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Pathophysiological Significance of Blood Rheology

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Abstract: Tissue perfusion is determined by both blood vessel geometry and the rheological properties of blood. Blood is a non-Newtonian fluid, its viscosity being dependent on flow conditions. Blood and plasma viscosities, as well as the rheological properties of blood cells (e.g., deformability and aggregation of red blood cells), are influenced by disease processes and extreme physiological conditions. These rheological parameters may in turn affect the blood flow in vessels, and hence tissue perfusion. Unfortunately it is not always possible to determine if a change in rheological parameters is the cause or the result of a disease process. The hemorheology-tissue perfusion relationship is further complicated by the distinct in vivo behavior of blood. Besides the special hemodynamic mechanisms affecting the composition of blood in various regions of the vascular system, autoregulation based on vascular control mechanisms further complicates this relationship. Hemorheological parameters may be especially important for adequate tissue perfusion if the vascular system is geometrically challenged.

Key Words: Hemorheology, tissue perfusion, metabolic autoregulation, shear stress

Introduction

It is a very basic medical fact that proper tissue/organ function strongly depends on adequate blood flow. Obviously, "adequacy" does not denote a steady state condition, but the ability to match the supply with the demand of a given tissue. Any disturbance of this delicate balance results in clinical problems. Higher level living organisms are well equipped with powerful control mechanisms to maintain this balance and to keep the organism in good health, accordingly.

Factors affecting blood flow

Blood flow in the vascular system is determined by the pressure difference (i.e. perfusion pressure), hydraulic conductivity of the blood vessels and the fluidity of the blood. The last 2 factors can be combined into a resistance parameter (R), yielding a simple relationship between perfusion pressure (ΔP) and blood flow (Q): $\Delta P = Q \times R$. In other words, blood flow under a given perfusion pressure is inversely proportional to hydraulic resistance. Adequate blood flow to a given tissue requires the maintenance of a sufficient pressure gradient across the tissue that is generated by the heart.

The vascular component of flow resistance is determined by the geometry of the blood vessels network. This component is usually called vascular hindrance (1). Jean-Marie Poiseuille described the vascular hindrance of a given blood vessel segment as being directly proportional to the length of the segment and inversely proportional to the fourth power of the vessel radius (2), based on his experimental studies. Flow resistance is also directly proportional to the viscosity of blood flowing in that segment. This simple relationship is known since the 19th century; however, under the strong influence of cellular pathology theory, medical scientists ignored the role of blood viscosity in flow through a given vascular network mainly for 3 reasons (3): 1). The fourth power factor of the blood vessel radius definitely suppressed the importance of the viscosity factor that is represented by a power of 1. 2). Static, microscopic observations of dead, fixed tissues had long been the only

basis of medical diagnosis, and functional parameters, like blood viscosity, have been ignored for a long time. 3). The viscosity factor was considered a constant, rather than a variable in the famous Poiseuille equation.

Despite the efforts of several distinguished medical scientists (e.g., Robin Fahraeus) (4,5), the importance of blood rheology (i.e. the flow properties of blood) was not appreciated during the first 60 years of the 20th century.

Blood rheology as a determinant of blood flow

The role of blood rheology as a determinant of blood flow and tissue perfusion received considerable attention with the development of hemorheological theory after the 1960s. Both the basic science and clinical aspects of this relationship have been investigated extensively, together with the unique rheological behavior of blood.

The rheology (i.e. flow behavior) of a fluid can physically be described by its viscosity. In laminar fluid flow as described by Newton (6), viscosity is the ratio of the force that moves the fluid layers or laminae (shear stress) to the velocity gradient in the fluid (shear rate), representing internal resistance between the laminae (6,7). Such a fluid flow can be modeled as flow streamlines moving on a steady surface or, more realistically, as concentric cylinders moving in the direction of flow in a cylindrical tube (8).

Blood is a 2-phase liquid. It can be considered a solid-liquid suspension if the cellular elements (red blood cells (RBG), white blood cells (WBCs) and platelets) are regarded as solid particles. It can also be considered a liquid-liquid emulsion based on the fluid drop-like behavior of RBCs under certain conditions (i.e. under high shear forces) (9). Therefore, depending on the flow conditions, blood tissue can be regarded as a suspension or an emulsion. This transition is one of the main reasons for the special rheological behavior of blood.

Blood is a non-Newtonian, shear thinning fluid (7); its viscosity is not constant, even with unchanged composition, and varies as the flow conditions change. Blood becomes thinner (or more fluid) as the shear forces that generate flow increase. This is a reversible change and blood viscosity increases as shear forces get smaller.

The viscosity of blood under a given shear stress is determined by hematocrit value, plasma viscosity (as the suspending phase) and the rheological properties of RBCs, which constitute 99% of cellular elements (6,7). WBCs and platelets do not play a significant role in determining the fluidity of blood under bulk flow conditions, because of their smaller number, but should be considered when studying microcirculation (10).

Two special features of RBCs that underlie the non-Newtonian rheological behavior are cellular deformability and aggregation (11-14). Deformability (i.e. the ability of the entire cell to reversibly adopt a new shape in response to deforming forces) is a unique property (13) and partly contributes to the thinning of blood under high shear conditions (9,14) by promoting the orientation of RBCs to the flow streamlines thereby reducing the friction between them (Figure 1). Aggregation denotes the formation of reversible clumps of RBCs under sufficiently low shear stresses (15-17). This behavior tends to increase the particle size under low shear conditions and increase the distortion of the flow streamlines (Figure 1), and hence frictional resistance between them (11). Therefore, the effect of RBC aggregation is to increase blood viscosity under smaller shear forces, contributing to the non-Newtonian behavior. A detailed description of the mechanisms related to RBC deformability and aggregation can be found in the literature (18-21); this topic is outside the scope of this review.

Following the above discussion, it can be stated that any alterations in the above-mentioned parameters (e.g., hematocrit, plasma viscosity, RBC deformability and aggregation) may result in alterations of blood flow resistance and tissue perfusion. Unfortunately, the

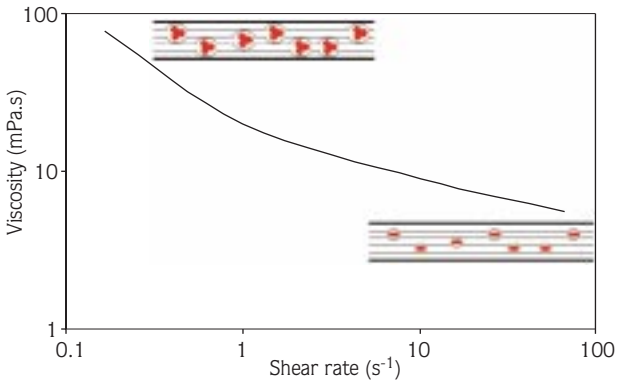

Figure 1. Shear rate-viscosity curve of normal blood. RBC deformability reduces the resistance between flow stream lines at higher shear rates, while the resistance is increased due to increased RBC aggregation (hence increased particle size) at lower shear rates.

interaction between blood rheology factors and hemodynamic mechanisms are highly complex and the exact role of blood rheology in physiopathological processes is still debatable. However, this uncertainty did not prevent the extensive investigation of hemorheological parameters under a wide variety of clinical and experimental conditions.

Alterations in blood rheology

Pathophysiology

Hematocrit value is a dynamic parameter and may vary depending on the fluid balance of the body. Under various physiological and/or pathological conditions hematocrit may reach values high enough to increase blood viscosity considerably (22). Plasma viscosity is also sensitive to both general and local homeostasis (23).

RBC deformability is determined by the material properties, as well as the metabolic status of RBCs. Various genetic, structural alterations in the cytoplasm and membrane lead to altered RBC deformability (13,24). RBC deformability also depends on intact metabolic pathways and an adequate ATP supply to support the ion transport systems (25). Failure of these systems would result in increased intracellular sodium and calcium concentrations. Impaired sodium exclusion is the cause of altered fluid-electrolyte balance of this simple cell and is usually accompanied by alterations in cellular volume in metabolically depleted RBCs. An increased cytosolic calcium concentration has been shown to be related to impaired RBC deformability by affecting the RBC membrane skeleton (26,27).

It should be noted that such a metabolic depletion might be the result of a local stasis in an area of impaired tissue perfusion. Adequate supplies of metabolites to the RBCs are also required to regenerate several co-factors of antioxidant mechanisms (e.g., NADH, NADPH) and a lack of these factors may shift the balance between oxidant stress and antioxidant defense to yield increased oxidant damage in RBCs (28). Alternatively, increased generation of oxidants in ischemic or inflamed tissues may contribute to this shift. Oxidant damage is a well known cause of impaired deformability (29). Other alterations in the micro-environment of RBCs (e.g., change in pH, osmolarity, temperature) may also affect RBCs' mechanical properties (13).

RBC aggregation is determined by both plasma and cellular factors (17). Increased plasma fibrinogen concentration is one of the main causes of enhanced RBC aggregation (16). Such an alteration is a common consequence of acute phase reaction and accompanies most inflammatory processes yielding enhanced RBC aggregation (30). Considerable evidence has been accumulated implying that RBC surface properties also play significant role in the aggregation process (17,31). Changes under the influence of metabolic disturbances in damaged tissues (e.g., increased production of oxidants) may result in altered RBC aggregation (29).

Clinical considerations

The pathophysiological considerations above are backed up by a huge number of clinical observations that can be accessed through specific journals in the field (e.g., Biorheology, Clinical Hemorheology and Microcirculation) and a number of textbooks (32,33). Most of these observations are based on the measurement of hemorheological parameters in blood samples outside the vascular system (i.e. ex vivo). A very brief classified summary of clinical observations in important disease categories is presented below.

Cardiovascular diseases

Cardiovascular diseases are among the clinical conditions with well established hemorheological consequences. Increased blood viscosity, impaired RBC deformability and increased RBC aggregation are reported in a variety of cardiovascular diseases (32). Among these, peripheral vascular diseases are the most widely investigated (34). Ischemic diseases of various organs are known to be associated with hemorheological impairment (35,36). It should be noted that in all vascular insufficiencies and ischemic diseases, hemorheological alterations may result from the disturbance of local homeostasis as mentioned above. Therefore, hemorheological alterations in cardiovascular diseases can easily be considered a result (or an indicator) of insufficient circulatory function. Alternatively, alterations in hemorheological parameters may affect tissue perfusion and be manifested as circulatory problems.

Hypertension is an interesting example of clinical disorders characterized by hemorheological alterations.

Hypertension is a complex pathohphysiological process (37). Especially the advanced forms of hypertension are certainly associated with vascular damage and this damage is claimed to be the cause of hemorheological alterations. However, impaired hemorheology can also be expected to be the cause of increased blood pressure, by contributing to increased peripheral resistance (38). Recent evidence suggests that altered RBC rheological properties might be the underlying cause, at least in some types of hypertension (39).

Diabetes mellitus

Diabetes is another important disease process that is accompanied by generalized microcirculatory disturbances. There are a number of studies documenting increased blood and plasma viscosity, enhanced RBC aggregation and altered RBC deformability in diabetes mellitus (40,41). Impaired deformability of polymorphonuclear leukocytes was also reported in diabetes and this alteration may also be associated with tissue perfusion problems (42).

Sepsis syndrome

Sepsis syndrome represents one of the most dramatic disturbances of the general homeostasis; therefore, it is not surprising to detect important hemorheological alterations in sepsis. Both clinical and experimental studies indicated that sepsis is characterized by significantly impaired RBC deformability (43-45) and increased aggregation (46). Such alterations in RBCs may well contribute to the generalized vascular problems encountered in sepsis syndrome.

Hematological diseases

Hematological diseases are exceptions in that hemorheological alterations can easily be identified as the cause of tissue perfusion problems. Sickle cell disease is the most striking example in which the dramatic clinical manifestations can be directly related to the extreme rheological changes in RBCs containing hemoglobin S (47,48). Other examples of hematological diseases with hemorheological consequences include various hemoglobinopathies (e.g., thalasemia), membrane protein deficiencies (e.g., band 4.2 deficiency) and enzyme deficiencies (e.g., glucose-6-phosphate deficiency) (49,50). A detailed discussion of the rheological alterations in hematological problems is outside the scope of this paper.

Non-clinical conditions

Not only disease processes, but certain extreme physiological conditions are also characterized by altered hemorheology. Strenuous exercise has been demonstrated to have significant effects on blood rheological parameters (51,52). The effect of exhausting exercise on RBC deformability was immediate, with a partial recovery in 15-30 min. There was a late component of the effect of this exhausting exercise starting at 60 min; this late effect was characterized by marked granulocytosis, altered RBC aggregation and further impairment in RBC deformability. It is quite possible that these hemorheological alterations play a role in exercise-related mortality (53). Alternatively, regular exercise (i.e. training) is known to increase RBC deformability and decrease blood viscosity, improving the rheological component of flow resistance. Additionally, recent evidence suggests that training may reduce the magnitude of the hemorheological alteration after exhaustive exercise (52,54), and therefore may have a protective effect against the expected hemodynamic extra-load.

The “chicken versus egg” story

The pathophysiological and clinical aspects of hemorheological alterations summarized above point out a special feature of blood rheology: alterations in hemorheological parameters might be the result of local and/or generalized disturbances in homeostasis. From another aspect, hemorheological alterations might be responsible for tissue perfusion problems and consequent functional deteriorations. It is not always easy to determine whether the hemorheological alteration is the cause or the result of a pathophysiological process.

This uncertainty about the exact nature of hemorheological alteration did not keep the medical scientists from studying hemorheological alterations in a very wide range of clinical disorders and extreme physiological conditions. The development of techniques to measure hemorheological parameters (e.g., blood and plasma viscosity, and RBC deformability and aggregation)

encouraged clinicians to study hemorheological parameters in blood samples obtained from their patients. They reported statistically significant hemorheological alterations in a variety of pathophysiological conditions.

Pathophysiological significance: Hemorheological alterations

Hemorheological alterations in various clinical disorders were statistically significant; however, the pathophysiological significance of these alterations is debatable. The main reason for this discrepancy is the experimentally detected differences between in vivo and ex vivo (i.e. outside of the vascular network) rheological behaviors of blood tissue (55,56). Therefore, it is not possible to apply the results of ex vivo measurements directly to in vivo flow conditions.

Calculations based on perfusion pressure and blood flow measurements obtained under real flow conditions revealed that blood viscosity in vivo is lower than the value measured ex vivo, using rotational viscometers (3). The underlying reasons for this difference can be understood by examining the composition of blood in various segments of the vascular system. Careful experimental studies indicated that especially the cellular content of blood at different levels of circulatory system varies over a wide range (57-59). This variation is even true for different positions at the cross-section of a single blood vessel (60). Particles that can adapt themselves to hydrodynamic forces (e.g., deformable particles like RBCs) tend to move to the central regions of tubes, a more "silent" region in terms of hydrodynamic forces (61,62). This phenomenon is called axial migration and in blood vessels results in a plasma-rich zone near the vessel wall (Figure 2), with relatively lower RBC content (i.e. lower hematocrit). The side branches of these vessels are fed by this marginal stream with lower hematocrit (plasma skimming), leading to significantly lower hematocrit values in blood vessels smaller than 500 μm in diameter (tissue hematocrit), compared to samples obtained from large blood vessels. It has been demonstrated that mean hematocrit values in these vessels directly perfusing tissues might be as low as 40-50% of systemic hematocrit (58,59). Therefore, the composition of blood samples obtained from large blood vessels may not represent the blood in all blood vessels.

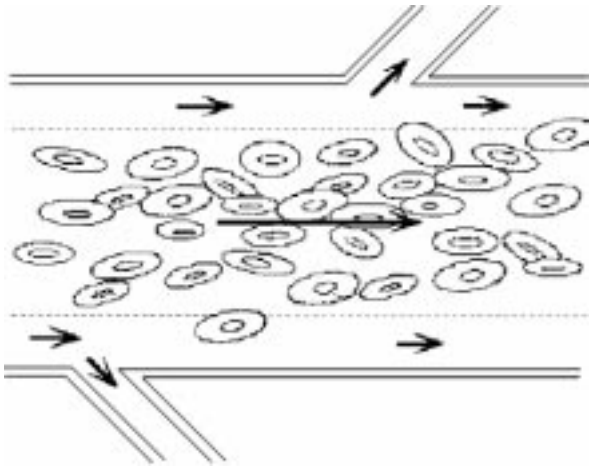

Figure 2. Accumulation of RBCs in the central flow zone. Side branches of this vessel are fed by the plasma-rich zone and have lower hematocrit values compared to the main vessel (Redrawn from 3).

The fluid zone closest to the vessel wall has the greatest contribution to flow resistance, as the frictional energy loss in this region is maximal (61,62). Frictional resistance in this zone is determined by the velocity of fluid layers and viscosity in this region. Decreased RBC concentration and the related drop in viscosity result in decreased local hydrodynamic resistance and also affect general hydrodynamic resistance in the whole vascular system. Alterations in either plasma composition or in cellular properties may influence the thickness and composition of this zone. Increased RBC aggregation was demonstrated to increase the thickness of this plasma-rich zone by increasing the axial migration of RBCs (60). A series of experimental studies revealed that blood flow resistance may decrease due to increased RBC aggregation, especially in low shear rate zones (63-65). It can be concluded from the above discussion that the composition, fluidity and contribution to the flow resistance of blood strongly depend on the flow conditions and cannot be fully described based on simple rheological measurements obtained ex vivo.

The contribution of RBC deformability to flow resistance in vivo is more clearly understood. RBC deformability may affect flow resistance at various levels of the circulatory system with different hemodynamic conditions. Blood viscosity under bulk flow conditions (i.e. blood flow in large blood vessels) is mainly affected by the orientation of RBCs to the flow streamlines, reducing the frictional resistance (viscosity) between

them (12,13). The degree of this orientation is a direct function of deformability. Flow velocity becomes smaller as blood moves towards the microcirculation and RBC aggregation dominates in determining blood fluidity and flow resistance. However, as the blood approaches blood vessels with diameters comparable with the size of the cellular elements, then the ability to adopt a new shape becomes the only important factor determining the transit of these elements through microcirculation (66). However, despite this clear logic behind the role of RBC deformability in hemodynamics, there is no consensus on the degree of alteration in deformability that may result in tissue perfusion problems (67).

There is also accumulating evidence for the significant role for WBCs' rheological properties in pathophysiological processes (68). It is well established that WBCs' mechanical properties change extensively during the activation process of these cells (69,70). It has been demonstrated that WBCs may significantly affect microvascular blood flow, despite their relatively small numbers (68). In contrast, WBCs have no effect on the rheological properties of blood studied ex vivo.

Pathophysiological significance: Normal versus geometrically challenged vascular bed

Vascular geometry is the most important determinant of blood flow in a given vascular network, as described by J.M. Poiseuille in 19th century. The importance of vascular geometry is amplified by the fact that blood vessel diameter is a regulated parameter (71). It is well known that the diameter of resistance arteries is controlled by powerful regulatory mechanisms, on one hand determining the peripheral resistance in the circulatory system, and on the other hand blood flow to the microcirculatory network. The adequacy of microcirculatory blood flow is the control parameter of this regulatory mechanism.

Vascular geometry is altered by changing the vascular smooth muscle tone. The most important determinant of vascular smooth muscle tone is the metabolic demand of the perfused tissue (71,72). Any imbalance between the supplied blood flow and metabolic demands of the tissue results in altered smooth muscle tone, aiming at eliminating the imbalance. Therefore, under normal, physiological conditions any disturbance of the tissue perfusion resulting from a hemorheological alteration (e.g., increased blood viscosity, impaired RBC deformability) can be corrected by compensatory changes in vascular hindrance. Obviously, in order to compensate for a hemorheological extra-load, the vascular network should be capable of decreasing the vascular hindrance enough to correct the imbalance introduced by altered hemorheology. In other words, there should be enough vasodilatory reserve to maintain sufficient blood flow with the continuing hemorheological extra-load. Figure 3 indicates that the degree of alteration in flow resistance with given hemorheological alterations (i.e. impairment in RBC deformability) strongly depends on the vascular control mechanisms. In an experiment conducted using an isolated-perfused rat hind limb preparation it was demonstrated that the change in flow resistance was about three fold that of the control in preparations with paralyzed smooth muscles (73). Based on this experiment, it can be argued that the degree of tissue perfusion problem induced by a certain degree of hemorheological alteration strongly depends on the vasodilatory reserve (74). Vasodilatory reserve can frequently be found to be diminished under clinical conditions and hemorheological alterations may induce dramatic manifestations under such conditions.

Hemorheological parameters may also affect vascular control mechanisms by modulating the nitric oxide (NO) output of endothelium. NO synthesis in endothelial cells is controlled by a variety of factors including the shear forces acting on the vessel wall (75). The shear forces

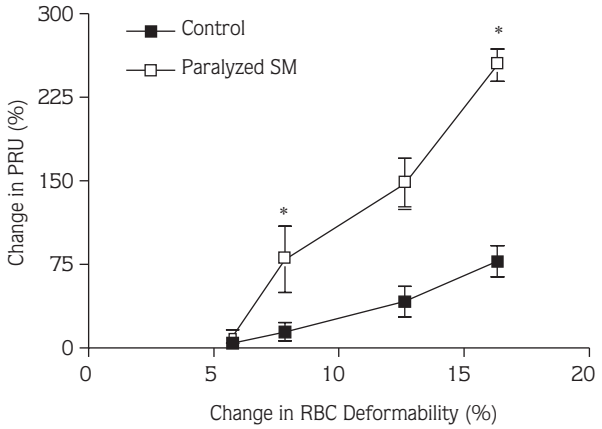

Figure 3. Change in flow resistance (PRU %) plotted against change in RBC deformability (%) induced by low concentration of glutaraldehyde, in isolated rat hind limb preparations. Vascular smooth muscle (SM) was paralyzed with 10^{-4} papaverin. Data is presented as mean ± standard deviation. (n=4; *: Difference from control, $P < 0.05$).

near the vessel wall are in turn determined by the blood flow rate and the viscosity of fluid in close contact with the endothelial cells (76). The composition and the viscosity of blood in the marginal region of the blood vessels are known to be influenced by the rheological properties of blood and blood cells (e.g., RBC aggregation). It has been demonstrated that chronically enhanced RBC aggregation results in down regulation of NO-related control mechanisms of skeletal muscle resistance arteries in rats (77)).

Conclusion

The understanding of pathophysiological significance of blood rheological alterations in disease processes is seriously challenged by experimental observations that demonstrate discrepancies between the ex vivo and in vivo behavior of blood. This disagreement can be explained in part by hemodynamic mechanisms such as the axial migration of RBC, plasma skimming and reduced tissue hematocrit. However, the detailed understanding of the role of vascular control mechanisms and especially the vasodilatory reserve is equally important from a pathophysiological point of view. Hemorheological alterations can be well tolerated by these mechanisms, if there is enough vasodilatory reserve. However, if the vascular system is geometrically challenged tissue perfusion problems might be clinically manifested.

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