, intimal thickening occurs. The OSI is employed to describe the oscillatory nature of the WSS throughout the cardiac cycle; and the RRT is included the effects OSI and TAWSS, that is employed to identify regions in which high particle residence time occur.

Ethics approval. This study was approved by the Research Ethics Committee of the Guangdong General Hospital, Guangdong Academy of Medical Sciences, and was performed per the Declaration of Helsinki.

Informed consent. The need of informed consent was waived by the Research Ethics Committee of the Guangdong General Hospital, Guangdong Academy of Medical Sciences.

Results
The change of blood flow flux with the cardiac cycle. For all the cases, LAD has the largest flow flux over all the time, followed by LCX, D1, and OM, respectively (Fig. 2b). Moreover, there is a deviation of flow rate among the five cases during the cardiac cycles, especially at the periods of early-systole and early-diastole. This suggested that the blood flow flux at the periods of early-systole and early-diastole are easily disturbed by external conditions. In detail, at the period of early-systole, Case 1 shows the highest blood flow rate in the arterial ends of LAD while Case 2 indicates the smallest flow rate (see “insert views” in Fig. 2b). The flow rate...
among Control and Case 3 and Case 4 have no significant difference. However, at the period of early-diastole, the situations of flow rate are totally reversed (see “insert views” in Fig. 2b), at which Case 2 shows the highest blood flow rate.

The streamline profiles at the different periods during the cardiac cycle. Figure 3 illustrates velocity profiles during the cardiac cycle for the five simulations. The flow patterns at the six different periods are significant difference from each other. Precisely, the coronary system keeps the smallest velocity at the period of early-systole while it holds the largest velocity at the period of early-diastole. At the period of early-diastole, strong secondary flow and recirculation zone at bifurcation regions can be observed. At the period of mid-diastole, the size of recirculation zone at bifurcation regions are different among the five cases (Fig. 3f). In detail, Case 1 has the largest recirculation zone in the bifurcation regions, followed by Case 4. However, there is no clear recirculation zone appearing in the bifurcation regions for the simulations of Case 2, Case 3, and Control. This suggested that rigid and thickened arterial hold the most complex flow at the bifurcation regions. As the elasticity of vessel decreased when the arterial wall thickness increased39, consequently, the thickened wall of the coronary artery will have lower elastic property when compared with non-thickened ones. In other words, superior elasticity of the arterial wall could decrease the complexity of the local flow field in the coronary bifurcation system.

The distribution of hemodynamic parameters on the luminal wall. Figure 4 shows the WSS distributions during the cardiac cycle for the five simulations. The results show that the WSS at the deceleration period of cardiac cycle is lower than that at the acceleration period of cardiac cycle, especially at the period of end-deceleration. For all the simulations, at the period of end-systole, the luminal surface has the lowest WSS, followed by the period of end-diastole. However, at the period of early-diastole, the luminal surface has the highest WSS. Figure 5a–d respectively displays the distribution of time-averaged hemodynamic parameters of TAWSS, OSI, RRT and TAWSSG for the five cases. The distribution of these time-averaged hemodynamic parameters for all the simulation conditions are similar among the five cases. The TAWSS of Case 2 is slightly higher than that of the other four cases (Fig. 5a). The regions with low TAWSS, high OSI are near the vascular bifurcations
Moreover, the TAWSS in upstream and outside of LCX is relatively lower when it is compared with the downstream and inner wall. Results show that high-RRT regions on the arterial wall are mainly located at the low-TAWSS regions (Fig. 5a,c). Large areas of low TAWSSG are located at the downstream of four branch arteries (Fig. 5d). Extremely high TAWSSG can be easily found in the regions of vascular bifurcation, such as the bifurcation of LAD and LCX.

The distribution of three-pore model related indicators on the luminal wall. Figure 6a shows the fraction of leaky junctions (∅) distribution on endothelium for the five simulation cases. The distribution of ∅ on the arterial wall is similar among the five cases. The regions of high ∅ consistent with the places of low TAWSS regions (Figs. 5a, 6a). Figure 6b,c respectively shows the fluid volume fluxes and LDL mass fluxes through the endothelium for the five simulation cases. Higher fluid volume flux (Jv) regions are mainly located at the outer wall of LAD and LCX where the TAWSS was relatively low (Figs. 5a, 6b). The values of Jv for Case 3 are significantly higher than that of the other four cases, while Case 4 had the lowest Jv among the five cases (Fig. 6b). Moreover, the value of Jv on the LCX and OM is relatively higher than that on the LAD and DI. The highest value occurs at bifurcations where the LMA stem branches into LAD and LCX, the value at which is as high as $2.63458 \times 10^{-8}$ m/s. Low Jv regions are mainly located at inner side of twisting arteries, the lowest value is under $2.63456 \times 10^{-8}$ m/s. According to the three-pore model, the value of Jv into the arterial wall is not only determined by volume fluxes, but also by the concentration of LDL on the near wall. Moreover, the LDL transport in the bloodstream is calculated by the convection–diffusion equation (Eq. 3). As the distribution of all the hemodynamic parameters (TAWSS, OSI, RRT, TAWWSG) for the five different cases is similar from each other (Fig. 5a–d), hence, the distribution of LDL on the luminal wall would be also similar too. Nevertheless, LDL concentration profiles would be changed very much at the different places in the same model of the arterial wall surfaces. Figure 6c shows the distribution of LDL mass flux (Js) through the endothelium. Case 3 has the highest Js, while Case 4 has the lowest Js among the five cases. The regions with high value of Js are always occurred at LCX and low value regions are mainly located at the downstream of LAD and LCX and the upstream of LMA. The highest value of Js are mainly located at the recirculation zones where the WSS is usually very low. Overall, the distribution trend of Js is similar with Jv, but the absolute values are not completely the same between them. In addition, although the color-coded maps of ∅ didn't appear to show much difference among the five different
cases, $J_v$ and $J_s$ are still showing significant differences among the five different cases, especially case 3 (increased blood pressure) and case 4 (increased wall thickness).

**The distribution of the percentage difference of the $J_v$ and $J_s$ on the luminal wall.** Figure 7a,b respectively shows the percentage difference of $J_v$ ($J_v'$) and $J_s$ ($J_s'$) between Case (1, 2, 3, 4) and Control case. The relatively high values of $J_v'$ between rigid and elastic models (Case 1 vs. Control) are located at the regions of...
compared to the condition of the vascular wall with elastic properties (Fig. 3). Moreover, when flowing blood in the wide-angle bifurcations, such as the branches into the D1, branches into the OM, and the LAD and LCX branches into the OM) (Figs. 3, 4, 5). Our present study further indicates that in addition to the influence of hypertension, the progression of the atherosclerotic disease involved a significant accumulation of LDL in the arterial wall (Fig. 7a). This suggested hypertension increased the plasma fluid and LDL mass flux through the endothelium, while the thickened arterial wall decreases this process.

Discussion

This paper applied an FSI method to study the influence of different physical factors on the LDL uptake from flowing blood to the arterial wall in the left coronary artery. The results revealed that: (1) High elastic property of the arterial wall can decrease the complexity of the local flow field in the coronary bifurcation system. (2) The regions of high LDL uptake are located in the regions of low wall shear stress. (3) Hypertension can promote LDL uptake in the arterial wall, quite the contrary, thickened arterial wall can decrease the uptake of LDL.

The important feature of atherosclerosis is the narrowing of the arteries. It can block the blood flowing in the vessel. Atherosclerosis is characterized by patchy intimal plaques that encroach on the lumen of medium-sized and large arteries; the plaques contain lipids, inflammatory cells, smooth muscle cells, and connective tissue. As we know, risk factors of atherosclerosis include dyslipidemia, LDL, diabetes, cigarette smoking, family history, sedentary lifestyle, obesity, and hypertension. There was much evidence suggesting that the initiation and progression of the atherosclerotic disease involved a significant accumulation of LDL in the arterial wall. Moreover, a large number of LDL uptake is the key factor leading to the accumulation of LDL. Therefore, early accumulation of LDL could be the most important reason for the intimal thickening, which is the first step of the arterial narrowing (initiation of intimal thickening). Although our present study did not directly predict intimal thickening, it still can be effective in predicting the distribution and uptakes of LDL in the arterial wall. Hence, the present results may partially predict the intimal thickening according to the amounts of LDL uptakes in the coronary artery.

Previous studies showed that vascular geometric structure, such as the branches, curvatures, and bifurcations have a significant effect on the local flow field distribution. Our recent research also confirms that complex flow, such as strong secondary flow and recirculation flow, are easily discovered around the bifurcation regions. In addition, the blood flow at the wide-angle bifurcations, such as LMA stem branches into LAD and LCX, are more complex when compared with the narrow-angle bifurcations (e.g. LAD branches into the D1 and the LCX branches into the OM) (Figs. 3, 4, 5). Our present study further indicates that in addition to the influence of vascular geometric structure on the blood flow field, other factors, such as the pulsatile and the elasticity of the arterial wall, also have much effect on the blood flow field (Figs. 2, 3, 4). It is shown that the flow patterns at different periods during the cardiac cycles are significantly different. The results also show that rigid wall condition leads to the largest recirculation zone and the most complex streamlines at the bifurcation regions when compared to the condition of the vascular wall with elastic properties (Fig. 3). Moreover, when flowing blood
flows in the wall-thickened coronary artery, the flow field is also complex than that of the un-thickened ones. This indicates that the effect of the rigid wall and the thickened wall on the flow field are very similar. Study by Bastida et al. showed that thickened arterial wall has lower elastic property when compared with thinner arterial wall\textsuperscript{39}. This suggested that the higher elasticity of arterial wall can decrease the complexity of the local flow profiles. The dysfunction of the endothelium led to atherogenesis, this process is stimulated by the complex hemodynamic forces\textsuperscript{32}. Therefore, the elasticity of human blood vessels may play a self-protection role in preventing vascular atherosclerotic lesions.

For all the simulations, the regions of high blood plasma flux coincide with the regions of high LDL flux and the regions of low TAWS, high OSI, high RRT, and high TAWSSG (Figs. 5, 6). Other previous studies also indicated that LDL accumulation increased with lower wall shear stress\textsuperscript{26,45}. Studies by John et al. suggested that the transport processes of LDL are determined by both blood flow and endothelium\textsuperscript{46}. It was showed that the fluid mechanics may be influential when mass transfer coefficient is much smaller than the surface reaction rate coefficient (the process was termed “fluid-phase-limited”), conversely, luminal wall could be influential when mass transfer coefficient is greater than the surface reaction rate coefficient (the process was termed “wall-limited”)\textsuperscript{46}. Previous studies show that blood plasma flux can not only through leaky junctions, but also through normal junctions\textsuperscript{45,47}. However, LDL particles are too large to pass through normal junctions\textsuperscript{41}, which means that the effect of convection effect of blood plasma transmural flow on LDL accumulation are largely affected by the percentage of leaky junctions, not normal junctions. There are two main ways for LDL particles transport through the endothelial wall, the portion of LDL transport via vesicular transcytosis mechanism is less than 10%, whereas the portion of LDL transport through leaky junctions mechanism is over 90%\textsuperscript{47}. This suggested that the LDL transport into the arterial wall is largely affected by the number of leaky junctions. According to the three-pore model, the fraction of leaky junctions on endothelium is a function of local WS\textsuperscript{31}. The regions of low WS are consistent with the places of higher number of leaky junctions (Figs. 4a, 6a). Hence, in the low WSS regions, the transmural resistance on the endothelium to flow is decreased considerably\textsuperscript{13}. This leads to an increase in the flux of blood plasma in those low WS regions of the coronary wall. Due to the convection effect of blood plasma in the leaky junctions, the increased plasma flux, in turn, leads to increased transportation of LDL particles from the lumen into the arterial wall (Fig. 6b,c).

On the other hand, increased transmural pressure also leads to an increased filtration velocity through leaky junctions, consequently, resulting in an increased convective flux of LDL through the endothelium. These results are consistent with previous numerical findings\textsuperscript{13,26,48}. There are many reasons for this phenomenon. Firstly, according to the principle of fluid dynamics, higher blood pressure is usually accompanied by lower flow velocity, hence leads to lower wall shear stress. The effect of low wall shear stress on the LDL uptake has been demonstrated above. On the other hand, studies suggested that the increased transmural pressure could induce arterial wall distension and stretch, which leads to an increased number of mitosis and apoptosis\textsuperscript{49}. This phenomenon will result in an increased number of leaky junctions, therefore, leads to an increase of endothelial diffusive permeability\textsuperscript{45,51}. Moreover, pressure-driven convective flow at higher transmural pressure also enhances LDL uptake\textsuperscript{31}. It is well accepted that the early atherogenesis tends to be hallmark by an abnormally high accumulation of LDL\textsuperscript{13}. Our results confirm that plasma flux and LDL mass flux of hypertension case is significantly higher than that of the control individual (Fig. 7). This suggested that that hypertension may increase the susceptibility to atherosclerosis by increasing the accumulation of LDL on the endothelium. Furthermore, as the blood pressure in the proximal end of coronary is usually greater than that in the distal end, therefore, the uptake of LDL is relatively high in the proximal end (Fig. 6). This gives us a hypothesis that the near heart arteries could be more susceptible to atherosclerosis. Therefore, it may partially be explained why atherosclerosis easily happened in large arteries, such as LMA and aorta.

Unlike the effect of blood pressure, the wall thickness played an opposite role on the uptake of LDL in coronary. The results in our recent studies show that thickened wall can act to inhibit LDL entry into the arterial wall. This may indicate that the earlier formation rate of atherosclerotic plaque is relatively faster. As the atherosclerotic plaque grew, and over time, the growth rate will become slower in the later period of plaque formation. This finding is consistent with the study by Liu et al. that the atherosclerotic plaque grows at a decreasing rate in the progression process\textsuperscript{52}. Moreover, although high blood viscosity condition increases the TAWSS on the arterial surface, it played a minor role in the effect of LDL uptake (Figs. 5a, 6c). This may because blood viscosity may affect the LDL transport only in the vessel lumen, but the uptake of LDL in the arterial wall could be mainly dominated by the surface passages of the endothelium\textsuperscript{52}.

**Limitations:** All the simulations of the present study are based on a flat inflow boundary condition, and the ends of the artery branches are prescribed as constant pressures. This may not perfectly reproduce the pulse wave propagation. However, it should be pointed out that our method for the boundary conditions setting are still reasonable. It can help us to predict reasonable results on the distribution trend because the present boundary conditions set could only affect the absolute values, but not the trend. Furthermore, the arterial wall in our present study is regarded as a sing-layer with a constant thickness. The distribution of vascular wall thickness may be different along the luminal wall of the coronary arteries under the physiological conditions. However, it is unrealistic for us to build a model with different wall thicknesses along the vessel because the patient-specific CTA image used for generating the computational models is from a patient by medical examination in the hospital. There is no accurate information about arterial wall thickness, we can only obtain the contour of the blood vessel wall from the CTA image. Therefore, in this study, the parameter data of wall thickness are from the previously published paper. Another limitation of the present study is that all the simulations are based on a Newtonian fluid assumption with a constant viscosity. The shear-thinning and viscoelastic properties of blood can affect the blood flow under various flow rates. Nevertheless, this study can be convenient for us to quantitatively study the effect of different viscosities on the LDL accumulation.
Conclusions

By using the numerical method of FSI technique for studying the LDL uptake in human left coronary arteries, we can know that high elastic property of the arterial wall can decrease the complexity of the local flow field in the coronary bifurcation system. This may suggest that the elastic property of the arterial wall is good for preventing atherosclerotic disease. Moreover, we can also know that the places of high levels of LDL uptake coincided with the regions of low wall shear stress; the thickened arterial wall can decrease the uptake of LDL; the present study revealed that hypertension significantly promoted LDL accumulating in the arterial wall. This study found that hypertension may play the chief culprit role in atherosclerotic lesions. More importantly, as the places of atherosclerosis lesion usually consistent with the regions with high LDL uptake, hence the present computer strategy has a great potential for the prediction of the local atherosclerosis lesion.

Data availability

The datasets supporting the conclusions of this article were included within the main paper.

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