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Biomechanics of Human Blood

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Abstract

Hematology is known as the study of blood regarding health and disease which revolves around issues with red blood cells (RBCs), white blood cells (WBCs), platelets, lymph nodes, blood vessels, bone marrow, and the proteins involved in bleeding and clotting. As biomedical engineers, it is especially vital to understand the mechanics of the various components of blood to avoid unwanted results from implantations such as heart valves. A comprehensive review on the biomechanics of blood is discussed in this chapter. We will also discuss that even though human blood is a non-Newtonian fluid, depending on the instance, it can be considered a Newtonian fluid.

Keywords: bloodstream, viscosity, hemodynamics, RBC, multiphase flow, pulsatile flow, non-Newtonian flow

1. Introduction

Blood is known to be one of the connective tissues in the human body as the blood connects every single cell, tissue, and organ in the body together [1]. All necessary substances are transported through the vascular system. The science of blood flow and the mechanics of blood flow is known as hemodynamics. Hemodynamics is a significant element of cardiovascular mechanics and engineering as it simply clarifies the physical laws that direct the bloodstream within the blood vessels [2]. A considerable number of dysfunctions that occur due to cardiovascular diseases and disorders such as hypertension and congestive heart failure are linked to systemic hemodynamics. For example, clinical studies advocate that local wall shear stress rates and forms moderate the location and the advancement of atherosclerotic plaques.

The shear stress and wall shear stress in the bloodstream throughout the entire cardiovascular system is significantly impacted by the physics and mechanics of the blood. In particular, these values play and important role in the design and development of medical devices for cardiovascular applications. In the area of cardiovascular engineering and technology and medical devices, hemodynamics and the mechanics of blood are undisputedly vital to be well understood and considered.

2. Blood cells

The major components of blood are considered to be plasma, RBCs, WBCs, and platelets. The liquid component of the blood, known as plasma, is made up of water, salt, sugar, fat, and protein and is responsible for transportation of blood cells throughout the body. Antibodies, oxygen, waste products, chemical messengers such as hormones and proteins, and clotting proteins are also transported throughout

the body within the blood. WBCs which are responsible for protection of the body against infection are much fewer in number than RBCs (1 to ~800)[3]. Platelets are not considered as cells but rather a small fragment of cells. Platelets mainly participate in the clotting process, also known as coagulation. They gather at the site of injury and stick to the lining of the injured vessel, forming a frame-like structure on which blood coagulation can take place. This process is also known as the formation of a fibrin clot in which the wound is covered and the leakage of blood is stopped. Fibrin also contributes to the structure of a scaffold upon which new tissue can grow and form, a step known as the healing process.

Red blood cells: RBCs are about 40–45% of the blood volume. Their shape is like a biconcave disk with a flattened center [4]. RBCs are made up of a compound known as hemoglobin which is a protein for carrying oxygen. Hemoglobin consists of two alpha subunits and two beta units. Each subunit holds a heme group and each heme holds a Fe^{2+} ion which can bind to an O_2 molecule. Oxyhemoglobin is essentially a hemoglobin that has molecules for bonding to oxygen molecules. RBCs undergo two major states while circulating through the body, oxygenated and deoxygenated. Oxygenated cells are bright red color and contain large quantities of oxyhemoglobin. They circulate through the body to deliver oxygen to the body tissues. When an RBC reaches the intended tissue, oxygen molecules are removed from hemoglobin. The first two O_2 molecules are easier to remove than last two, which cause a gradient of release. Deoxygenated cells have less oxyhemoglobin existing in the hemoglobin compound, however blood is never actually deoxygenated as not all oxygen is removed [5].

Blood disorders: Some common blood disorders include anemia, malaria, and cancer. Anemia occurs when the number of red blood cells is comparatively low. Common causes of anemia include iron deficiency, B_{12} deficiency, chronic diseases of the kidney or bones, and red blood cell destruction due to shearing forces. Malaria is a mosquito-borne infectious disease. Minor symptoms include fever, fatigue, vomiting, and headaches, however severe symptoms can include seizures, coma, and possibly death. The main cancer associated with blood is leukemia which begins in the bone marrow and results in high numbers of abnormal white blood cells. These abnormal white blood cells, known as blasts, are not fully developed and cannot function properly. This causes symptoms such as bleeding and bruising, fatigue, fever, and an increased risk of infection. Certain disorders such as thalassemia and leukemia have varying types for which symptoms and ideal treatment varies.

Thalassemia: Thalassemia is an inherited blood disorder where the hemoglobin produced by the body is abnormal and does not function properly. Thalassemia develops due to a genetic mutation in one of the genes involved in the production of hemoglobin. The disorder leads to the destruction of RBCs which results in anemia [6].

There are three main forms of thalassemia known as alpha thalassemia, beta thalassemia, and thalassemia minor [6]. Thalassemia minor is the less severe form, whereas alpha thalassemia and beta thalassemia are more serious conditions. Alpha thalassemia occurs when at least one of the alpha globin genes has a mutation, while beta thalassemia occurs due to mutations in the beta globin genes. Alpha and beta thalassemia also have two subtypes. Beta thalassemia has the subtypes major and intermedia. Beta thalassemia major is the more severe form of this disease and is generally diagnosed early on when the child is in infancy. Patients with beta thalassemia major have a complete lack of beta globin genes and experience the most severe symptoms. In addition to severe anemia which can be life-threatening, other symptoms may include paleness, poor appetite, jaundice, and enlarged organs [6]. Beta thalassemia intermedia is the less severe form of beta thalassemia and arises due mutations in the beta globin genes. Unlike beta thalassemia major, the genes are present within the DNA just not in their normal form.

Alpha thalassemia has the two subtypes hemoglobin H and hydrops fetalis. Hemoglobin H is developed when a patient is missing up to three alpha globin genes or has mutations in up to these alpha globin genes. Complications from this disease can cause bone issues where the cheeks, forehead, and jaw overgrow. Individuals may also experience jaundice, malnourishment, and an extremely enlarged spleen [6]. Alpha hydrops fetalis thalassemia is an extremely severe form of the disease and occurs in the developing fetus. This condition develops when all four alpha globin genes are altered or missing [6]. Due to such early development babies with this form of thalassemia are usually stillborn or die shortly after birth.

The only treatment for patients with thalassemia is regular blood transfusions every 2–4 weeks. This causes the patients to have excess iron which can cause iron overload in the body and lead to dangerous side effects. Due to this, patients also need to take drugs called iron-chelating agents that bind to excess iron and help the body remove it from their systems [7, 8].

Leukemia: In leukemia the DNA of immature blood cells, most commonly, WBCs is damaged which causes WBCs to grow and replicate continuously. Unlike healthy WBCs, these abnormal blood cells continue to accumulate in the bloodstream, forcing out healthy cells. As the damaged WBCs grow, they start to affect the normal functions of healthy WBCs by filling up large amounts of space within the blood. Individuals with leukemia generally suffer from poor blood clotting, anemia, and weak immune systems. Other symptoms that can be experienced are nausea, fever, chills, night sweats, flu-like symptoms, weight loss, bone pain, and tiredness [8].

Leukemia is split into two sets of types classified as acute or chronic and lymphocytic or myelogenous. Chronic leukemia is a rapidly moving form of cancer, whereas acute leukemia progresses significantly slower. Once divided into either acute or chronic, leukemia is then subdivided by the type of affected blood cell. Lymphocytic leukemia describes cancerous cells affecting the bone marrow that makes lymphocytes. Whereas myelogenous leukemia covers cancers that occur in the bone marrow that produce other types of white blood cells, platelets, and RBCs.

Treatments for leukemia vary depending on the classification of the cancer as well as the age and general health of the patient. Treatments for acute leukemia should be started as soon as possible due to the aggressive nature of the cancer and include chemotherapy and bone marrow transplants. Chronic leukemia is treated differently depending on the stage. The types of treatment include targeted therapy, interferons, chemotherapy, radiation therapy, and stem cell transplants [8].

The life cycle of RBCs: RBCs are produced in the bone marrow through a process known as erythropoiesis. The production of RBCs involves erythropoietin, monosaccharides, lipids, vitamin B_{12}, amino acids, folic acid, and iron. RBCs are released into the bloodstream once they are developed and have a lifespan of 120 day after which they expire due to mechanical or structural damage. Dead RBCs are then removed from the bloodstream through the spleen, liver, and bone marrow. The dead cells are crushed into their main components known as heme, comprised of iron and bilirubin, and globin, comprised of amino acids. Amino acids and iron are reused by bone marrow, whereas the bilirubin is removed through feces and urine [9].

RBC configuration: RBCs have a discrete biconcave shape, similar to a disk (**Figure 1**). Normal cells are 7.5–8.0 μm in diameter and ~2.0 μm in height, however RBCs must adapt their shape in order to pass through capillaries as some capillaries are only ~3 μm wide [9]. This adaptation means RBCs feel significant passive deformation through their 120-day lifespan. The properties of a RBC must be physically and mechanically stable so that to resist disintegration and the mechanical properties have to do significantly with their deformation in terms of the bending, shear, area expansion moduli, and relaxation times.
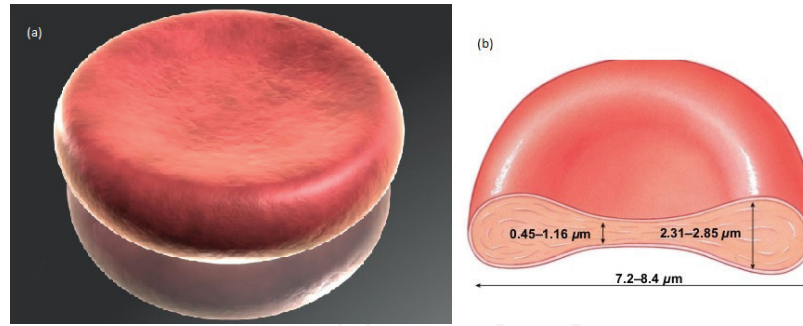
Figure 1.
The geometry of human RBCs. (a) The normal biconcave-shaped RBC cut in half along the y-z plane.
(b) A RBC with the cytoplasm [10].

Microfluidic channels are implemented to simulate human capillaries and study RBC deformability. Microfluidic channel are formed from stationary DPD particles and are filled with fluid particles containing RBCs. The microfluidic channels are comprised of two wide channels on each other edge and a cuboid channel in between. The wide channels are normally 20.0 μm wide and 3.0 μm high whereas the cuboid channel is 4.0 μm wide, 3.0 μm high, and 30.0 μm long [9]. Adaptive boundary conditions for fluid DPD particles are used to control density fluctuations. An individual RBC undergoes a continuous and severe transition from its normal biconcave shape to an ellipsoidal shape. This deformation includes elongation in the flow direction (longitudinal axis), and shortening in the cross-flow direction (transverse axis). The RBC enters into the narrow channel by undergoing these deformations. Once the entire RBC enters the constriction, it deforms further to pass through the microfluidic channel.

RBC deformation: Three distinct cellular components contribute to RBC's deformability—cell geometry, cytoplasm viscosity, and membrane elasticity.

Cell geometry: The geometry of a RBC determines the ratio of cell surface area to cell volume. The deformation of a cell is directly related to the surface area to cell volume ratio. Therefore, cells that achieve a higher value of surface area to volume ratio can deform with more ease.

Cytoplasm viscosity: The cytoplasm viscosity is regulated by the mean corpuscular hemoglobin concentration (MCHC). This suggests that the viscosity is directly related to alterations in cell volume. Therefore, cells with greater volumes have a higher cytoplasm viscosity and will deform with more difficulty.

Membrane elasticity: The membrane of RBCs consists of a lipid bilayer supported by an attached spectrin-based cytoskeleton. The resistance of the lipid bilayer to bending elasticity is controlled by the bending rigidity (k_c). The spectrin network's resistance to shear strain is characterized by the in-plane shear modulus, (μ_s). The deformability of the membrane, along with the mechanical stability of the cell, can be attributed to the elastic modulus, bending modulus, and yield stress.

Membrane simulations: RBC membrane properties can reveal the complex behavior that takes place within the membrane when it deforms. Twisting torque cytometry (TTC) is used to simulate membrane rheology and can obtain RBC membrane properties such as yield stress, shear thinning, and viscoelasticity. A microbead is bonded to the surface of a cell membrane and a magnetic twisting cytometry applies both static and oscillating magnetic field. The wall adhesion is simulated by keeping 15% of vertices stationary on the bottom of the lipid bilayer component of the RBC membrane. Microbead adhesion is simulated by including several RBC vertices in the lipid bilayer component near the bottom of the microbead in its rigid motion.

The complex elastic moduli of a RBC can be computed from the phase angle between the storage and loss moduli as such:

$$g' = \frac{\Delta T}{\Delta d} cos\varphi \tag{1}$$

$$g'' = \frac{\Delta T}{\Delta d} sin\varphi \tag{2}$$

Here, φ is the phase, g' is the two-dimensional storage, g'' is the loss modulus, T is the torque, and d is the microbead displacement amplitudes.

3. Hemodynamics and flow types

Blood circulation: Blood flow in the circulatory system is determined by the pulsing drive that is developed from the heart, the individual mechanical and flow properties of the fluid, and the structure and mechanical properties of blood vessels. These factors combined at appropriate levels ensure that the cells of the body receive adequate amounts of oxygen as well as maintain waste management.

Flow pulse development: The main function of the heart is to circulate blood throughout the human body. It is composed of four chambers: two chambers known as ventricles on the lower half of the heart and two chambers known as atria composing the upper section as shown in **Figure 3**. Upon the propagation of bioelectricity through these different components of the heart, contraction of each chamber occurs, moving blood throughout the body in a system known as the cardiac cycle [11]. The cardiac cycle can be easily separated into two main time events: systole and diastole. These two events refer to the action of either the heart pumping blood into the circulatory system or receiving blood from the venous system. In addition to these events, other factors of the blood such as velocity are initialized from the cardiac output of the heart.

Systole and diastole: Systole is when the pressure in the circulatory system is the highest due to the force of the heart that is used to pumping blood into the aorta and pulmonary artery, whereas during diastole the blood is moved into the heart due to a pressure difference between the vena cava and the right atrium, and pressure is lowest [12]. These periodic variations in pressure is what causes blood flow to be considered "pulsatile" [13]. This pulsatile action is what makes blood flow unable to be effectively modeled by standard flow models unless specific assumptions are applied.

Cardiac output: The amount of blood that flows out of the heart in 1 minute is known as the cardiac output and varies dependent on the weight of an individual. Standard values of cardiac output are within the range 4.0–8.0 L/min [13]. Cardiac output is dependent on four main components: heart rate, contractility, preload, and afterload.

The heart rate is directly proportional to the velocity of the blood moving throughout the body because under normal circumstances the blood maintains a constant volume. As heart rate increases, the velocity increases, which affects the viscosity and turbulent effects of the flow. A similar relationship is seen with contractility as the greater the force the heart initially enacts while emptying the left ventricle, the larger the pressure will be that is pushing the blood from the heart, increasing the initial blood velocity. Preload is the degree of myocardial extension prior to shortening which maintains a direct relationship with cardiac output [3]. Afterload is the force that the ventricle must overcome in order to push

the blood into the system of blood vessels. These components combined affect the initial velocity, pressure, and forces applied on the blood flow. However, this system is only effective if the components of the heart are working properly and can differ if there are defects present in the heart.

Heart murmurs: A heart murmur is a sound that is developed in the heart that occurs due to the presence of turbulent flow near the heart valves [14]. Heart murmurs can be classified into two main types: innocent and abnormal murmurs. These murmurs can then be categorized based on if they occur during systole or diastole and by what type of flow characteristic they possess, namely, regurgitation or ejection [15]. Due to the fact that heart murmurs occur due to turbulent flow, they have a tendency to be increased in those who are diagnosed with anemia (due to the decreased hematocrit) and those with heart valve defects. In addition to these two cases, anything that causes irregular or disturbed flow has the potential to cause increased turbulence in the flow and therefore increase the possibility of heart murmurs. Examples of such include heart valve replacements which introduce new stresses and area contact points in the flow and heart valve infections which cause inflammation [15].

Blood circulation begins by the heart pumping deoxygenated RBCs to the lungs which are then oxygenated and released back to the heart through the pulmonary circuit. These oxygenated RBCs are then pumped through the systemic circuit to deliver oxygen to various tissues. The RBCs become deoxygenated after releasing and depositing oxygen within the tissues and travel back to the heart through the system circuit to repeat the cycle.

The flow of fluid within the circulatory system is dependent on a variety of factors but can be characterized by considering the laminar and turbulent properties of the flow. In addition to the laminar and turbulent properties of the flow, it is also important to consider the motion of the suspended particles within the heterogenous fluid allowing it to cohere to adequate blood flow needs.

Laminar and turbulent blood flow: In homogeneous fluids, flows are laminar up to a Reynolds number of roughly 2300 and become turbulent at a Reynolds number of 4000. This logic cannot be applied to the flow of blood as blood is not a homogenous fluid and blood vessels are not perfectly cylindrical and possess viscoelastic properties. Though directly corresponding to Reynolds numbers will not accurately represent the type blood flow, it is generally considered that the possibility of turbulence will increase as the Reynolds number increases, regardless of the precise critical Reynolds number values for transition. Adhering to this logic, as seen in Eq. (3), the possibility for turbulent flow will increase as the velocity increases, the diameter increases, the density increases, or as the viscosity decreases:

$$\Re = \frac{\rho N D^2}{\mu} = \frac{\rho V D}{\mu} \tag{3}$$

As a flow develops into turbulence unsteady vortices appear and interact with each other leading to the development of eddy currents, small currents where the flow differs from that of the general flow. Turbulence occurs naturally in locations of the circulatory system where the Reynolds numbers are comparatively elevated such as the ventricles and ascending aorta. In addition to this, turbulence can also be initiated due to branches or curves in the flow, irregularities due to surgical implants, and improper function of circulatory valves [16]. Under diseased or abnormal conditions, other segments in the circulatory system can experience turbulent flow which can have negative effects on epithelial function [16].

In individuals with conditions affecting the viscosity of their blood, such as anemia, due to the decreased hematocrit in the blood the opportunity for one's blood to enter turbulence is increased [5]. Other individuals experience increased turbulence

opportunity due to a foreign object being placed in the circulatory system such as a replaced heart valve, as turbulence is developed from an increased contact area between the blood flow and the valve. Due to the chaotic nature of the flow, turbulent flows require more energy to properly travel throughout the system as much of the energy is lost due to misaligned flows and eddy currents. Even though turbulent flows occur in the circulatory system, RBCs go through a series of motions and deformations which help sustain the efficiency of blood flow.

Movement of RBCs: Dependent on shear rate, RBCs can move throughout the circulatory system in one of three manners known as tumbling, swinging, and tank-treading [17]. At the lowest shear rates RBCs have the tendency to move in a pattern known as tumbling (**Figure 2**). This is where the RBCs spin completely around their axis and maintain little to no deformation. As shear stress is increased RBCs experience a transition motion known as swinging where they experience quasi-deformation and their rotation abilities alter from 180° at tumbling to a range of 5–26° while swinging [5]. Following this, RBC motion develops completely into tank-treading motion which is defined by large amounts of RBC deformation and quasi-steady motion. During tank-treading, RBCs explore a small volume of the flow, leading to less collisions and disturbances, which decreases the viscosity of the fluid. This phenomenon coheres with the fact that as shear rate increases, the viscosity of the blood decreases.

Viscosity: The viscosity of the blood is due to the internal friction between the flow, incorporating the effects of the suspended particles present in the blood, inclusive of RBCs, WBCs, and platelets. As this internal friction increases, more force is required from the heart in order for it to maintain the desired cardiac output of the blood in the circulatory system. This requires a heightened contractility from the muscles of the heart which can result in the fatigue of the heart and, in major cases, heart collapse [19]. The opposite case where there is a lack of proper internal friction in blood flow will cause a decrease in the ability of one's blood to clot, which imposes risk when blood vessels are damaged and the blood continues to flow out of the site of damage for a prolonged period of time.

The viscosity of blood is dependent on many factors such as the properties of blood plasma, the hematocrit levels, and the individual mechanical properties and influence of the suspended particles in the flow; however, this is inherently dependent on whether blood is considered as a Newtonian or non-Newtonian fluid. The true nature of blood is that it exhibits non-Newtonian properties under specific
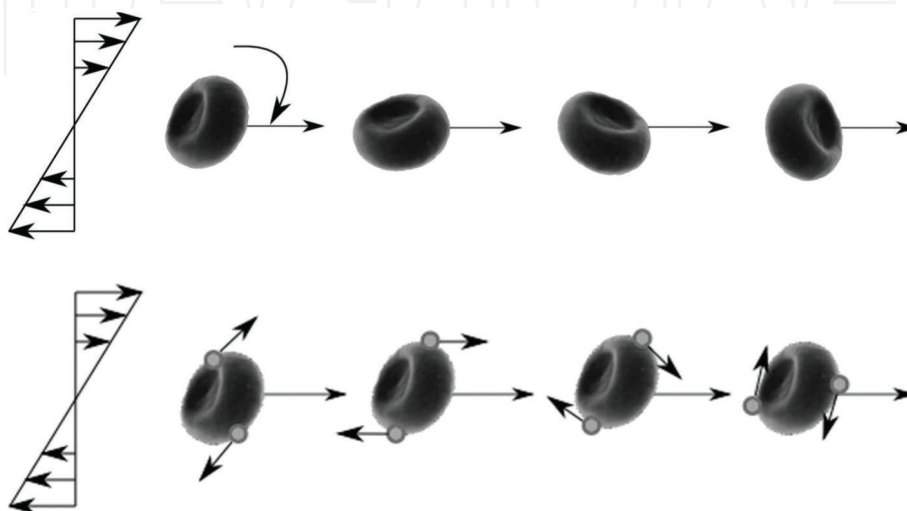

Figure 2.
Two conceptual motions are considered for RBCs, (1) linear shear field, the solid-like, also known as tumbling motion (top), and the vesicular, also known as tank treading motion (bottom) [18].

conditions; however, these conditions arise at very few locations throughout the circulatory system.

Newtonian and non-Newtonian conditions: Blood possesses non-Newtonian properties when the shear rate is above 100 s^{-1} [20] and follows shear-thinning effects. High shear rates occur in the capillaries and the larger arteries coming directly from the heart because the shear rate of a fluid through a vessel increases with increasing velocity and decreasing diameter. Due to the fact that the main non-Newtonian properties of blood occur in small diameter vessels, it is argued that the non-Newtonian effects that occur within the largest arteries can be ignored [21, 22]. In blood vessels that possess a diameter in the more medial range or where there is decreased velocity, such as veins and arterioles, these non-Newtonian factors have minute effects on the properties of the flow, causing them to be neglected for these areas as well:

$$\acute{\gamma} = \frac{4Q}{\pi r^3} \tag{4}$$

Eq. (4) is not an accurate representation of proper blood flow as blood flow is subject to fluctuations based on the viscoelastic properties of the vessel walls, the alternating pressures from systolic and diastolic, and when present the non-Newtonian properties of the blood itself; however, it is used here to outline the relationship between the shear rate and vessel size and diameter.

Considering the above, the non-Newtonian effects of blood are only active within a small portion of overall blood flow and acquire more importance when blood flow at those selected areas are specifically studied. When being considered as a Newtonian fluid, the viscosity of blood in addition to being impacted from the vessel size and blood velocity is also affected by the blood plasma and the concentration of suspended particles in the flow.

Factors of blood as a Newtonian fluid: The blood plasma is mainly composed of water (roughly 91% by volume) proteins, hormones, and glucose and acts as a Newtonian fluid with standard values between 1.1 and 1.3 mPas at the human body temperature of 37°C [9]. Blood plasma accounts for approximately 55% of the volume of the blood in the body and due to the incredibly high water content in the substance, the viscosity of plasma is highly affected by the hydration levels of the individual. As a human becomes dehydrated this percentage decreases and the blood becomes more viscous [23]. In addition to hydration levels, blood plasma viscosity is also directly affected by the amount of proteins and lipids in the blood post consumption. The higher the concentration of these elements, the more viscous the plasma will become [24].

In addition to the direct effects on plasma, the shear in the flow is also affected by the amount of suspended particles in the flow. In heterogeneous fluids where particulates are present, these particulates alter the velocity profile of the fluid due to the increased shear at the fluid particle interface. As aside from plasma, the majority of the remaining volume of the blood is composed of RBCs, RBCs are the particles that impose this effect to the flow in the greatest magnitude. Aside from the direct viscosity of the plasma itself, plasma also affects the viscosity of the blood by the housing of certain proteins such as fibrinogen that cause aggregation in the suspended particles [25].

Factors of blood as a non-Newtonian fluid: The percentage comparison of the volume of blood cells to the total volume of blood is known as hematocrit and is the main factor contributing to the viscosity of the blood. This is because the blood's ability to flow is highly dominated the ease of movement of RBCs. At high shear rates the deformability of RBCs is what effectively determines the viscosity of the

fluid; however, at low shear rates the viscosity is controlled by the unique property of RBCs to aggregate [26, 27].

Physical capabilities and tendencies of RBCs: The deformability of RBCs is controlled by three main factors: the relatively high surface area to volume ratio due to RBCs enucleated nature, the viscosity of the cytoplasm, and the viscoelastic properties of the cell membrane [28]. The viscoelastic properties of the cell membrane are dominated by three moduli known as the shear elastic modulus, the area compressibility modulus (κ), and the bending modulus. The definitions of the previous as well as determined experimental values for healthy RBCs are denoted in **Table 1**. The bending modulus (E_K) is calculated as such:

$$E_K = 2KH^2 \tag{5}$$

$$H = \frac{1}{2}\left(\frac{1}{R_1} - \frac{1}{R_2}\right) \tag{6}$$

During the same experiment as the calculation for the elastic moduli, the cytoplasmic viscosity was tested as well, producing a value with an average that is approximately six times greater than the viscosity of plasma.

This viscosity is important because it outlines how quickly the cell can reshape itself. Similar to the viscosity of plasma, this is dependent on the hydration levels of the individual in which the blood is present [30]. Deformability of RBCs is relevant in locations of high shear rates such as the capillaries because, in order to maintain proper blood flow they must adhere to the vessel to sustain motion. To do this effectively, the RBCs fully elongate into ellipsoids and align with the flow, reducing the possibility of collisions, decreasing the overall viscosity.

At low shear rates, RBCs have the tendency to aggregate together, most commonly into stacks called Rouleaux. It is suggested that this specific formation occurs due to the incredibly high surface area RBCs possess. This combining of RBCs severely increases the frictional resistance between flow streamlines, increasing the viscosity of the fluid. However, as seen in **Figure 3** at high shear forces this tendency is overruled and the blood cells separate and align in the direction of the flow [31].

Aside from RBCs, other suspended particles such as platelets and WBCs are present in the blood which also maintain aggregative properties; however due to the fact that they compose roughly 1/800th and 1/600th of the volume of the blood, respectively, they are often not considered a vital part of the viscosity of the blood [31–34].

Flow effects on RBCs: As blood moves from a large vessel to a vessel less than 0.3 mm [35] the RBCs realign to the center of the vessel. Due to this, the velocity of the centric RBCs is increased relative to the layer of plasma present at the wall of the vessel and the RBCs leave the vessel at a faster rate at which they enter them.

Modulus type	Definition [29]	Tested value [4]
Shear elastic modulus	The ratio of shear stress to shear strain	5.5 +/− 3.3 (µN/m)
Area compressibility modulus	The energy per unit area required to uniformly stretch an interface to produce an area change according to Hooke's law	399 +/− 110 (mN/m)
Bending modulus	The energy per unit area required to produce a mean curvature (H) according to Eqs. (3) and (4)	1.15 +/− 0.9 ($\times 10^{-19}$Nm)

Table 1.
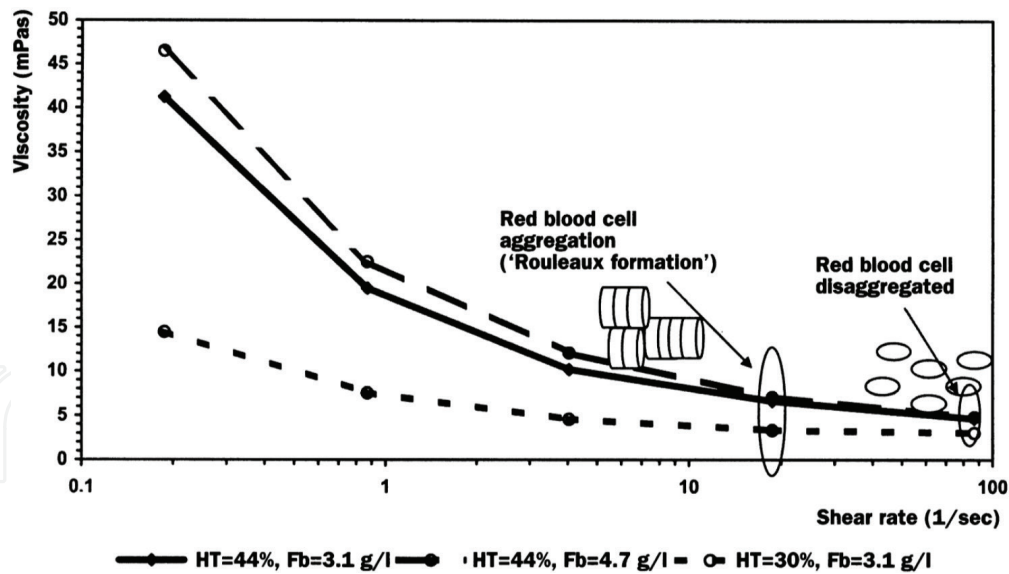*Viscoelastic factors for RBCs.*

Figure 3.
Shear rate to RBC aggregation comparison [31].

This causes the hematocrit level to decrease through the vessel, also known as the Fahraeus effect. This causes another effect known as the Fahraeus-Lindkvist effect which states that the viscosity of the blood decreases as the vessel size decreases. Though as viscosity in extremely small vessels is affected by the deformability of RBCs as discussed earlier, the increase in velocity of the RBCs increases the velocity of the entire flow, respectively, causing the viscosity to decrease.

Hemostasis: Hemostasis is the process by which bleeding is stopped and it can be broken up into three main steps: vasoconstriction, platelet activation, and blood clot formation [36]. The clotting process begins by the blood vessel contracting in order to reduce the flow of blood into the injured vessel. After a rupture, tissue factor is released which causes platelets to aggregate to each other and the walls of the vessel. As platelets become sticky, they help to impede the flow of blood through the rupture. In addition chemicals are released from small sacs inside the platelets called granules [37] that attract more cells to the site and further the clumping of platelets creating a platelet plug. On the surface of these activated platelets, many clotting factors work together in a series of complex chemical reactions known as the coagulation cascade which results in the formation of a fibrin clot [38].

Blood diluters: Blood diluters are commonly used in the medical industry for a variety of reasons. The main reason that a doctor may prescribe a blood thinner to a patient is if the patient has a high risk of blood clots, which can cause organ damage or in some cases death. Blood thinners are commonly used for patients suffering from heart disease, poor blood circulation, abnormal heartbeat, and congenital heart defects [6, 8, 39–41]. There are two types of blood thinners, anticoagulants and antiplatelets. Anticoagulants inhibit the coagulation cascade, whereas antiplatelets prevent platelets from aggregating. Antiplatelet drugs are commonly issued for patients with heart disease or have had prior heart attacks and anticoagulant drugs are used before open heart surgery on heart valves or congenital heart defects [41]. Using blood thinners inhibits vital aspects of the human body which can cause many side effects. Patients can suffer from increased bruising, red- or pink-colored urine, bloody stools, increased bleeding during menstrual period, purple toes, and blackish areas in their fingers, toes, or feet [9]. Common anticoagulants include heparin and warfarin. Well-known antiplatelet drugs are clopidogrel and ticagrelor [42].

Viscoelasticity of blood: Viscoelasticity is the property of materials that exhibit both viscous and elastic characteristics when undergoing deformation [43–49].

Viscous materials resist shear flow and strain linearly with time when a stress is applied, while elastic materials strain when stretched and quickly return to their original shape after the stress is removed. The blood is viewed most commonly as a viscous fluid, but due to RBCs ability to store elastic energy, it actually displays viscoelastic properties. Elastic energy is most commonly stored in RBCs as a result of the heart pumping the blood.

The factors contributing to the viscoelastic properties of blood are the plasma viscosity, plasma composition, temperature, shear rate, and the level of hematocrit. When conducting experiments on blood to test the viscoelasticity properties there are two main control factors, the level of hematocrit and the temperature.

Hematocrit is a significant factor as RBCs are the main reason for the elastic properties of blood. **Figure 4** shows the level of viscoelasticity with respect to the amount of RBCs present in the blood. It is easy to discern from the graph that as the amount of RBCs present in the blood increases, the viscoelasticity properties of the blood increase as well.

It is important for scientists to properly recreate the same environment experienced within the human body to achieve accurate results. As shown in **Figure 5**, the temperature affects the levels of viscosity and elasticity within the blood.

Blood clot factors: In stagnant flow regions or where the blood flow moves very slowly, the risk for blood to clot increases [50]. This occurs due to a high exposure time of RBCs to large variation in shear stress. It has been shown that the pulsatile flow is significant in the regulation of the stagnation areas regarding blood clot formation [50, 51]. In addition, blood clotting is known to occur because of both the jet velocity and turbulent shear stress where Re number is high in the stagnation region [52]. Factors that are said to be in charge of triggering blood clot formation are listed in **Table 2**.

Numerical models for blood clot formation: The process of blood clotting begins by activated platelets which aggregate with a damaged blood element. It is well known that the level of platelet activation and blood cell damage are significantly impacted by the magnitude and duration of the applied shear stress, known as residual time [59].

There have been a few models developed based on the measured residual time and the amount of shear stresses as outlined in **Table 3**.
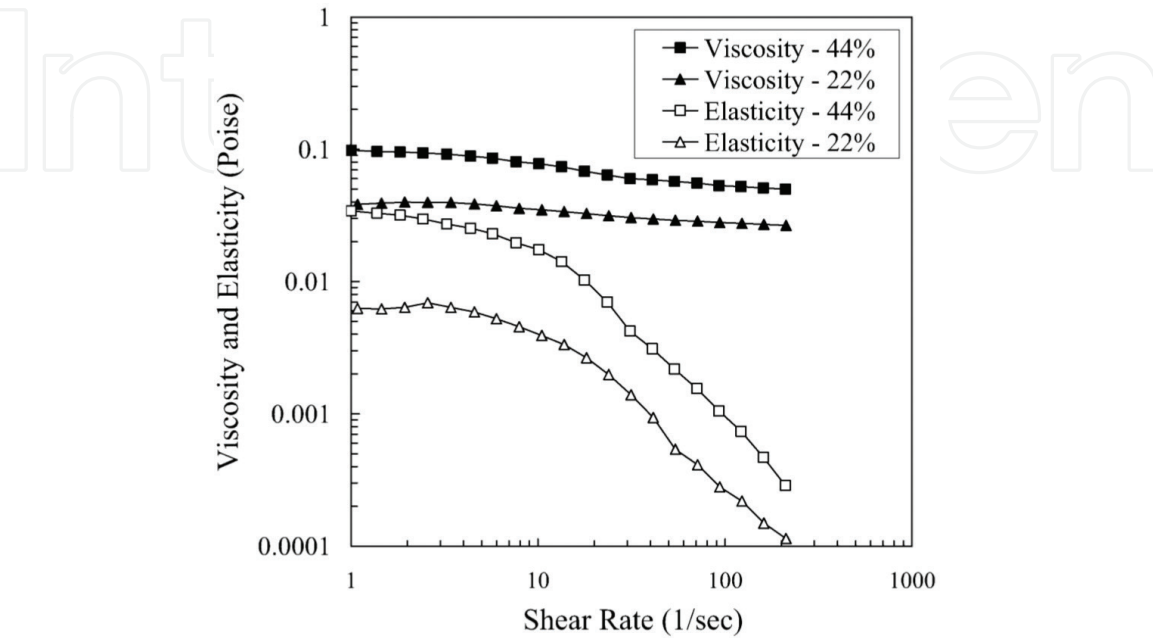

Figure 4.
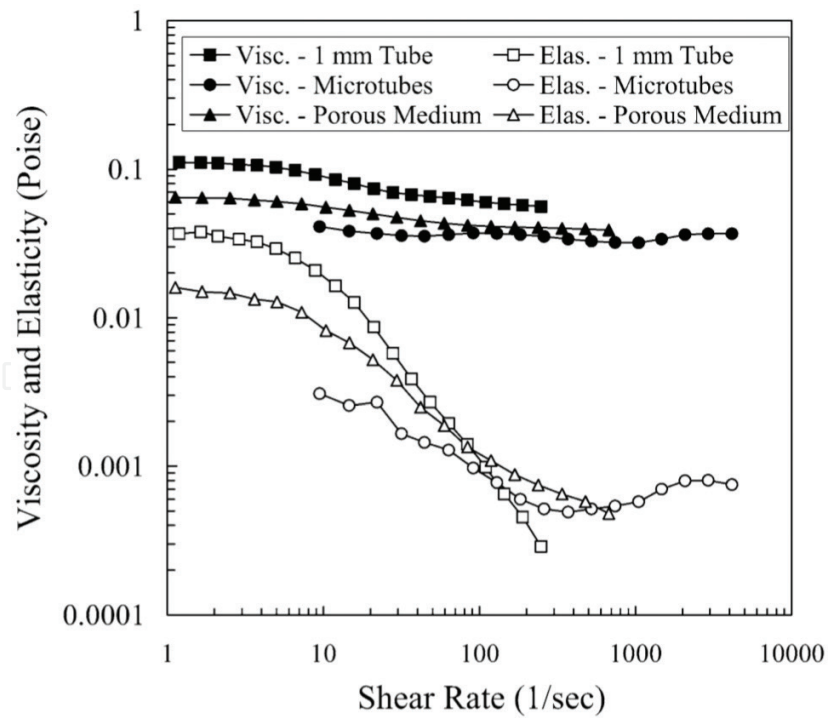*Viscosity and elasticity measured at 2 Hz, 22°C, and at a shear rate of 10/s rms [43].*

Figure 5.
Viscoelastic properties of blood with respect to shear rate. Hematocrit is set to %45 and measurements are performed at 2 Hz in three arrangements: cylindrical tube of diameter of 0.10 cm and length of 6 cm, in a microtube with a diameter of 0.005 cm and a length of 0.120 cm and porous medium with an equivalent diameter of 0.00812 cm and a length of 0.165 cm.

Factor	Triggering criteria for blood clots
Cavitation	Water hammer and squeeze flow
Reynolds shear stress	>>200 dynes/cm^2 [54]
Cardiac output	Slow movement of leaflet
Stagnant flow	If occurs adjacent to the valves, it could promote the deposition of damaged blood elements, leading to thrombus formation on the prosthesis [55]
Vortex shedding	Yields repeated vortex pairing within the wake, which is responsible for the formation of larger platelet aggregates [56]
Recirculation	Allows many platelets to be trapped [57]
Pressure drop	A larger pressure drop means that the heart with the MHV prosthesis has to work harder [58], thereby reducing cardiac output

Table 2.
Blood clot factors [53].

Model	Expression	
Linear damage accumulation/BDI	$\sum_{t=0}^{t=end}(\dot{\tau} \times \Delta t)$ dynes/cm^2	[60]
Platelet activation state (PAS)	Nondimensional level of platelet activation within the interval of [0, 1], in which 0 and 1 correspond to nonactivated and fully activated platelets, respectively	[61]
Power-law model	$C\tau^\alpha\dot{\tau}^\beta$	[62]
λ_2 criterion	$\lambda_2 = 20.0 s^{-2}$ is responsible for blood clot formation	[63, 64]
Adhesion model	$S \leq S_{th}$, where S_{th} is shear rate threshold, taken as 100	[65]

Table 3.
Available models for the estimation of blood clot formation and threshold [53].

4. Conclusion

Biological processes are amazing in their complexity and optimization. The blood, being no exception, is extremely evolved and adapted to the different scenarios necessary to maintain life. Consisting of plasma, WBCs, platelets, and RBCs, it is able to transport vital molecules around the body including oxygen, and clot in case of injury. Since RBCs make up approximately half the volume of blood, blood flow mechanics are largely related to the properties of red blood cells defined under a soft solid. Large deformability is essential in the life cycle and function of red blood cells as capillaries are extremely small. Blood clotting is a very important function of blood, in which platelets are the main contributors to the clotting process. When platelets come into contact with damaged tissue, the platelets activate and construct a web to coagulate blood. Due to vWF's shear dependent binding, under high shear stresses platelets can be bound together and form clots without activating.

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