THE INFLUENCE OF ERYTHROCYTE DEFORMABILITY IN THREE TYPES OF FLOW SITUATIONS: CONTINUOUS, CONTINUOUS BUT NON UNIFORM, AND TWO PHASES

M. THAO CHAN, E. FRANZINI
Laboratoire d'Hémorhéologie. Laboratoires Hoechst. 3 avenue du Général de Gaulle. 92080 Paris La Defense.

SUMMARY

The effect of erythrocyte deformability is discussed in three types of flow situation (continuous situation continuous but non uniform situation, and two phases situation), in which the length scale (diameter of the vessels) is similar or not to the diameter of the red cell.

INTRODUCTION

How we deal with vascular disorders is directly related to our increasing understanding of the dynamics of blood flow and the clinical importance of a new branch of medical science known as clinical haemorheology.

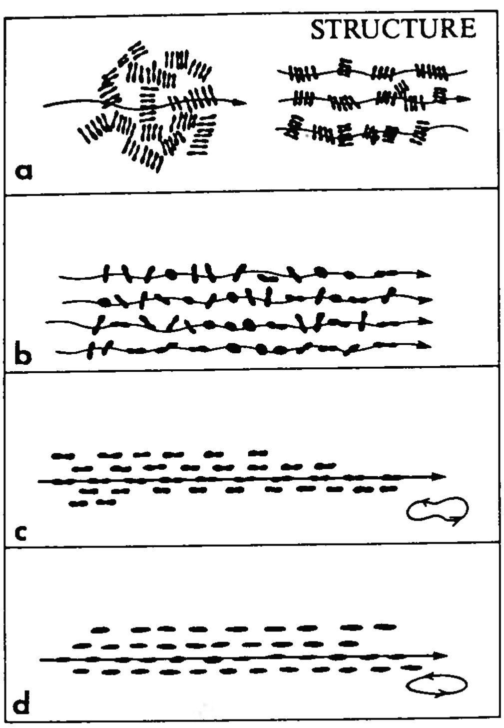

Figure 1: Microscopic structure of the flow. (From LELIEVRE et al. 1)

The study of the circulatory system has long been limited to the study of the vessels, without any attention being paid to their content: the blood.

The rheological behaviour of blood is dependent both on properties of the individual cells and on the way they interact with each other to influence the overall resistance to flow, that is the whole-blood viscosity.

Blood viscosity is determined by four factors:

1. Plasma viscosity
2. The overall number of cells
3. Red cell aggregation
4. Red cell deformability.

The viscosity of plasma is determined mainly by the concentration of plasma proteins, the most important of which are albumin, the globulins and fibrinogen. In patients with vascular disorders, there is often an increase in the fibrinogen concentration.

The overall number of cells is another important factor in viscosity: white cells and platelets may be present, but the most prevalent components of whole blood are the red cells, which represent approximately 97 % of the cellular volume of the blood (5 million/mm3). The amount of red cells in the blood is usually defined by their concentration per unit of volume in the suspension (the haematocrit). In human beings, the average haematocrit is on the order of 40 to 50 %. In a disease such as polycythaemia, for example, hyperviscosity is directly attributed to the increase in the number of red cells.

Blood viscosity is also partly dependent on blood flow. In the absence of flow or in circulation with a low flow rate, red cells affect whole-blood viscosity by their tendency to aggregate and form *rouleaux*. Or, at high flow rates, the cells change their shape and their deformability properties reduce the viscosity. This red blood cell property to deform is particularly important at the microcirculation level. Despite these complexities in the rheological behaviour of blood, a distinction can be made between flow situations in which the range diameter of the vessels is similar or not to the diameter of the red cells. This distinction is a way of quantifying, through macroscopic or microscopic approaches, the rôle of erythrocyte deformability in types of flow situations:

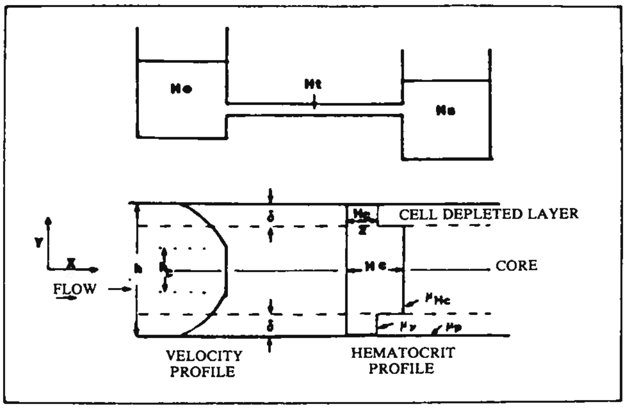

Figure 2: Hematocrit distribution (velocity profile and hematocrit profile). (From M. THAO CHAN 17)

— The continuous situation,
— the continuous but non uniform situation,
— the two-phase situation.

We will comment successively on the E.D. rôle in each phase, and particularly in the continuous but non uniform situation in which there is the obvious presence of anomalous effects such as the Fahraeus and the Fahraeus-Lindqvist effects, and of a cell-depleted layer near the capillary walls.

1. CONTINUOUS SITUATION

For large scale flow situations (where the vessel diameter is up to 50 x that of red cell) it is perfectly acceptable to consider blood as a continuous and uniform medium. In the absence of flow, the red cells aggregate face to face. These aggregates of about 10 red cells are known as *rouleaux* and these rouleaux also aggregate together.

Four types of flow may be identified at a microscopic level (Fig. 1).[1, 2]

a) If shearing is very slight, the aggregated structure is organized in networks and, as a result, networks and rouleaux are converted by the flow.
b) When shearing is slightly greater, but still moderate, the red cells are dispersed, disoriented and move in a pattern of rotation in the direction of the flow.
c) If shearing is increased further, the red cells remain dispersed, but are progressively oriented in the flow without being deformed, even the membrane makes a *tank-treading* movement around the intra-erythrocyte contents.
d) If shearing becomes very marked, the red cells remain dispersed, still oriented in the flow, but are deformed and sometimes take on a biconvex shape.

Under these circumstances, the deformability enables the red cells to orient themselves in the direction of flow and to occupy the smallest space possible. These phenomena thus reduce the friction between the red cells and endow blood, with its low resistance to flow.

2. CONTINUOUS BUT NON UNIFORM SITUATION

The first interesting quantitative findings in the continuous but non uniform situation (20 μm < capillary diameter < 500 μm) for the blood date from 1842, when, in microscopic studies, Poiseuille noted that blood flow in narrow tubes differed from that of water. These phenomena were subsequently studied by Fahraeus and Lindqvist in 1931, using human blood in cylindrical capillaries ranging from 40 to 500 μm:[3] Following these findings, numerous studies have sought to identify the rheological properties in the blood in the so-called continuous but non uniform situation. Mention may be made of the works of Braasch,[4] Chien,[5] Cokelet,[6] Dintenfass,[7] Stoltz.[8] These authors have confirmed the non newtonian nature of the blood (viscosity decreasing when the shear stress is increased), as well as the appearance of anomalous phenomena such as:

a) The existence of a plasma layer poor in red cells close to the wall.
b) Flattening of the speed profile (piston flow or plug flow).
c) The Fahraeus effect (hematocrit in the capillary is lower than the hematocrit at both the point of entry, as well as exit, from the capillary).
d) The Fahreus Lindqvist effect (apparent viscosity decreases when the diameter of the capillary decreases).

Furthermore, the possibility must be accepted of the existence of lifts of hydrodynamic origin, which can propel the red cells far from the wall. In 1962, Segre and Silberberg,[9] using very dilute suspensions of spheres, showed that the particles emigrate towards the position of equilibrium characterized by the capillary radius of approximately 0.6 R, implying the presence of both centrifugal and centripetal lifts. Several theoretical analyses predict centripetal lift acting on a single sphere placed in a shearing flow, but the existence of a centrifugal lift remains very uncertain.

Despite the complexity of blood flow in its non uniform situation, a number of studies (10, 11, 12, 7) have attempted to correlate the phenomena. The Fahraeus Lindqvist effect may be explained in part by the Fahraeus effect,[13] which, in its turn, is explained by the existence of a plasma layer due to red cell migration phenomena.

For in vitro experiments, this migration effect may also be quantified by the ratio between the haematocrit of the central nucleus (Hc) and that of alimentation (Ho) which can give a migration index of these red cells [17] (Fig. 2). This ratio (Fig. 3a, 3b, 3c) is slightly greater at high haematocrit than at low haematocrit levels. For suspensions of normal red cells, this migration index (noted as $\gamma_H = H_c/H_o$) increases considerably for capillaries of a thickness less than 50 μm. At 40 % haematocrit, this ratio rises from 1.04 at 50 μm to 1.32 for h = 21 μm.

For suspension of red cells, where deformability has been reduced by heat (H. RBC) (Fig. 3b), the γ_H ratio becomes lower. The red cells are less able to be packed in the nucleus because of the reduction in erythrocyte deformability. Furthermore, it is found that this ratio γ_H is greater for an haematocrit of 30 % than for an haematocrit of 40 % in contrast to the case of N. RBC.

For suspensions of red cells hardened by glutaraldehyde (G.RBC) (Fig. 3) this migration index γ_H) becomes negligible, though a slight increase in γ_H may be detected for a thickness of 60 μm, in comparison with large thicknesses, in particular for a low haematocrit (20 %).

In this flow situation, a number of studies [10, 11, 12, 17] working on the Fahraeus effect and the Fahraeus Lindqvist effect, have demonstrated the following two phenomena:

— at low shear rate, deformability favourizes the formation of aggregates and facilitates increase in the thickness of the parietal layer (layer of fluid close to the wall, poor in red cells known as *lubricating layer*);
— at high shear rate, where the radial migration force is great, deformability allows for rotating movements of the membrane and cell contents, and it is also found that the thickness of the parietal layer depends upon erythrocyte deformability;[17] it decreases when the red cells become less deformable. Value of the thickness of the parietal layer, calculated as δ, for N. RBC is 7.95 μm, decreasing to 5.75 μm for H. RBC and 4.92 μm for G. RBC.

As a result, at both high and low shearing, deformability favourizes the formation of a thicker parietal layer and amplifies the Fahraeus and Fahraeus Lindqvist effects. Therefore, these phenomena cause a decrease in the resistance to flow.

3. TWO PHASE SITUATION

When the diameter of the microvessels becomes similat to that of the red cells, the problem becomes very complex and it is no longer possible to retain the hypothesis of a continuous medium.

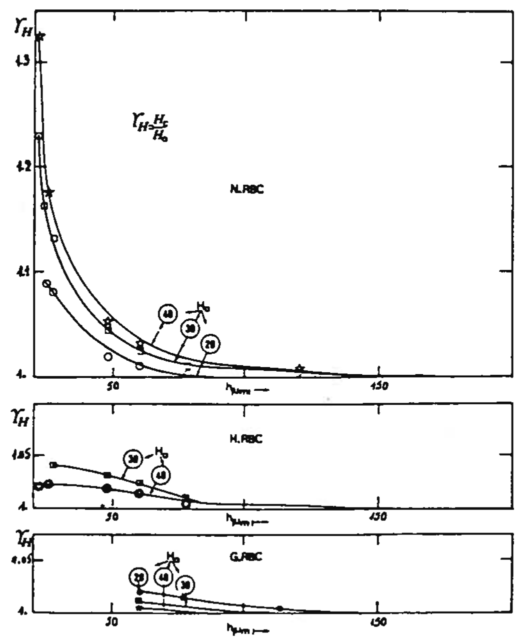

Figure 3: Migration effect of different types of suspensions as a function of channel thickness.

However, it remains valid to treat the plasma as a continuous fluid, since the diameter of the smallest capillary is still 2,500 times greater than that of one molecule of water. By contrast, red cells are large bodies which, in certain capillary lumen. The problem of rheology in these vessels must thus be studied as a two phase flow problem.

Expressed in mechanical terms, it consists of the flow of a non compressible and Newtonian continuous fluid (the plasma) in a cylindrical conduit (the microvessel), loaded with deformable free particles (red cells). In such capillaries, shear stress is relatively high,[14] which results in marked red cell deformation. As a result, there is a second problem (coupled with the first) which is that of the deformation of red cells which are also continuous bodies. At the time of transit of the particle, independently of the flow effects in the inlet region of a circular pore, which are not negligible, the link of the particle with the wall or with other paricles have equally to be investigated in the study. The nature of these links is very complex: hydratation phenomenon, electrostatic and electrodynamic phenomena, Van der Waals's bond.

From a theoretical standpoint, two major types of approach may be envisaged for the study of this phenomenon:

— a macroscopic type of approach, which has given rise to phenomological laws (Darcy law in porous medium, Poiseuille law in Newtonian fluid). This approach results in concepts of permeability, porosity, friction coefficient, apparent viscosity, etc...

— a microscopic or microrheological approach, which takes into account respectively the three variables of the red cell, which are the rheology of the particle, the surface properties of the particle, which may be linked together on the capillary walls, and, finally, local hydromechanical conditions of measurement.

In the two phase situation, deformability plays a particularly important role in local hemodynamic consequences:

— an increase in red cell rigidity decreases the local velocity of the particle. This phenomenon thus results in distubances in mass exchange (O_2, lactate, potassium) between the blood and tissues.

— rigidification of the red cells is also reflected by *traffic-jam* in the microcirculation. If rigid red cells are included only in a proportion of 1 % in the particularly fluid medium, local haematocrit levels are disturbed distally in all of the branches.[15] This hemodynamic disturbance may result in three situations of fundamental pathological importance: blood stasis, intravascular red cell aggregation and the use of arteriovenous anastomoses.

CONCLUSION

It would seem that discovery of erythrocyte deformability is as old as that of the red cell itself.[18] However, it was only at the beginning of the 20th century that the physiological importance of red cell deformability was fully realized.

It is now known that the property of deformability enables red cells in the complex conditions of the circulation to ensure optimal irrigation of the capillary network and endows the blood with its low resistance to flow. From an hemorheological standpoint, its reduction, in other circumstances than in certain hematological disorders is the common denominator between the various cardiovascular risk factors.[16] As a result, the physiopathological interest of red cell deformability still offers enormous possibilities of exploitation and wide research studies.

REFERENCES

1. LELIEVRE, J. C.: Approche viscosimétrique de la déformabilité érythrocytaire. VIIth Meeting of the French Study Group on Red Cell filtration (1982). Ed. Thao Chan. Laboratoires Hoechst.
2. FISHER, T.; SCHMID-SHONBEIN, H.: Tank treading motion of red cell membranes in viscosimetric flow: behaviour of intracellular and extracellular markers (with film). *Blood Cells*, 1977; 3: 351-365.
3. FAHRAEUS, R.; LINDQVIST, T.: The Viscosity of the blood in narrow capillary tubes. *Amer. J. Physiol.*, 1931; 96: 562-568.
4. BRAASCH, D.: Red cell deformatility and capillary blood flow. *Rhysiol. Rev.*, 1971; 51: Nr 4.
5. CHIEN, S.; USAMI, S.; KUNG MING, J.: Fundamental determinants of blood viscosity. The symposium on Flow, Pittsburgh, Pennsylvania, May 1971; 10-14.
6. COKELET, G. R.: The rheology of human blood in Biomechanics. In: *Its Foundations and Objectives.* Eds.: FUNG, Y. C.; PERRONE, N.; ANLIKER, H.: Prentice hall Englewood Cliffs, N. J. 1972; 63-203
7. DINTENFASS, L.: Inversion of the Fahraeus Lindqvist phenomenon in blood flow through capillaries of diminishing radius. *Nature London*, 1957; 215: 1099-1100.
8. STOLTZ, J. F.; VIGNERON, C.: Viscosité sanguine et déformabilité des hématies. 1976. Publ. Hoechst Laboratories.
9. SEGRE, C.; SILBERBERG, A.: Behaviour of macroscopic rigid spheres in Poiseuille flow *J. Fluid Mech.*, 1962; 14: 115-136.
10. AZELVANDRE, R.; OIKNINE, C.: Effet Fahraeus et effet Fahraeus Lindqvist. Résultats expérimentaux et modèles théoriques. *Biorheology*, 1976; 13: 325-335.
11. BARBEE, J. H.; COKELET, G. R.: Prediction of blood flow in tubes with diameter as small as 29 μm. *Microvasc. Res.*, 1971; 3: 6-21.
12. BUGLIARELLO, G.; SEVILLA, J.: Velocity distribution and other characteristics of steady and pulsative blood flow in fine glass tubes. *Biorheology*, 1970; 7: 85-107.
13. THAO CHAN, M.; JAFFRIN, M. Y.; SESHADRI, V.; McKAY, C.: Flow of red blood cell suspensions through narrow two dimensional channels. *Biorheology*, 1982; 19: 253-267.
14. COPLEY, A. L.: Hemorheological aspects of endothelial fibrin and lining of fibrinogen gel clotting: their importance in physiology and pathological conditions. *Clin. Hemorheology.*, 1972; 1: 9-72.
15. HEALY, J. C.: Physiologie de la déformabilité érythrocytaire et méthode de mesures. *Actualités d'Angéiologie*, 1983; Nr sp. 7: 7-10.
16. MARCEL, G. A.: Pharmacological improvement of altered red cell deformability. Symposium on Recent Developments in Microcirculation Research. *Exercpta Medica*, 1981; 4-14.
17. THAO CHAN, M.: Etude des propriétés rhéologiques des suspensions d'hématies dans les capillaires plans. Effets de la déformabilité et de la géométrie des capillaires. Thesis for Doctorate (Biomedical) — University of Technology of Compiègne — France (Jan. 1981).
18. LEEUWENHOECK VAN, A.: 65th missive. In: Microcirculation. Beuchmark Papers in Human Physiology. Ed. M. P. Wiedemann. Stroudsburg: Huntchinson & Ross Inc. 1974; 35.