

## HEMORHEOLOGY AND HEMODYNAMICS

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**Keywords:** hemorheology, hemodynamics, viscosity, erythrocyte deformability, erythrocyte aggregation, rheology, tissue perfusion, blood flow.

### Contents

1. Introduction
    - 1.1. Historical Perspectives
    - 1.2. Principles of Rheology
    - 1.3. Definition of Hemorheology
  2. Rheology of Blood
    - 2.1. Structure of Blood
    - 2.2. Blood Viscosity, *ex vivo*
    - 2.3. Determinants of Blood Fluidity
      - 2.3.1. Plasma Viscosity
      - 2.3.2. Hematocrit Value
      - 2.3.3. Contribution of Red Blood Cell Rheologic Behavior to Blood Fluidity
    - 2.4. Red Blood Cell Deformability
    - 2.5. Red Blood Cell Aggregation
    - 2.6. Contribution of White Blood Cells to Blood Flow at Tissue Level
  3. Clinical Aspects of Blood Rheology
    - 3.1. Hematocrit as a Determinant of Whole Blood Viscosity
    - 3.2. Pathologic Alterations of Red Blood Cell Mechanical Properties
      - 3.2.1. Effects on Red Blood Cell Deformability
      - 3.2.2. Effects on Red Blood Cell Aggregability
      - 3.2.3. Role of Oxidant Stress in Hemorheological Disturbances
      - 3.2.4. Role of White Blood Cell Activation in Hemorheological Disturbances
  4. Role of Hemorheology in Hemodynamics
    - 4.1. Flow Behavior of Blood in Cylindrical Tubes
    - 4.2. Flow Behavior of Blood *in vivo*
      - 4.2.1. Role of Red Blood Cell Deformability
      - 4.2.2. Role of Phase Separation and Red Blood Cell Aggregation
      - 4.2.3. Role of Vascular Control Mechanisms
    - 4.3. Importance of Hemorheological Factors for Tissue Perfusion
- Acknowledgement  
Glossary  
Bibliography  
Biographical Sketches

### Summary

Blood is a two-phase liquid exhibiting non-Newtonian rheological behavior. Viscosity of blood depends on the acting shear forces and is determined by hematocrit value, plasma viscosity and the mechanical properties of red blood cells (RBC) under given shear conditions. RBC are highly deformable bodies and this property significantly contributes to blood flow both under bulk flow conditions and in microcirculation. Another important rheological property of RBC is their tendency to reversible aggregation. The size of RBC aggregates is inversely proportional to the magnitude of shear forces, as the aggregates are dispersed when the shear forces get higher. RBC aggregation also affects the fluidity of blood, especially in the low-shear regions of the circulatory system. Blood rheology has been reported to be altered in various physiopathological processes. Alterations in hematocrit value significantly contribute to hemorheological variations in diseases and in certain extreme physiological conditions. RBC deformability and aggregation are also sensitive to local and general homeostasis. RBC deformability is affected by the alterations in the properties and associations of membrane skeletal proteins, together with cell volume and cytoplasmic viscosity alterations as a result of fluid-electrolyte imbalance. Such alterations may result from genetic disorders or might be induced by local metabolic deteriorations in tissues, oxidant stress, activated leukocytes, etc. Aggregation is mainly determined by plasma composition and surface properties of RBC. Increased plasma concentrations of acute phase reactants in inflammatory disorders is a common cause of increased RBC aggregation. Additionally, aggregation tendency of RBC is modified by the alterations of surface properties. Such alterations can be induced by the aging process of RBC, oxygen free radicals, proteolytic enzymes, etc. Impairment of blood fluidity may significantly affect tissue perfusion and result in functional deteriorations, especially if the vascular properties are also disturbed by disease processes.

## **1. Introduction**

### **1.1. Historical Perspectives**

Prior to the realization of the cellular structure of living material, all medical theory and practice was based on the concept of "humors". The concept of "humors" was, in turn, a direct application of Greek natural philosophy to medicine; Hippocrates is known as the father of humeral pathology theory. According to this antique medical theory, the human body contained a well-balanced mixture of four juices (or humors): sanguine, choleric, phlegmatic and melancholic. Early physicians believed that the imbalance between various humors of the body would cause disease and treatment should be based on re-establishing this balance. It is interesting to note that the diagnosis of this imbalance was mostly done by inspecting blood samples from patients and determining the relative amounts of each humor. The melancholic humor was the lowest, dark part of clotting blood, the choleric humor was the serum separating from the clotting blood, and the sanguine humor was represented by red blood cells. Phlegmatic humor or juice was accepted to be visible only in the blood of patients and was located on top of melancholic humor, with the amount of this humor directly related to the severity of the disease. We now know that this phlegmatic portion of the blood is, in reality, the "buffy coat" in clotted or sedimented blood and is composed of white blood cells, platelets and polymerized fibrinogen.

According to the humoral pathology approach, the standard procedure to re-establish the balance between humors was phlebotomy (i.e. removal of blood from the body). Many physicians recognized that the properties of blood were altered in situations such as inflammation and that this alteration prevented adequate blood flow; phlebotomy helped to restore blood flow. Interestingly, most of these earlier observations were made prior to William Harvey's discovery of the circulation in the seventeenth century.

Herman Boerhaave, who introduced the laws of physics into medical thinking, also enriched medical ideas of the seventeenth century. Boerhaave's intravital microscopy studies resulted in a better understanding of blood flow disturbances that were believed to be caused by the imbalance of humors. In the mid-nineteenth century, JML Poiseuille made significant contributions to physiology and fluid mechanics by observing the flow behavior of fluids in glass capillary tubes and developing Poiseuille's Law for tube flow.

Although humoral pathology ideas began to be based on more scientific concepts towards the end of the nineteenth century, cellular pathology theory was also being evolved. Rudolf Virchow was very successful in establishing a new concept of disease that was based on the structural and functional disturbances of cells. These disturbances could be detected under a microscope by observing tissue samples that were fixed and dyed. Humoral pathology theory rapidly lost ground to the cellular pathology theory, and even the oldest method of medical treatment with proven value in many patients was abandoned: hemodilution by various means was eliminated from the practice of medicine.

The influence of Virchow's cellular pathology theory on twentieth century medicine was enormous, with every disease explained by microscopic disturbances observed in dead, fixed tissues. Although highly respected by the medical community, such an approach failed to consider the dynamic nature of living systems and resulted in a highly static view of disease processes. The cellular pathology approach grew very rapidly especially during the first half of twentieth century and, parallel to this growth, concepts that were seen as being related to humoral pathology theory were deemed to be non-scientific.

During the early part of the twentieth century, Robin Fahraeus, a Scandinavian pathologist, began exploring the flow properties of blood. He discovered that the suspension stability and fluidity of blood were altered during disease processes, explained the humoral pathology concepts by modern scientific ideas, and provided a basis for understanding medical practices of previous centuries.

These ideas of Robin Fahraeus were not widely appreciated until the latter part of the twentieth century, although the measurement of blood sedimentation rate, a test that he described, remains the most widely used routine laboratory procedure in modern medicine. During the last few decades, the dynamic nature of blood flow and flow behavior has been widely investigated. Development of appropriate techniques to study the flow behavior of blood and its components, together with the evolution of modern concepts of fluid dynamics, has thus lead to the growth of a new medical field: hemorheology.

## 1.2. Principles of Rheology

Rheology is the scientific field that deals with the flow and deformation behavior of materials. The simplest definition of this behavior can be provided by measuring the displacement (or shape or size change) of a given amount of material under the influence of a force of known magnitude. The materials under consideration might be solids or fluids (including liquids and gases).

*Deformation* can be defined as the relative displacement of material points within the body. Solids react to the application of a force by a given deformation. If a solid is elastic, the deformation is proportional to the applied force and the original shape is recovered when the force is removed. If a permanent deformation remains after the removal of force the solid is said to be plastic. Fluids continuously deform—or flow—due to the application of applied forces. Some materials exhibit viscoelastic behavior, which is a combination of fluid-like and solid-like behavior.

In studying the degree of deformation (or flow) of a material, the force applied per unit area must be considered. This deforming force, termed stress, may have several components including: 1) Shear stress, the force per unit area acting parallel to the surface; 2) Normal stress, the force per unit area acting perpendicular to the surface. The latter is defined as pressure in a fluid. The degree of deformation is termed strain, which also has various components associated with the different stress components. For example, shear stress results in shear strain, often termed shear rate, in which the layers of material move parallel to each other in a progressive manner.

Early studies in fluid mechanics revealed that, for a pipe of constant diameter and length and for a given fluid, the resistance to flow depended on the flow conditions within the pipe. Experimental data obtained during the second half of nineteenth century revealed that during slow flow the pressure drop (reflecting the resistance to flow) was proportional to the speed of flow. Under these conditions, it has been observed that the liquid particles move smoothly in adjacent planes (laminae) parallel to the tube wall; this type of flow is called laminar flow. With increasing flow rate, there is a tendency for the fluid flow to become irregular, with fluid moving in swirls and irregular patterns. This type of chaotic flow is termed turbulent, with the degree of turbulence increasing with flow rate. Under these conditions, the pressure drop is proportional to the square of the speed of flow: for the same pipe and fluid, resistance to flow is greater with turbulence.

Under laminar flow conditions, a shear stress-shear rate relationship is used to define the fluidity of liquids. This relationship reflects the internal resistance between fluid layers (laminae) and thus reflects the viscosity of the fluid; the viscosity of a liquid can be calculated by dividing the shear stress by the shear rate. From a rheological point of view, liquids can be divided into two main groups: 1) Newtonian liquids in which the viscosity is independent of variations in shear rate or shear stress. For these fluids the slope of the shear stress—shear rate relation—is constant over the range of shear stress examined, and thus the viscosity is constant; 2) Non-Newtonian liquids in which the apparent viscosity is not a constant but rather depends on the magnitude of the shear stress or shear rate. The apparent viscosity of a non-Newtonian fluid may decrease

(shear-thinning behavior) or increase (shear-thickening behavior) as the shear rate is increased. Non-Newtonian liquids may have a yield stress, below which the shear rate is zero (no flow), resulting in an infinite value for apparent viscosity. The flow behavior of non-Newtonian liquids may also be time-dependant; the viscosity of a thixotropic liquid decreases with time at a fixed shear rate. Note that for both classes of fluids, the viscosity of a liquid depends on its temperature. Several units have been used for viscosity, with the most common being milliPascals.sec (mPa.sec) which is numerically equal to centiPoise (cP); water at 20 °C has a viscosity of 1.0 mPa.sec or 1.0 cP.

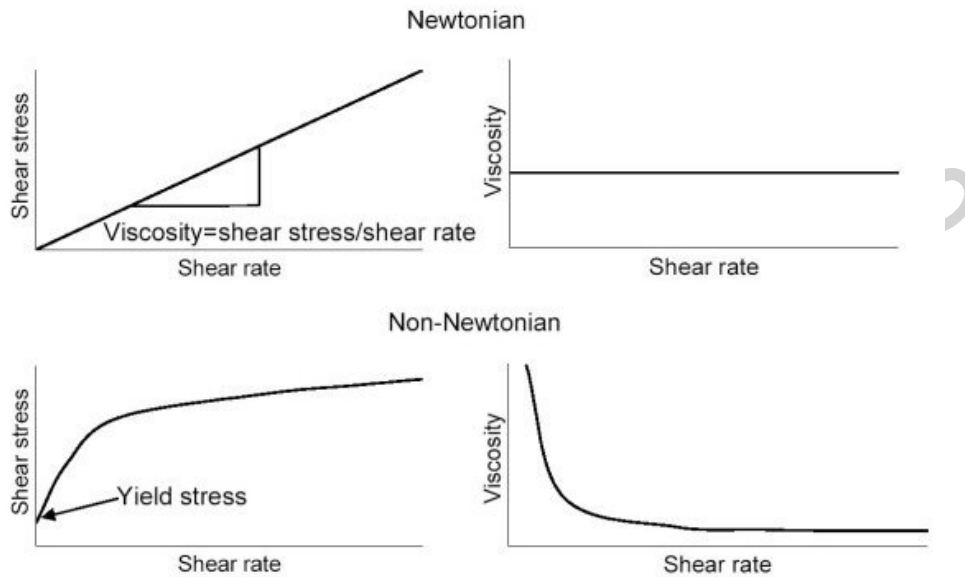


Figure 1. Shear stress-shear rate and viscosity-shear rate relationships for Newtonian and non-Newtonian liquids.

The viscosity of a liquid can be measured by a viscometer, which is a device built for studying the stress-strain relations in a liquid. Capillary viscometers are most widely used devices for measuring viscosity of Newtonian liquids. The working principle of a capillary viscometer is based on the measurement of flow rate of the liquid through a well-defined capillary tube under a certain pressure difference; at constant temperature, flow rate decreases with increasing viscosity. Capillary viscometers can also be used for flow measurements of non-Newtonian liquids, but estimation of viscosity is difficult since the shear rate varies across the diameter of the tube (i.e. maximum at the wall, zero at the center). Rotational viscometers of various types are thus more commonly used for studying non-Newtonian liquids. In a rotational viscometer, the liquid under investigation is sheared between two surfaces, either under constant shear stress or shear rate, and the response (resulting shear rate or stress respectively) is measured. The geometric design of the shearing portion varies between instruments, but is usually designed to provide a uniform shear rate or shear stress in the sample being studied.

### 1.3. Definition of Hemorheology

Hemorheology deals with the flow and deformation behavior of blood and its formed elements (i.e. red blood cells, white blood cells, platelets). The rheological properties of

blood are of both basic science and clinical interest: the details of blood rheology are still being studied, and blood rheology can be altered in many disease states. There is an increasing amount of clinical and experimental data clearly indicating that the flow behavior of blood is one the primary determinants of proper tissue perfusion.

## 2. Rheology of Blood

### 2.1. Structure of Blood

From a biological point of view, blood can be considered as a tissue composed of various types of cells (i.e. red blood cells, white blood cells, and platelets) and a liquid intercellular material (i.e. plasma). From a rheological point of view, blood can be thought of as a two-phase liquid; it can also be considered as a solid-liquid suspension with the cellular elements being the solid phase. However, blood can also be considered as a liquid-liquid emulsion based upon the liquid-like behavior of red blood cells under shear.

About 40 to 45% of the blood volume is occupied by the cellular elements; this volume percentage is termed hematocrit. The vast majority of the blood cellular elements are red blood cells (RBC): there are about 5 million RBC in one  $\text{mm}^3$  of blood, but only about 5000 white blood cells (WBC) and 300 000 platelets exist in the same volume. Given the relatively very small number of WBC and the small size of platelets, about 99% of cellular elements by volume are RBC.

The liquid phase of blood (plasma) approximates the composition of extracellular fluid, especially in terms of micro ions called electrolytes. In addition, plasma contains 6 to 8 grams of proteins per 100 ml, with the majority of these proteins divided into albumin and globulin fractions. Plasma also contains fibrinogen, a soluble protein that during the clotting process is converted to an insoluble, polymerized form called fibrin. Fibrinogen is also an important determinant of the flow behavior of blood, in that this protein is mainly responsible for the reversible aggregation of RBC and hence much of its non-Newtonian flow behavior.

### 2.2. Blood Viscosity, *ex vivo*

The viscosity of blood is usually measured, at constant temperature, by a rotational viscometer; in order to prevent clotting the blood sample is collected into a syringe or tube containing a chemical anticoagulant. Since blood is a non-Newtonian suspension, its fluidity cannot be described by a single value of viscosity. Rotational viscometers allow the measurement of viscosity over a range of shear stresses (or shear rates), yielding a flow or viscosity curve for a blood sample.

As shown in Figure 2, normal human blood exhibits shear-thinning behavior: at low shear rates or shear stresses the apparent viscosity is high, whereas the apparent viscosity decreases with increasing shear and approaches a minimum value under high shear forces. At high shear rates above 100 to 200  $\text{sec}^{-1}$ , the viscosity of normal blood measured at 37 °C is about 4 to 5 cP and is relatively insensitive to further increases of shear. The viscosity becomes more sensitive to shear forces below 100  $\text{sec}^{-1}$ , and

increases exponentially as the shear rate is decreased. Nominal values for the viscosity of normal blood are about 10 cp at  $10 \text{ sec}^{-1}$ , about 20 cp at  $1 \text{ sec}^{-1}$ , and about 100 cp at  $0.1 \text{ sec}^{-1}$ . Thus at lower shear rates, blood viscosity becomes extremely sensitive to the decrement in shear forces. At stasis, normal blood has a yield stress of about 0.1 mPa.

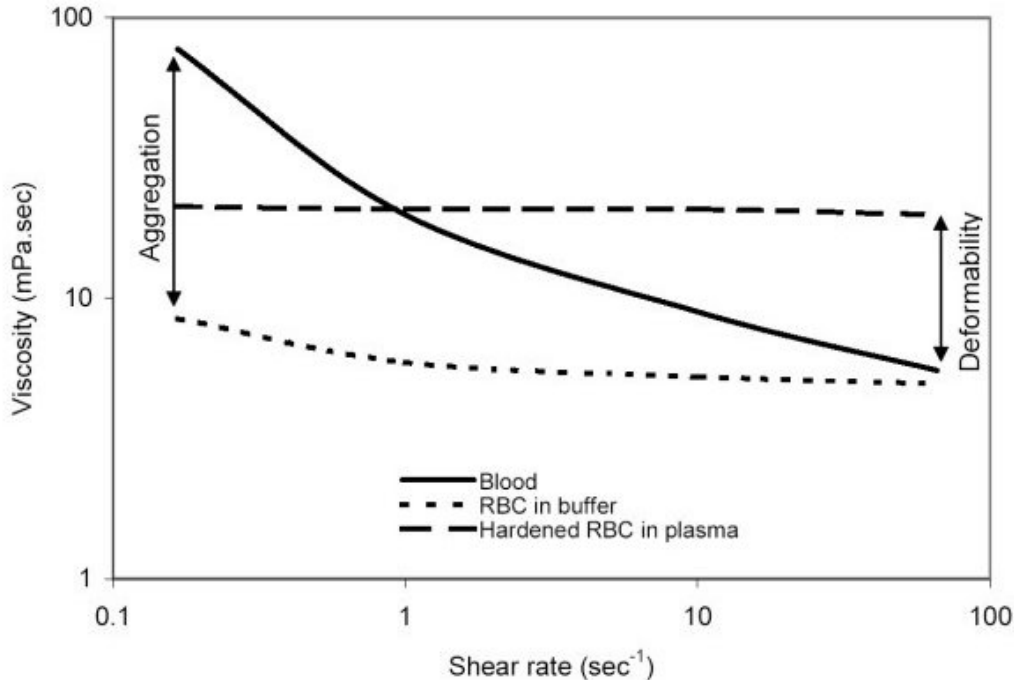


Figure 2. Shear rate-viscosity curves for normal blood, RBC suspended in protein-free buffer (no RBC aggregation) and rigidified RBC in plasma. The differences in viscosity at the lower and upper end of the shear rate range demonstrate the effects of RBC aggregation and deformability, respectively. (For explanation see Section 2.3.3).

### 2.3. Determinants of Blood Fluidity

Blood is a two-phase liquid and its fluidity at a given shear rate and temperature is thus determined by the rheological properties of the plasma and cellular phases, and by the volume fraction (i.e. hematocrit) of the cellular phase.

#### 2.3.1. Plasma Viscosity

Since plasma is the suspending phase for the cellular elements in blood, a change in its viscosity directly affects blood viscosity regardless of the hematocrit and the properties of the cellular elements. The normal range of plasma viscosity is between 1.10 and 1.35 cp at  $37 \text{ }^\circ\text{C}$ , yet this value may reach about 2 cp in various diseases; plasma is a Newtonian fluid yet technical artifacts have led some to report non-Newtonian behavior. In general, plasma viscosity is a good, non-specific indicator of disease processes, and is found to be increased in patho-physiological conditions associated with acute phase reactions. This increase is closely related to the protein content of plasma: acute phase reactants, such as fibrinogen, contribute significantly to the non-specific increase of plasma viscosity in disease processes. Plasma viscosity can increase up to 5-6 cP in

patients with abnormal protein levels such as seen in clinical states termed paraproteinemias.

### 2.3.2. Hematocrit Value

Under laminar flow conditions, the presence of cellular elements disturbing the flow streamlines is the primary reason why blood viscosity is higher than plasma viscosity. The contribution of this disturbance to the magnitude of blood viscosity can be appreciated by calculating the relative viscosity of blood (i.e. blood viscosity divided by plasma viscosity). With increasing amounts of cells, flow lines are progressively disturbed, and relative viscosity increases above its value of 1.0 for plasma alone. The degree of disturbance of flow streamlines and consequently the viscosity of blood is thus strongly dependent on the concentration of the cellular elements (i.e. hematocrit). As shown in Figure 3, there is an exponential relationship between the hematocrit value and blood viscosity, such that at higher levels of hematocrit, blood viscosity becomes increasingly sensitive to hematocrit alterations. At medium to high shear rates, there is about a 4% increase of blood viscosity per unit increase of hematocrit (e.g. a change from 50% to 51% hematocrit increases blood viscosity by 4%).

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### **Biographical Sketches**

**Oguz K. Baskurt** graduated from Hacettepe University Faculty of Medicine in Ankara, Turkey. After two years of medical practice in Malatya, he returned to Hacettepe University and completed his PhD in physiology, in 1988. He started to explore rheological properties of blood and blood cells during his PhD studies. In 1989, he was promoted to associate professorship after receiving his degree at Hacettepe University. He joined the Department of Physiology at Akdeniz University in Antalya, in 1990. He established a hemorheology laboratory at Akdeniz University and continued research activities in this area. In 1995, Dr. Baskurt visited Dr. Herbert J. Meiselman's laboratory in Los Angeles, where he spent a year as a Fulbright scholar. This was a very productive year and started a number of projects that are still continuing in both Dr. Baskurt's and Dr. Meiselman's laboratories. After returning from Los Angeles in 1996, Dr. Baskurt was appointed as full professor and chairman of Department of Physiology at Akdeniz University. Dr. Baskurt was elected as the president of International Society of Clinical Hemorheology in 1999. Dr. Baskurt's research interests covers the rheological properties of red blood cells and their role in hemodynamics. He received a number of scientific awards including the Lafon Hemorheology and Microcirculation Award given by the International Society of Clinical Hemorheology, Encouragement Award of Turkish Scientific and Technical Research Council, Sedat Simavi Health Sciences Award and Akdeniz University Science Award. Dr. Baskurt has published about 70 research articles and a book chapter.

**Herbert J. Meiselman** received his undergraduate training in chemical engineering at the Michigan Technological University, Houghton, MI and a doctorate, also in chemical engineering, from the Massachusetts Institute of Technology, Cambridge, MA. His doctoral research involved studies of blood rheology and the effects of various non-ionic polymers (e.g. dextran). He then carried out an extended post-doctoral training period at the California Institute of Technology, Pasadena, CA where he was involved in studies of *ex vivo* blood rheology and red cell flow dynamics in the living microcirculation. In 1972 he joined the Department of Physiology and Biophysics at the University of Southern California School of Medicine, Los Angeles, California. Since that time, his research program has focused on the rheological behavior of human blood in health and disease, with particular emphasis on red cell and white cell mechanical properties and on the factors that affect reversible red cell aggregation. He is part of the Comprehensive Sickle Cell Center at his University; in addition to studies of blood rheology in this genetic disease, his research also involves pathological states such as diabetes mellitus, myocardial infarction and severe sepsis. Dr. Meiselman has published about 200 research articles and has edited two books. While not involved in his duties as Professor of Physiology and Biophysics, husband and father, Dr. Meiselman finds time to enjoy two hobbies: 1) off-highway driving with a four wheel drive truck; 2) amateur short-wave radio with a call sign of K6HJM.