BLOOD FLOW IN MICROVESSELS

Y.G. Stergiou[1], A.T. Keramydas[1], A.D. Anastasiou[2], S.V. Paras[1]*

[1]Chemical Engineering Dept., Aristotle University of Thessaloniki, Greece

[2] School of Chemical and Process Engineering, University of Leeds, UK

*(*paras@auth.gr)*

ABSTRACT

The study of hemodynamics is particularly important in medicine and biomedical engineering as it is crucial for the design of new implantable devices and for understanding the mechanism of various diseases related with blood flow. In this study we measure the plasma *Cell Free Layer* (*CFL*) which is the result of *Fahraeus-Lindqvist* effect. To achieve it, the test section is illuminated by a light source placed under the microchannel and the flow is recorded with a high-speed camera. It is observed that the width of the *CFL* increases as the diameter of the tube is increased and decreases as the hematocrit (H_{ct}) is increased. Based on the experimental results we propose a correlation for the prediction of the *CFL* width as a function of Reynolds number (Re_∞) and H_{ct}. This correlation was used in a "*two-fluids*" computational model to describe the fluid behavior in microvessels with i.d. less than 300μm. The CFD results are found to be in relative accordance with the experimental data.

INTRODUCTION

The characteristics of blood flow in small arteries are of great interest for biomedical engineering. The results of such studies will provide information which will be useful in understanding *in vivo* blood flow conditions, in designing medical devices (e.g. organs on a chip) or in the development of more effective diagnostic tools. Blood flow in large arteries has been extensively studied[1]. However, little work has been done regarding the blood flow in small vessels, mainly because both *in vivo* and *in vitro* experiments in small arteries are difficult to perform. In an experimental study in our Laboratory, Anastasiou et al.[2] used a blood substitute, i.e. a fluid that has the viscoelastic properties of blood, and they conducted experiments in a 600μm i.d. conduit. However, it is well known that in blood vessels with i.d.<300μm the ***Fahraeus-Lindqvist*** effect[3] must be also taken into account, i.e. during blood flow in such microvessels the erythrocytes migrate towards the center of the channel resulting to the formation of *CFL* along the vessel wall. The *CFL* width is defined as the distance from the outer edge of the *RBC* core to the luminal surface of the endothelium[4]. This effect has been confirmed by both *in-vivo* and *in-vitro* experiments inside glass capillaries[5,6]. There are many parameters which affect the *CFL*, namely the diameter of the vessel, the H_{ct} and the flow conditions which can be described either by Re_∞ or as it can be found in many studies[7] by the pseudo shear rate (defined as mean velocity/vessel diameter). As expected, the *CFL* exhibits a lower viscosity than the rest of the fluid and this facilitates the blood flow through the microvessels. Although this phenomenon is significant for diameters< 300μm most of the published work[5] is focused on vessel diameters between 20-100μm.

Motivated by the importance of these parameters in biomedical engineering the aim of this study is twofold. The first one is to estimate the *CFL* extent. In this study, we investigate the effect of Re_∞ and H_{ct} on *CFL* characteristics in three microvessels with 50, 100 and 170μm hydraulic diameter. The experimental data will be used for formulating a correlation for estimating the *CFL* width under various flow conditions. The second one is to utilize the outcome of the experimental part in order to develop a simplified "two-phase" model using Computational Fluid Dynamics (*CFD)*, a common

practice in literature[8]. The *CFL* flow domain will be solved assuming the blood properties are that of a Newtonian fluid, whereas in the vessel core the blood rheology is formulated using a non-Newtonian model. Simulations will be executed for various blood velocities and various vessel diameters. The blood flow characteristics and patterns will be calculated, as well as the Wall Shear Stress *(WSS)* magnitude and the overall Pressure Drop (*ΔP*) across the vessels, to elucidate the phenomena of the cases studied experimentally.

EXPERIMENTAL PROCEDURE

The fluids used for our experiments were mixtures of red blood cells (*RBC*) and physical saline whose physical properties were found to be like those of blood. A small amount of *EDTA* prevents coagulation, thus, we can assume that the extent of cell aggregation is similar to that of a healthy man. The *RBC*s were collected from healthy adult volunteers and the process of purification comprises the following steps:

- Centrifugation (at 3200rpm) is performed in the whole blood sample for the separation of erythrocytes from plasma.
- The separated red blood cells are washed with saline water and are twice recentrifugated.

The acquired *RBC*s are then used to produce "*blood*" of known H_{ct}. The compositions of all fluids used in our experiments are presented in ***Table 1***. Viscosity measurements were performed using a cone plate rheometer (*AR-G2, TA Instruments*) at 24°C. To verify the similarity with "*real*" blood the *Quemada* model (***Eq. 1***)[9] was used for comparison with our *RBC* solutions:

$$\mu = \frac{\mu_p}{(1-0.5\cdot k\cdot H_{ct})^2} \quad (1)$$

where $k = \frac{k_0 + k_\infty \cdot \sqrt{\gamma_r}}{1+\gamma_r}$ (2)

and $\gamma_r = \frac{\gamma}{\gamma_c}$ (3)

where k_0, k_∞ and γ_c are, in general, functions of *RBC* concentration.

Table 1*: Fluids composition (%v/v).*

	RBC	***Saline***	***EDTA***
H_5	*5*	*94.5*	*0.5*
H_{10}	*10*	*89.5*	*0.5*
H_{20}	*20*	*79.5*	*0.5*
H_{30}	*30*	*69.5*	*0.5*
H_{40}	*40*	*59.5*	*0.5*

The comparison between the *Quemada* model and the experimental data showed that the fluids used exhibit non-Newtonian behavior and can be used in experiments that simulate blood. *RBC*s have the property of absorbing light and the measuring technique of *CFL* is based on this fact. Placing a light source at the bottom of the micro channel and recording the flow from above with a high speed camera, we were able to identify on the recorded images the areas of low *RBC* concentration, i.e. brighter areas (***Fig. 1***). All experiments were conducted in three channels with square cross section (50x50, 170x170 & 100x100μm), etched on a *PMMA* plate and sealed with the same material.

CFL MEASUREMENTS

The first objective of this study is to investigate the parameters that affect the size of the *CFL*. We

performed experiments with *RBC* solutions with H_{ct} 10, 20, 30 and 40% and Re_∞ 0.3-6. It must be noted that for calculating the Re_∞, as *reference* viscosity was used the one obtained from the *Quemada* model for very high shear rates (γ>1000s^{-1}). The effect of the channel diameter on the *CFL* was investigated by conducting experiments in three microchannels with hydraulic diameters of 50, 100 and 170μm. We have measured the *CFL* at steady state conditions by acquiring and analyzing an appropriate number of consecutive frames and then we used the data for constructing the *CFL* traces and for calculating the average *CFL* width (***Fig. 2***).

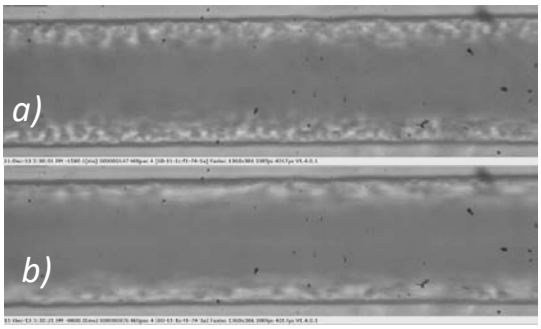

Figure 1. *Typical images for: a) Q=0.5ml/hr and b) Q=1.2ml/hr. (D=100μm, H_{ct}=20%).*

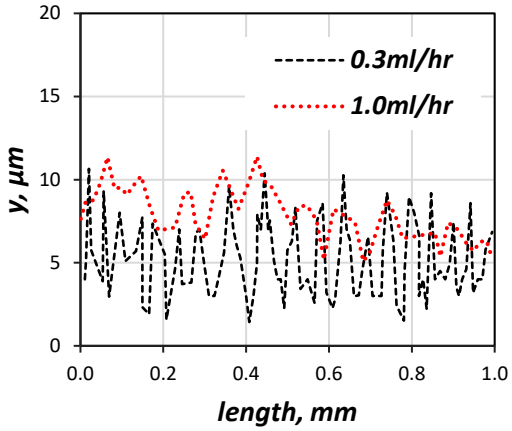

Figure 2. *Typical CFL traces for Q=0.1ml/h and Q=1.5ml/hr; H_{ct}=20%, D=100μm (wall y=0).*

The results showed that the *CFL* normalized with respect to the hydraulic diameter, *CFL/D*, decreases with increasing H_{ct}, an observation in accordance with Namgung et al.[5] This outcome is due to the fact that as the concentration of the *RBC*s increases, the viscous forces increase and hinder the movement of the cells in the middle of the channel. Additionally, it seems that the normalized *CFL* decreases as the diameter of the microchannel increases, a fact that is also confirmed by Namgung et al.[5] The results also showed that in the flow rate range where migration started, there is still a low cell concentration near the wall and not a total absence of cells.

The *CFL* measurements for several volumetric flow rates revealed that when the flow rate is low and *CFL* starts to be formed, there is a small increase rate of *CFL* until it reaches a constant value for Re_∞>4. This can be explained as follows. As the *RBC*s are migrating towards the center of the vessel their concentration increases up to a point that the viscous forces hinder additional migration. Using Response *Surface Methodology* (*RSM*) a 2nd order polynomial equation, also known as quadratic model (***Eq. 4***), which calculates the normalized *CFL* is formulated:

$$CFL/_D = a_0 + a_1 H_{ct} + a_2 Re_\infty + a_3 H_{ct}^2 + a_4 Re_\infty^2 + a_5 H_{ct} Re_\infty \quad (4)$$

The equation formulated in the present study (***Eq. 4***) calculates *CFL/D* as a function of Re_∞ and H_{ct}. The coefficients (***Table 1***) are determined using the experimental data for two (k=2) variables.

Predictions of the proposed correlation was checked with the limited available in the literature experimental data[7] and are found to be in good agreement ***(Fig. 4***).

Table 1. *Coefficients of the CFL correlation*

α_0	0.066384	α_3	0.000002
α_1	-0.000887	α_4	-0.001414
α_2	0.017796	α_5	-0.000005

Eq. 4 gives accurate results for Re_∞ between 0.3-6 and H_{ct} 5-40% with an uncertainty of 10%. The accuracy of the equation was calculated by comparing the correlation with the experimental results. It seems that this correlation predicts the behavior of the *CFL* as described previously. For Re_∞>4 the *CFL/D* is approaching a constant value which depends on the H_{ct}.

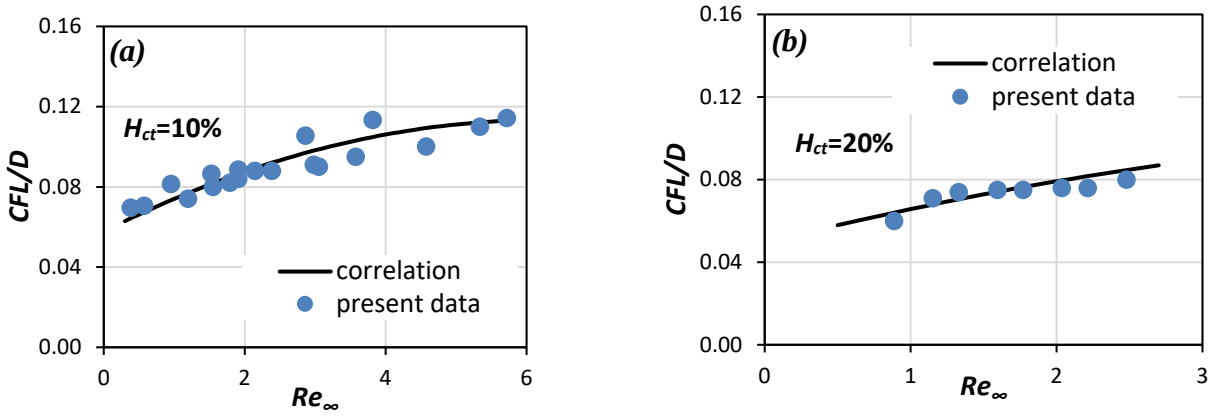

Figure 3. *Comparison of correlation with CFL experimental data for: a) H_{ct}=10% and b) H_{ct}=20%.*

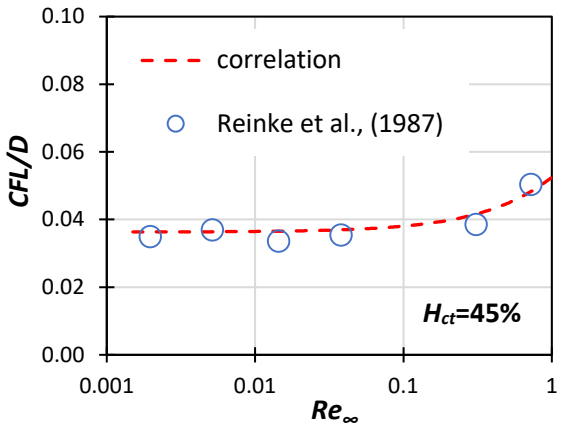

Figure 4. *Comparison of correlation with Reinke et al.[7] data.*

CFD SIMULATIONS

In our simulations the Fahraeus effect[10] was taken into consideration and was modelled using a relative correlation[11]. Moreover, the lateral variation of the H_{ct} in the core area was modelled using the Lih[12] model distribution, fitted for each case. The blood density is set at a constant value (ρ_b=1050kg/m^3). Blood is modelled as a Newtonian fluid having the viscosity of human blood plasma (μ_p=1.2cP) in the *CFL* zone, whereas, the blood in the core area is modelled as non-Newtonian shear thinning fluid. This is achieved through a modified[13] Quemada model where local μ is expressed by ***Eq. 1***, *K* is expressed by ***Eq. 2*** and its coefficients (k_0, k_∞, γ_c) are expressions of H_{ct} obtained by Das et al.[13]. CFD modeling in this study was conducted using the ANSYS CFX 19 commercial code.

The blood vessels (Length (*L*), 1mm) were modeled as two-dimensional computational domains with axial symmetry and an adjustable radius (*R*). The geometry of the domain and the mesh were designed on ANSYS Workbench package (v. 19). As Re_∞ numbers are low, the flow is laminar. Thus, the Direct Numerical Simulation (DNS) model was used while the high-resolution advection scheme was employed for the discretization of the momentum equations. The simulations were run in a steady state, the vessel walls were considered smooth and a no-slip boundary condition was employed. As for the meshing procedure, an optimum grid density was chosen by performing a grid dependency study. Consequently, cells with a maximum face size of 2.5μm were used, while mesh refinement was applied in areas where viscosity changes were pronounced.

Simulations were performed for diameters varying between 80 and 170μm, H_{ct} between 30% and 50% and, Re_∞ between 0.8 and 4.9. The parameters were mainly selected depending on the availability of previous literature *in vitro* velocity experiments, so that the results could be contrasted and juxtaposed with the literature data[14]. In ***Fig. 5***, the blood viscosity magnitude is illustrated for one of the cases tested (D=100μm, Re_∞=0.8, H_{ct}=30%). The *CFL* zone is depicted, where the viscosity is that of blood plasma, whereas in the non-Newtonian core the viscosity gradually decreases as radial distance increases. The comparison of the flow patterns of our simulation with relative experimental data are used as a form of code validation. In ***Fig. 6*** the axial velocity distribution of one case (D=80μm, Re_∞=0.3, H_{ct}=37%) are associated with experimental measurements by Gaehtgens et al.[14] There seems to be a relatively good accordance of experimental and computational results, bound with a deviation of 10%. The main problems (as shown in ***Fig. 6***) appear near the boundary between the core and the *CFL*.

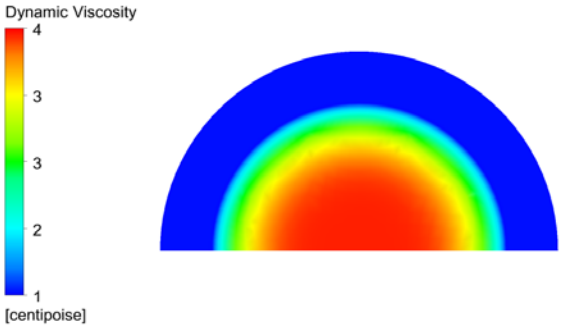

Figure 5. *Graphical representation of the viscosity distribution on a cross section (Re_∞ =0.8, H_{ct} =30%).*

The overall ΔP_{CFL} was calculated across the whole length of the vessel and was compared with two values: the ΔP_D calculated analytically using the Darcy law for straight circular tubes and considering the blood as a Newtonian fluid (μ_b=3.5cP) and the ΔP_{nCFL} calculated numerically considering that the *CFL* is completely absent and that the blood behaves as a non-Newtonian fluid (in the same way the non-Newtonian core was modelled previously). Typical results for some of the cases tested are summarized in ***Table 2.*** As presented in ***Table 2***, omitting to consider the existence of *CFL*, in vessels that the *Fahraeus-Lindqvist* effect occurs, leads to significantly **higher** pressure drop.

Table 2. *Pressure drop for various cases.*

Re_∞	D(μm)	H_{ct}(%)	ΔP_{CFL} (Pa)	ΔP_{nCFL} (Pa)	ΔP_D (Pa)	ΔP_{nCFL} / ΔP_{CFL}
0.8	*100*	*30*	*132*	*238*	*302*	***1.8***
1.4	*170*	*40*	*42*	*103*	*105*	***2.5***
2.5	*170*	*40*	*105*	*187*	*186*	***1.8***
4.9	*170*	*40*	*204*	*377*	*372*	***1.8***

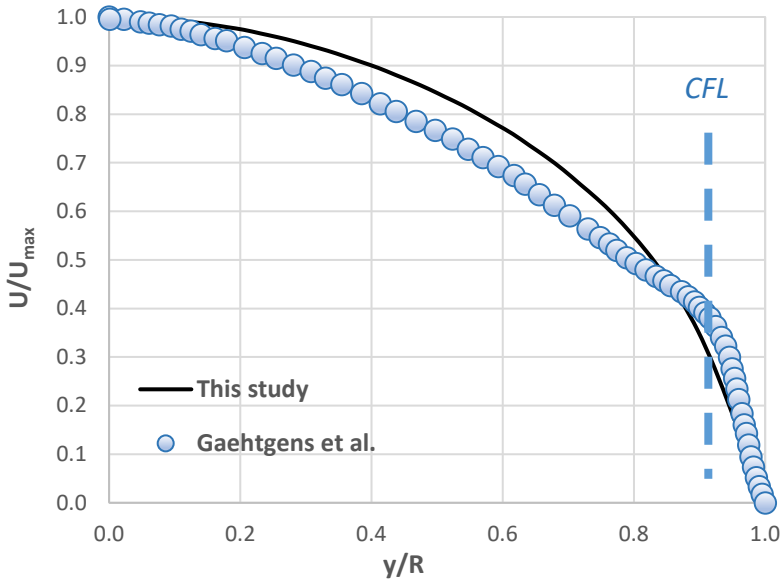

Figure 6. *Comparison of calculated axial velocity and axial velocity obtained by Gaehtgens et al.*[14]

CONCLUSIONS

The *CFL* width, which is a function of Re_∞ and H_{ct} tends to a constant value, which in turn is also affected by the concentration of the *RBCs*. A correlation for predicting *CFL/D* has been proposed and its validity has been checked both with the present results and the limited published experimental data. Additionally, the CFD simulations revealed that the proposed correlation for predicting the *CFL* thickness can be used as an input in numerical simulations. Lastly, the importance of including a *CFL* modelling technique in CFD simulations lies on the fact it greatly affects the predicted pressure drop values in such vessels (as much as 2-3 greater in methods without a CFL modelling).

REFERENCES

[1] R.F. Tuma, W.N. Duran, K. Ley, Microcirculation, Academic Press, 2011.
[2] A.D. Anastasiou, A.S. Spyrogianni, K.C. Koskinas, G.D. Giannoglou, S.V. Paras, Med. Eng. Phys. 34 (2012) 211–218.
[3] R. Fåhræus, T. Lindqvist, Am. J. Physiol.-Leg. Content 96 (1931) 562–568.
[4] P.K. Ong, B. Namgung, P.C. Johnson, S. Kim, Am. J. Physiol. - Heart Circ. Physiol. 298 (2010) 1870–1878.
[5] B. Namgung, M. Ju, P. Cabrales, S. Kim, Microvasc. Res. 85 (2013) 68–76.
[6] A.R. Pries, D. Schönfeld, P. Gaehtgens, M.F. Kiani, G.R. Cokelet, Am. J. Physiol. - Heart Circ. Physiol. 272 (1997) 2716–2725.
[7] W. Reinke, P. Gaehtgens, P.C. Johnson, Am. J. Physiol. 253 (1987) H540-547.
[8] M. Sharan, A.S. Popel, Biorheology 38 (2001) 415–428.
[9] S. Kim, R.L. Kong, A.S. Popel, M. Intaglietta, P.C. Johnson, Am. J. Physiol. Heart Circ. Physiol. 293 (2007) 1526-1535.
[10] R. Fåhraeus, Physiol. Rev. 9 (1929) 241–274.
[11] A.R. Pries, T.W. Secomb, P. Gaehtgens, J.F. Gross, Circ. Res. 67 (1990) 826–834.
[12] M.M. Lih, Bull. Math. Biophys. 31 (1969) 143–157.
[13] B. Das, P.C. Johnson, A.S. Popel, Biorheology 35 (1998) 69–87.
[14] P. Gaehtgens, H.J. Meiselman, H. Wayland, Microvasc. Res. 2 (1970) 13–23.