Effect of Temperature-Dependent Blood Viscosity on Low-Density Lipoprotein Transport: Numerical Study

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Abstract. The blood viscosity is correlated with the risk of developing atherosclerotic lesions. The environmental factor can play an important role in altering hemodynamics and low-density lipoprotein (LDL) especially the ambient temperature. The greenhouse gas emission from energy or power production can increase the ambient temperature. This study investigated the effect of temperature-dependent blood viscosity on the LDL transport within the axisymmetric artery with a 40% stenosis blockage via computational fluid dynamics simulation. The results showed that the changing of blood viscosity inducing the change in pressure drop. The penetration locations of the LDL were also shifted which increased the risk of having LDL penetrating into the arterial wall. In addition, the outcome will contribute to the initial development of atherosclerosis modelling.

1. Introduction
Cardiovascular disease (CVD) has been one of the leading causes of death in recent years [1]. Atherosclerosis is an inflammatory disease that causing by the buildup of the macromolecules i.e. low-density lipoprotein (LDL) and endothelial dysfunction [2]. The early-stage development of atherosclerosis begins with the accumulation of the lipid in the arterial wall. The topic has received interest from many researchers as the underlying process of the developments still unclear. As the formation of the disease is very complex, the simplified mathematical model representing some specific interest of the disease has been introduced [3–7]. The multi-layered arterial wall structure has been developed and widely used in the previous literature [8–12]. Recently, the model has been improved to include a more realistic presentation of the arterial wall i.e. porous media layer. The LDL transport model is an important part which connects the lumen with the arterial wall. The wall shear stress-dependent model so-called three-pore model is introduced to govern the transport of LDL through the endothelium. The uses of the numerical model become more comprehensive in the field to develop a realistic representation of the flow behavior [13–15].

The environmental pollution or greenhouse gas emission from energy or power production could increase the ambient temperature which affecting the blood properties [16]. The relationship between temperature and viscosities of blood and plasma had been investigated for their effects on blood pressure. The essential parameter correlating with the known risk factor of the formation of
Atherosclerotic lesion was the blood viscosity. The selection of viscous model had been analyzed for the suitability of the model to predict the blood flow. When decreasing temperature, the blood viscosity increased, vice versa, when increasing temperature, the blood viscosity decreased. The change in viscosity levels of blood was then an important factor affecting blood pressure. However, the effect of environmental temperature on the LDL transport has not been numerically investigated. The novelty of the present study is to integrate the multi-layered model coupled with the three-pore LDL transport model into ANSYS Fluent platform. The achieved model is further used to investigate the effect of temperature-dependent blood viscosity on the variables related to the transport of LDL which are the primary indicator of atherosclerosis formation.

2. Methodology
The idealized axisymmetric artery with the presence of a 40% blockage was used as the computation geometry. The presence of the blockage allows the induction of the recirculation flow in the downstream region. The geometry was based on Olgac et al. [5]. The geometry is illustrated in Fig. 1 which shows the computation zone including lumen, endothelium, and intima zones. In the lumen zone, the LDL species is transported together with blood flow. The blood and LDL flow can penetrate into the arterial wall (intima zone) as the function of wall shear stress. In the intima zone, the flow is governed by Darcy’s law equations, and the LDL species can be oxidized with the given rate of reaction.

2.1. Governing equations
The governing equations were based on the previous literature [4,5]. The sensitivity analysis was performed as the extension to compare and identify the significance of the temperature-dependent blood viscosity. The nomenclatures and the equations are referred to Olgac et al. and Cilla et al. [4,5]. The flow of blood in the lumen was governed by the general mass conservation and momentum equations. The density of the blood was taken as (1,050 kg/m³). The blood viscosity was the study factor representing the value of blood viscosity in a various manner, e.g. normal activity state, the fever/exercising state and hibernation/extremely. The numerical model only took account of the viscous resistance. The fluid porosity was considered as 1. The permeability of the arterial wall was given as \( K_p \) (1.2x10^{-18} m²). For the LDL transport equations in the intima zone, it was defined as:

\[
(1 - \sigma_f) \sigma_f u_c \cdot \nabla c_w - D_w \nabla^2 c_w + r_w c_w = 0
\]  

(1)

where the subscript \( w \) represents the variables within the arterial wall. The diffusivity of LDL in intima zone is given as \( D_w = 8x10^{-13} \) m²/s, respectively. \( c \) and \( u \) is the concentration (mol/m³) and velocity (m/s) of LDL, respectively. \( \sigma_f \) is the solute lag coefficient (0.8514). The LDL consumption rate is assigned to the transport equation of the LDL in the intima zone to represent the reaction of LDL to the oxidized LDL. The rate is given as \( r_w = 3x10^{-4} \) s⁻¹.
2.2. Model implementation
The computational framework using in this study was the commercial finite volume solver, ANSYS Fluent 2019R3. The model was implemented with the custom helper using user-defined functions (UDF) written in C. The SIMPLE algorithm was used for the pressure-velocity coupling of Navier-Stoke equations. The second-order upwind scheme was used for both flow and LDL concentration spatial discretization. The system was solved using a 64-bit parallel machine with a double-precision setting.

The interface between lumen and intima zone was connected with the endothelium layer which comprising of two 1 micrometer thick layers. The custom Dirichlet boundary condition in Eq. (2) was applied to the model using UDF. In order to apply the calculated value directly to the boundary interface, the value was assigned as the fixed value option in the cell zone condition setting. The interface boundary was representing the endothelium layer.

\[(1 - \sigma_f \vec{J}_f \vec{c}_f - D_f (\nabla \vec{c}_f) \cdot \vec{n}) = [(1 - \sigma_s \vec{J}_s \vec{c}_s - D_s (\nabla \vec{c}_s) \cdot \vec{n}) = J_s \] (2)

where the subscript \( f \) represents the variables for lumen zone. \( J_s \) is the flux of blood filtered through the arterial wall, \( D_f = 5 \times 10^{-12} \text{ m}^2/\text{s} \) which is the diffusivity of the blood and \( J_s \) is the flux of the solute.

2.3. Parametric study
The sensitivity of the environmental effect on the transportation of LDL as the primary indication of the formation of the atherosclerotic lesion was investigated. The relationship between viscosity and environmental temperature was studied. According to the measurement of the blood viscosity and body temperature, the increase in body temperature may decrease the blood viscosity, in contrast, the decrease in body temperature may increase the blood viscosity [14]. In this study, five body temperatures ranging from 22 °C to 39.5 °C which represents the extremely cold temperature up to the fever state, respectively, were selected for the evaluation. The parameter variation is expressed in Table 1. The changes in wall shear stress, fluxes of solute and solvent, and LDL concentration were compared.

The wall shear stress (WSS) is calculated from the velocity gradient normal to the endothelium interface.

\[ WSS = -\mu \frac{du}{dx} \] (3)

where \( \mu \) is blood viscosity (Pa·s), \( du/dx \) is the velocity gradient of the first cell adjacent to the endothelium interface (m). In addition, the accumulation of the LDL is also determined and represented in terms of the average LDL concentration within the intima. The average LDL concentration in the arterial wall was determined to evaluate the risk of potential atherosclerotic lesion development. The LDL concentration calculation was made by volume averaging given as:

\[ c_{\text{LDL,avg}} = \frac{\int c_{\text{LDL}} dV}{\int dV} \] (4)

where \( c_{\text{LDL,avg}} \) is the volume-average LDL concentration, \( c_{\text{LDL}} \) is the local LDL concentration and \( V \) is the cell volume.

| Case | Temperature (°C) | Blood viscosity (Pa·s) | Condition            |
|------|------------------|------------------------|----------------------|
| 1    | 39.50            | 2.689x10^{-3}          | Fever state          |
| 2    | 38.00            | 2.844x10^{-3}          |                      |
| 3    | 36.50            | 3.000x10^{-3}          | Normal               |
| 4    | 29.25            | 3.392x10^{-3}          |                      |
| 5    | 22.00            | 3.784x10^{-3}          | Severe Hypothermia   |
3. Results and discussion

3.1. Model validation

The model implementation was validated against the results given by previous studies [5]. Fig. 2(a) shows the wall shear stress (WSS) plot along with the endothelium interface. Wall shear stress plays a significant role in determining the solute and solvent flux through the interface. The plot showed the highest value of wall shear stress in the area where there was a 40% blockage of the artery vessel. With the reduction of the artery diameter, the blood flow velocity increased. The velocity gradient in the near-wall region was also increased causing the high peak value of wall shear stress at that maximum reduction of diameter location. This was where the flow was started to separate from the main flow direction. The wall shear stress was slightly decreased at the location behind the blockage as the flow velocity in this region was low due to the formation of the recirculation zone. The filtration velocity \( J_f \) was showing the same agreement with the wall shear stress plot. The filtration velocity was in reverse relationship with wall shear stress. The peak location of the filtration velocity was found in the same region as previous studies [4,5,18]. The filtration velocity profile along the endothelium interface is shown in Fig. 2(b). The results were observed that the filtration velocity was greatly reduced at the location of the blockage where the wall shear stress was high. In addition, the peak was also found high behind the blockage area. It was identified this area as the reattachment point where the main flow and the flow in the recirculation were reattached. The flow was mainly forced to move toward the wall direction perpendicular to the main flow direction. Fig. 2(c) shows the normalized LDL concentration \( c^* \) profile along with the endothelium interface. The LDL concentration profile was agreed upon with the filtration velocity. The LDL concentration tended to be high where the filtration velocity and the solute flux were high. These three figures were plotted along with the results from Olgac’s study. It was apparently showing that the model was successfully implemented into ANSYS Fluent and was able to produce accurate results comparing with the work using COMSOL. This model was used for the parametric study in the following section.

![Figure 2](image-url)

**Figure 2.** (a) Wall shear stress profile with endothelium interface in the normalized \( z \)-direction \( (z^* = r/2R) \), (b) Filtration velocity profile along with the endothelium interface in the normalized \( z \)-direction \( (z^* = r/2R) \) and (c) Normalized LDL concentration profile \( (c^* = c/c_0) \) along with the endothelium interface on the intima side in the normalized \( z \)-direction \( (z^* = r/2R) \).
3.2. Effect of temperature-dependent blood viscosity

Five blood viscosities according to the different range of five body temperature were studied. The value was in the range of $2.689 \times 10^{-3}$ to $3.784 \times 10^{-3}$ Pa·s. The blood viscosity represents the resistance of blood to flow. The higher blood viscosity, the higher it resisted the flow motion. The pressure drop of the flow in each case is shown in Table 2. The loss of pressure due to the reduction of the vessel diameter tended to be high, in this case, the vessel diameter had been reduced by 40%. In case 1 with the lowest blood viscosity, the pressure drop showed the lowest value as it is easier for the blood to flow across, resulting in the lowest loss of pressure. Thus, the case with the highest blood viscosity (case 5) itself showed the highest pressure drop value.

| Case | Pressure Drop (Pa) | Volume-Average LDL Concentration (mol/m³) |
|------|--------------------|------------------------------------------|
| 1    | 251.30             | 0.01781                                   |
| 2    | 262.60             | 0.01674                                   |
| 3    | 273.64             | 0.01567                                   |
| 4    | 302.03             | 0.01378                                   |
| 5    | 330.49             | 0.01242                                   |

The plot in Fig. 3(a) depicts the wall shear stress for each case. The pattern of the wall shear stress plot of each case was similar as they shared the same geometry. The peak of the plot indicated the separation point. The velocity gradient in this point showed the highest as it had the smallest cross-sectional area. Consider the Eq. (3), the velocity gradients for all 5 cases were in the same order of magnitude, but the viscosity values were much higher in magnitude which led to the dominant of the blood viscosity for the wall shear stress results. As expected, the wall shear stress in case 5 with the highest wall shear stress showed the highest peak of all. The results showed the lowest wall shear stress in case 1 with the value of 31.01 Pa and gradually increased for the cases 2 to 5 with the value of 31.86, 32.95, 34.98, and 36.82 Pa, respectively. The filtration velocity profile along the endothelium interface plot for each case is shown in Fig. 3(b). The magnitude of filtration velocity of all cases was similar to each other, but the location of the peak was shifted forward closer to the blockage area in case of the high blood viscosity. In contrast, case 1 with low blood viscosity showed that the plot was shifted further away from the blockage. This was due to the lower internal friction of the fluid.

![Figure 3](image-url)

**Figure 3.** (a) Wall shear stress profile along with the endothelium interface in the normalized z-direction ($z^* = r/2R$) and (b) Filtration velocity profile along with the endothelium interface in the normalized z-direction ($z^* = r/2R$).

The LDL concentration has been computed and plotted in both axial and radial direction as shown in Fig. 4(a) and Fig. 4(b), respectively. The axial LDL concentration profile on the lumen side showed the accumulation of LDL on the arterial wall. In all five cases, the $c^*$ showing the value above 1
indicating that the LDL was started to aggregate along with the endothelium interface. Apart from the permeability of the arterial wall, the solute flux was also delegated to the concentration of the LDL. It can be implied that the case with the highest value of LDL concentration accumulates on the interface will also have the highest LDL penetrating. The radial LDL concentration is plotted in Fig. 4(b) can confirm that the concentration of LDL in case 1 with the lowest value of viscosity showing the highest among others. The left side of the graph where \( r^* = 0 \) is representing the endothelium interface on the intima side. The concentration value was gradually decreased as it convected to the depth of the wall. According to the profile in Fig. 4(a), the concentration in case 1 was high on the lumen side of the interface. The concentration difference on both ends of the interface was the major driving force for the LDL to penetrate the wall. The results also corresponded well with the volume-average LDL concentration in the wall. It was also found that case 1 had the highest average LDL concentration as can be seen in Table 2.

![Figure 4](https://example.com/figure4.png)

**Figure 4.** (a) Normalized LDL concentration profile along with the endothelium interface on the lumen side in the normalized z-direction \((z^* = r/2R)\) and (b) Normalized LDL concentration profile across the intima in normalized by intima thickness in r-direction \((r^* = r/2t)\).

4. Conclusion

The study presented the effect of blood viscosity according to the changes in the environmental temperature. The study investigated blood flow and LDL transport using computational fluid dynamics techniques. The temperature depended viscosities were used to determine the transport of LDL in different conditions. The blood viscosity had a notable effect on the wall shear stress which led to the shift of the penetration locations and also the risk of LDL penetration into the arterial wall. Within the specific range of the study parameter, the low viscosity showed the highest value of LDL penetration flux, thus, the LDL concentration also showed the highest among the others. The low viscosity condition also shifted the penetration location further down the artery. The outcome from the study showed the feasibility of the temperature-dependent blood viscosity that may play roles in the location predicting of the lesion growth. However, the temperature changes may not affect the long-term deviation of the blood viscosity. The study yields extensive support for the initial development of atherosclerosis modelling.

5. References

[1] Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics - 2018 update: A report from the American Heart Association. Circulation 2018. https://doi.org/10.1161/CIR.0000000000000558.

[2] Ross R. Atherosclerosis - An inflammatory disease. N Engl J Med 1999. https://doi.org/10.1056/NEJM199901143400207.

[3] Kenjereš S, De Loor A. Modelling and simulation of low-density lipoprotein transport through multi-layered wall of an anatomically realistic carotid artery bifurcation. J R Soc Interface 2014;11:20130941. https://doi.org/10.1098/rsif.2013.0941.

[4] Cilla M, Pena E, Martinez MA. Mathematical modelling of atheroma plaque formation and development in coronary arteries. J R Soc Interface 2013;11: 20130866–20130866. https://doi.org/10.1098/rsif.2013.0866.
[5] Olgaç U. Computational modeling of coupled blood-wall mass transport of LDL: effects of local wall shear stress. Am J Physiol Heart Circ Physiol 2008. https://doi.org/10.1152/ajpheart.01082.2007.

[6] Cameron JN, Mehta OH, Michail M, Chan J, Nicholls SJ, Bennett MR, et al. Exploring the relationship between biomechanical stresses and coronary atherosclerosis. Atherosclerosis 2020. https://doi.org/10.1016/j.atherosclerosis.2020.04.011.

[7] Silva T, Jäger W, Neuss-Radu M, Sequeira A. Modeling of the early stage of atherosclerosis with emphasis on the regulation of the endothelial permeability. J Theor Biol 2020. https://doi.org/10.1016/j.jtbi.2020.110229.

[8] Yang N, Vafai K. Modeling of low-density lipoprotein (LDL) transport in the artery-effects of hypertension. Int J Heat Mass Transf 2006. https://doi.org/10.1016/j.ijheatmasstransfer.2005.09.019.

[9] Chung S, Vafai K. Effect of the fluid-structure interactions on low-density lipoprotein transport within a multi-layered arterial wall. J Biomech 2012;45: 371–81. https://doi.org/10.1016/j.jbiomech.2011.10.002.

[10] Jesionek K, Kostur M. Effects of shear stress on low-density lipoproteins (LDL) transport in the multi-layered arteries. Int J Heat Mass Transf 2015. https://doi.org/10.1016/j.ijheatmasstransfer.2014.09.075.

[11] Roustaei M, Nikmaneshi MR, Firoozabadi B. Simulation of Low Density Lipoprotein (LDL) permeation into multilayer coronary arterial wall: Interactive effects of wall shear stress and fluid-structure interaction in hypertension. J Biomech 2018. https://doi.org/10.1016/j.jbiomech.2017.11.029.

[12] Filipovic N. Chapter 1 - Computational modeling of atherosclerosis. In: Filipovic NBT-CM in B and B, editor., Academic Press; 2020, p. 1–39. https://doi.org/https://doi.org/10.1016/B978-0-12-819583-3.00001-1.

[13] Kenjereš S, van der Krieke JP, Li C. Endothelium resolving simulations of wall shear-stress dependent mass transfer of LDL in diseased coronary arteries. Comput Biol Med 2019;114:103453. https://doi.org/10.1016/j.compbio.2019.103453.

[14] Pandey R, Kumar M, Majdoubi J, Rahimi-Gorji M, Srivastav VK. A review study on blood in human coronary artery: Numerical approach. Comput Methods Programs Biomed 2020. https://doi.org/10.1016/j.cpmb.2019.105243.

[15] Hirschhorn M, Tchantchaleishvili V, Stevens R, Rossano J, Throckmorton A. Fluid–structure interaction modeling in cardiovascular medicine – A systematic review 2017–2019. Med Eng Phys 2020. https://doi.org/10.1016/j.medengphy.2020.01.008.

[16] Brook RD, Weder AB, Rajagopalan S. “Environmental Hypertensionology” the effects of environmental factors on blood pressure in clinical practice and research. J Clin Hypertens 2011. https://doi.org/10.1111/j.1751-7176.2011.00543.x.

[17] Çınar Y, Şenyol AM, Duman K. Blood viscosity and blood pressure: Role of temperature and hyperglycemia. Am J Hypertens 2001. https://doi.org/10.1016/S0895-7061(00)01260-7.

[18] Olgaç U, Poulikakos D, Saur SC, Alkadhi H, Kurtcuoglu V. Patient-specific three-dimensional simulation of LDL accumulation in a human left coronary artery in its healthy and atherosclerotic states. AJP Hear Circ Physiol 2009. https://doi.org/10.1152/ajpheart.01182.2008.

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