Influence of non-Newtonian viscosity of blood on microvascular impairment

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Abstract. The present research investigated the role of blood viscosity on flow within a microvascular network to identify the conditions of blood flow stagnation. When the yield stress of blood was less than 0.005 Pa, there were no stagnant regions in the microvasculature. However, when the yield stress increased to 0.05 Pa, stagnant or reduced flow areas began to appear, which grew and expanded rapidly with further increase in the yield stress. Thus, the yield stress determined from blood viscosity profile of a patient can be utilized to evaluate the risk of circulatory impairment.

Keywords: Yield stress, wall shear stress, hemostasis, Herschel-Bulkley model, microvascular flow, microvessels, capillary network

1. Introduction

Fluid viscosity represents the frictional (or viscous) resistance between a moving fluid and the stationary wall of vessels. When the fluid viscosity decreases with increasing velocity in a conduit, it is called non-Newtonian shear-thinning viscosity. There are many liquids that exhibit such a non-Newtonian shear-thinning behavior. Due to the large number of suspended particles, paint is a good example of such a fluid. Since human blood contains a large number of cells in plasma in the range of 30–60%, it also exhibits non-Newtonian shear-thinning viscosity [12].

Both atherosclerosis and microvascular disorders are known to be influenced by the rheological properties of blood [9, 11, 14, 26]. The blood in large arteries moves relatively fast, typically in a range of 10–70 cm/s [24]. In order to evaluate the significance of the inertial forces relative to the viscous forces in blood flow, a dimensionless parameter called the Reynolds number, is used [24]:

\[ \text{Re} = \frac{\rho u D}{\mu} \]
where $\rho$ and $\mu$ represent the density and viscosity of whole blood, $D$ is the lumen diameter of blood vessel, and $u_m$ is the mean velocity. For example, the Reynolds number corresponding to blood flow in a large artery is in the range of 100 to 850 [24], indicating that the inertial force is much greater than the viscous force.

On the other hand, blood moves very slowly in a range of 0.1 cm/s or less in microvessels [21]. Accordingly, the Reynolds number corresponding to the flow in microvasculature is in the range of 0.001 to 0.0005, indicating that the viscous force is much greater than the inertial force. Thus, from a hydrodynamic point of view, microvascular flow is essentially controlled by the viscous force. Actual measurements of the flow of erythrocytes in capillaries in humans were measured using the velocity of erythrocytes passing nailfold capillaries [16]. Furthermore, the microvascular network is characterized by numerous branches and anastomoses interconnected in a narrow space, where the local velocity is further reduced due to flow separation and reattachment.

Blood flow in microvessels becomes further complicated because the diameters of capillary vessels are often smaller than those of the red blood cells (RBC). When red blood cells lose their deformability, they may not be able to travel through the capillaries [10], resulting in circulatory impairment. In addition, red blood cells can aggregate due to their extremely small velocity in microvessels, forming Rouleaux [4, 13]. Hematocrit, fibrinogen, and LDL-C molecules can also affect the aggregation among red blood cells [5]. When flow resistance increases due to increased RBC deformability or aggregation [20], blood velocity can decrease locally to near zero, increasing the risk of circulatory impairment.

The yield stress is a parameter can be useful in describing lower shear rate flows. Yield stress can be considered as the limiting value of the wall shear stress or the minimum wall shear stress required to continuously maintain blood flow in a vessel [17, 22]. When a patient’s blood becomes abnormally viscous, the yield stress can pathologically increase, increasing the risk of a local circulatory impairment in microvessels and the eventual loss of capillary vessels. The consequences of the so-called “collateral blood viscidation” which may lead to a yield point of blood were first described by Schmid-Schonbein [28]. The typical value of the yield stress in a human adult is in the range of 0.003 ~ 0.013 Pa [11, 22].

When microvascular ischemia occurs, no flow phenomenon is observed when capillaries disappear from the monitor of an intra-vital microscope using green light absorption by hemoglobin in the erythrocytes. Functional capillary density is defined as the number of capillaries per unit area, which are perfused by erythrocytes. When microvascular ischemia is persistent and long-standing, capillary vessels have been observed to disappear over time. It was reported that patients with chronic hypertension and chronic renal failure have significantly reduced capillary density of the myocardium [1]. The present research proposes a hypothesis that the hyperviscosity of blood can produce local circulatory impairments, leading to reduced blood supply to the microvasculature and surrounding tissue domain. In other words, one may be able to reduce the risk of circulatory impairment and subsequently the risk of capillary loss by normalizing the hyperviscosity of blood in patients with microvascular diseases.

As such, the purpose of this research was to investigate the effect of the rheological properties of blood, specifically the yield stress of blood, on microvascular flow.

2. Methods

The microvasculature typically consists of arteriole, capillary network, and venule, where three capillary networks are interconnected with each other [7]. In the present research, a simplified model was selected as shown in Fig. 1. The diameter of both the inlet and outlet of the capillary network was 15 μm, whereas
the diameter in the microvasculature was about 5–7 μm. While the entire length of the microvascular network was 470 μm, the length of both the inlet and outlet portions of the network was about 25 μm where flow was fully developed due to the slower velocity. For flow simulation, the continuity equation and the momentum conservation equation are given as follows [19, 23]:

\[
\frac{\partial u_i}{\partial x_i} = 0 
\]

\[
\rho u_i \frac{\partial u_i}{\partial x_j} = -\frac{\partial p}{\partial x_i} + \frac{\partial}{\partial x_j} \left( \mu \frac{\partial u_i}{\partial x_j} \right) 
\]

Since the contraction and expansion of the walls in a microvascular structure are relatively small at basal flow conditions, the present study assumed a rigid wall. In addition, a no-slip boundary condition was assumed at the wall. Although the inlet and outlet pressures of the entire microvasculature shown were approximately 25 mmHg (3,300 Pa) and 15 mmHg (2,000 Pa), respectively [2, 15, 27], the inlet and outlet pressures were assumed to be 200 and 100 Pa, respectively, in the portion of the microvascular network shown in Fig. 1 such that the peak-systolic velocity was approximately 1 mm/s.

For the non-Newtonian whole blood viscosity term in the conservation of momentum equation, one can consider Casson and Herschel-Bulkley models, both of which contain the yield stress term. The present research selected the latter as it is included as part of the Ansys-Fluent software program (Lebanon, NH) used in the study. The original Herschel-Bulkley model [8] was modified to better fit the Whole Blood Viscosity (WBV) profile over a wide range of shear rate in the present research as shown below:

\[
\eta = \eta_0 + k \gamma^{n-1} \quad \text{for} \quad \tau > \tau_0 
\]

where \(\tau_0\) and \(\mu_0\) are the yield stress and zero-shear viscosity, respectively, \(k\) is a model constant, representing the high shear viscosity, and \(n\) is the power-law index, similar to the one used in power-law model. Note that the original Herschel-Bulkley model consists of only the first two terms in Eq. (4).

The microvasculature used in the present numerical simulation consisted of triangular and rectangular elements that represented a complex structure of microvascular vessels. The total number of meshes used in the grid system was 29,432. For the flow simulation, the study utilized a finite volume method (Ansys-Fluent 13). SIMPLE algorithm with the central difference method over space with the second-order accuracy was used for the determination of both velocity and pressure. When the range of tolerance for all variables was within \(10^{-4}\), the computation was considered to have converged.
3. Results

Figure 2 shows five profiles of whole blood viscosity with a representative value of the yield stress, \( \tau_0 \) for each viscosity profile. In addition to the yield stress, three other model constants \((k, n, \text{ and } \mu_0)\) were varied to obtain the viscosity profiles shown in Table 1. Note that all five WBV profiles are in physiological range [18].

Figure 3 shows the results of the velocity distribution in the microvasculature for three different cases of yield stress. For \( \tau_o = 0.005 \text{ Pa} \), the velocity varied in a range of 0–2.5 mm/s, which was in the range of velocity in the microvessels [21]. In particular, the velocity in the laterally-connected branch vessels was less than 0.25 mm/s as shown by dark blue color in Fig. 3a. In the case of \( \tau_o = 0.05 \text{ Pa} \), the area of the capillary vessels where the velocity fell below 0.25 mm/s (i.e., the region shown by dark blue color) significantly increased even in the main lumen (see the top main lumen in Fig. 3b). In the case of \( \tau_o = 0.20 \text{ Pa} \), the area of the capillary vessels where the velocity fell below 0.25 mm/s greatly enhanced into the entire microvasculature.

Figure 4 shows the areas marked in red color where the wall shear stress, \( \tau_w \), was less than the yield stress of blood, \( \tau_o \). For example, in the case of \( \tau_o = 0.005 \text{ Pa} \), there was no area marked in red. In the

![Fig. 2. Whole blood viscosity profiles and corresponding yield stresses determined from Herschel-Bulkley model. H-B model constants are given in Table 1.](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>( \tau_o ) [Pa]</th>
<th>( K )</th>
<th>( n )</th>
<th>( \mu_0 ) [Pa·s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.005</td>
<td>0.0130</td>
<td>0.801</td>
<td>0.150</td>
</tr>
<tr>
<td>2</td>
<td>0.020</td>
<td>0.0129</td>
<td>0.803</td>
<td>0.070</td>
</tr>
<tr>
<td>3</td>
<td>0.050</td>
<td>0.0127</td>
<td>0.805</td>
<td>0.040</td>
</tr>
<tr>
<td>4</td>
<td>0.100</td>
<td>0.0126</td>
<td>0.807</td>
<td>0.035</td>
</tr>
<tr>
<td>5</td>
<td>0.200</td>
<td>0.0125</td>
<td>0.808</td>
<td>0.030</td>
</tr>
</tbody>
</table>
case of $\tau_o = 0.05 \text{ Pa}$, there was an area marked in red color at the lateral branch positioned normal to the main vessel near the inlet of the microvascular network (e.g., marked as A in Fig. 4b), indicating flow stagnation. In addition, near the exit of the microvasculature, there was another small area marked as B in Fig. 4b, where $\tau$ was less than $\tau_o$. In the case of $\tau_o = 0.1 \text{ Pa}$, the size of the area of $\tau_w < \tau_o$ at B grew bigger, while the region around B had several small locations where $\tau_w$ was less than $\tau_o$. As the yield stress further increased 0.2 Pa, the areas of $\tau_w$ less than $\tau_o$ rapidly expanded into the entire microvascular network, suggesting that blood flow locally ceased in a number of places and the microvasculature may eventually be lost.

4. Discussion

The maintenance of blood flow in microvessels is essential to provide oxygen to tissues. When microvascular flow impairment occurs, the tissue can become ischemic, and subsequently the organ comprised of infarcted tissue can be affected or lost. The hypothesis of the present research was that as the viscosity of whole blood increased abnormally in a patient, blood flow could be impaired in microvessels. The most important rheological parameter in clinic is the hematocrit of patient, and whole blood viscosity is known to increase exponentially with increasing hematocrit. The criterion of the flow impairment was
that $\tau_w$ was less than $\tau_o$. The condition of $\tau_w < \tau_o$ is rarely met in a large artery which has a relatively large velocity. However, this can occur in microvessels in the case of hyperviscosity as demonstrated by the present study.

The differences between the present computer simulation and real clinical phenomena can be described as follows: RBC deformability to pass capillary, flexibility or collapsibility of micro-vessel itself like an elastic tube, arteriol-to-venule shunt or bypass from the diameter change of arteriol and/or venule, considerations of lymphatics-RBC free high oncotic fluids, pushing and sucking power concepts from both artery side and vein side.

A clinical manifestation of the circulatory impairment in microvessels is microangiopathy, including retinopathy, nephropathy, and neuropathy. In particular, capillary loss observed in chronic hypertension or chronic renal failure patients [1] could also be related to circulatory impairment in capillary vessels as a result of $\tau_w < \tau_o$.

Hence, the WBV profile together with the yield stress of blood may be useful in the analysis of blood flow in small vessels. Of note is that the blood viscosity is a relatively easily modifiable parameter.
as both lipid-lowering drugs [3] and anti-platelet drugs have been reported to reduce it effectively. In addition, phosphodiesterase inhibitors, hemodilution therapy and particularly apheresis treatment [6] also have been reported to reduce the blood viscosity. Microcirculatory flow abnormalities in a patient with macroglobulinemia were successfully treated using plasmapheresis for decreasing viscosity and improvement in microvascular flow shown with videomicroscopy as an example of critical role of viscosity on microcirculatory flow [25]. Hence, one can consider the normalization of whole blood viscosity as a possible therapeutic tool to reduce the risk of the microvascular disease. The present study was limited to the computational simulation of blood flow in microvessels. The observation in the study should be validated through the results of an animal study in the future. There should be some evidence between the physiological phenomenon of circulatory impairment and the pathological structural change often seen in chronic diseases caused by long-standing persistent ischemia followed by impaired microvascular flow.

5. Conclusions

The present research investigated the role of the blood viscosity profile as well as the yield stress of blood on the flow in the microvascular network. When the yield stress was less than 0.005 Pa, there were no stagnant regions in the microvasculature used in the study. However, when the yield stress increased to 0.05 Pa, stagnant areas began to appear, which grew and expanded rapidly with further increases in the yield stress. The research provided supporting data on the hypothesis that when \( \tau_w < \tau_o \), blood flow cannot be maintained. Hence, the present paper recommends further research and investigation of the monitoring of blood viscosity, from which one can evaluate the risk of circulatory impairment in microvessels.

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Conflict of interest statement

The authors do not have any conflict of interest that could inappropriately influence their work.

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