Iatrogenic Hyperviscosity and Thrombosis

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Abstract

It is well known that hemostatic–thrombotic mechanisms are influenced by hemodynamic factors, such as shear forces affecting platelets or red blood cell aggregation, in turn affecting flow in stenotic regions. Endothelial cell function is also significantly influenced by shear forces acting on the vessel wall. Further, the distribution of shear forces in the vasculature is complex and closely associated with factors determining the flow properties of blood. Therefore, there is a link among alterations in the rheological properties of blood and its elements and the risk for thrombosis, with this linkage confirmed by numerous clinical studies. After discussing relevant rheological and hemodynamic concepts, this review focuses on selected drug-induced conditions that are known to be associated with both hyperviscosity conditions and increased thrombotic risk: oral contraceptives, diuretics, intravenous immunoglobulin, erythropoiesis-stimulating agents, chemotherapy, and radio-contrast media. Alterations of relationships between blood rheology and thrombotic risk related to artificial circulatory environments and physical exercise are also briefly discussed.

Keywords

- blood rheology
- erythrocyte deformability
- erythrocyte aggregation
- hemodynamics
- coagulation

Blood Flow in Vivo

Adequate blood flow is a critical requirement for normal physiological tissue and organ function. This critical requirement depends on three major determinants: pressure gradient, vessel geometry, and blood fluidity. Although these determinants of blood flow can be expressed in simplified mathematical models (e.g., Poiseuille law), the complex interrelations between them prevent the application of these simple models to in vivo flow conditions. These interrelations include, but are not limited to, the following:

- Pressure gradient in the vasculature is the determinant of wall shear stress, which in turn regulates vascular geometry. This effect on geometry is an additional role for pressure gradient beyond serving as the driving force for blood flow.
- Shearing conditions in a given vascular segment also affect the flow properties of blood (i.e., a non-Newtonian fluid), another variable influenced by the pressure gradient. The flow properties of blood, especially the mechanical properties of red blood cells (RBC), affect shear rate–

shear stress distributions over the cross-section of blood vessels.

- It is well recognized that hemostatic and thrombotic mechanisms are influenced by shear forces affecting platelets and/or endothelial cells. This last relationship introduces a connection to the pathological disturbance of blood flow, with the association to thrombosis involving all three major determinants of blood flow in the vasculature (i.e., pressure gradient, vessel geometry, and blood fluidity).

The significant contributions of RBC mechanical properties to blood flow dynamics, especially near the vessel wall, have important implications for hemostatic–thrombotic mechanisms. Therefore, the flow properties of blood are briefly described below with special emphasis on RBC rheological behavior.

Flow Properties of Blood and Shear Forces

Blood is a Non-Newtonian Fluid

Blood viscosity strongly depends on the effective shearing conditions.¹ Blood flow in most parts of the vascular system

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Fig. 1 Blood viscosity in centipoise (cP) measured at shear rates over the range of 0.01 to 1000 s^{-1} .

under physiological conditions is laminar; therefore, shearing conditions can be defined in terms of shear rate (i.e., the velocity gradient of lamellae across the cross-section of a blood vessel expressed as s^{-1}) or shear stress (the product of shear rate and local effective viscosity, expressed as dyn/cm^2 or Pascal). The difference in blood viscosity measured at high shear rate (i.e., $> 100 s^{-1}$) and low shear rate (i.e., $< 0.1 s^{-1}$) is on the order of 10^2 (►Fig. 1). Therefore, blood exhibits marked non-Newtonian flow behavior, and is characterized by a nonlinear shear rate–shear stress relationship; blood is thus a shear-thinning fluid whose viscosity decreases as shear rate increases.

The rheological properties of blood are determined by the fluid mechanical properties of plasma and cellular elements of blood and the relative proportion of these two phases (i.e., hematocrit). Plasma, the fluid phase of blood, is a Newtonian fluid whose viscosity is independent of shear rate. RBCs are the most numerous of blood cells, and hence the contribution of the cellular phase is mainly determined by RBC properties; in general, hematocrit has the greatest effect on viscosity and any increment above the physiological range results in exponential increases of viscosity.² This sensitivity of viscosity to hematocrit essentially amplifies the impact of RBC mechanical properties on blood viscosity; these properties are briefly described in the next section.

Red Blood Cells as Determinants of Non-Newtonian Behavior of Blood

It is well known that the presence of RBCs as the second phase of blood distorts the fluid lamellae, thereby increasing the resistance between them (i.e., increasing viscosity).³ The impact of RBCs on this resistance increase is determined by the cell's mechanical properties. Under sufficiently high shear forces, RBCs deform and alter their shape and orient to flow streamlines, thus reducing frictional resistance and hence viscosity; conversely, under low shear forces, RBCs form aggregates, increasing the lamellae distortion and impact of RBCs on blood viscosity. At constant hematocrit, blood viscosity in the high shear rate zone is mainly influenced by RBC deformability (i.e., the reversible shape change of RBCs under shear stress), while RBC aggregation (i.e., the reversible clumping of RBCs) is the major determinant of viscosity at low shear rates.

Red Blood Cell Deformability

RBC are highly evolved cells and are adapted for optimal transport of respiratory gases; their extreme simplicity is the basis for their remarkable ability to reversibly change shape when subjected to shear stress. The RBC cytoplasm is an amorphous solution of hemoglobin and other functionally important bio-molecules. The RBC membrane is an unique viscoelastic structure^{4,5} that maintains the biconcave-discoid shape of the cell at rest, yet allows it to easily adopt a new shape dictated by local shear forces.⁶ Note that the biconcave shape is also an important factor affecting the cell's ability to change shape because it provides excess membrane surface area for the contained volume and hence allows the cell to easily undergo shape changes without changes of membrane area.⁶ RBC deformability may be impaired in certain pathological conditions, including hemoglobinopathies (e.g., sickle cell anemia),^{7,8} altered cellular hydration,⁹ and enhanced oxidant stress.^{10,11}

Red Blood Cell Aggregation

RBCs tend to form regular, linear, face-to-face structures (i.e., rouleaux) at stasis or under very low shear forces; rouleaux can associate to form three-dimensional aggregates.¹² This aggregation is a reversible process (i.e., RBC dispersed by high shear reform rouleaux at low or zero shear) and is significantly different from irreversible agglutination that occurs as a result of immunological reactions. The extent of RBC aggregation, which can be expressed as the average number of RBCs in each aggregate under stable conditions, is a function of both plasma composition and cellular properties.¹³ RBC rouleaux formation requires the existence of high molecular weight macromolecules (e.g., fibrinogen, high-molecular weight dextrans) in the suspending medium.

RBC aggregate size strongly correlates with plasma fibrinogen concentration, and therefore aggregate size is significantly enhanced in inflammatory conditions leading to acute phase reactions.¹² RBC aggregation may also be enhanced due to changes in RBC surface properties such as those encountered in sepsis,^{14–16} diabetes mellitus,^{17,18} and hypertension.^{19,20}

Red Blood Cell Properties and the Distribution of Shear Forces in Blood Vessels

RBC properties are important determinants of blood viscosity, but they also influence the distribution of shear forces in blood vessels under physiological or pathological flow conditions. Fluid flow in a cylindrical tube is characterized by a nonlinear velocity profile²¹ that, for a Newtonian fluid, can be estimated by the Navier-Stokes equation.²² The shape of this profile is parabolic and indicates that the shear rate (i.e., the velocity gradient) across a cylindrical tube or vessel is not constant, but rather changes from a minimum in the axial region to a maximum in the fluid layers adjacent to the wall (►Fig. 2). This velocity profile is significantly altered for blood flowing in a cylindrical vessel: because blood is a non-Newtonian fluid, the profile changes to a more blunted shape with the degree of blunting determined by the flow properties of blood (e.g., the level of RBC aggregation) and flow conditions (e.g., flow rate) (►Fig. 2, dotted curve).^{23–25}

Fig. 2 Velocity profile in a cylindrical tube for a Newtonian fluid (solid line) and for strongly aggregating blood sample (dotted line). Velocity is shown as the percentage of the maximum velocity in the center of the tube, with axial position (i.e., distance from center) expressed normalized to the tube radius. The velocity profiles are calculated using the Navier-Stokes equation, with a bluntness parameter of 2 for a Newtonian fluid and hence a perfect parabolic profile, whereas a value of 4 was used for blood with red blood cells aggregation and a significantly blunted profile. Note the difference in the velocity gradient in the region close to the tube wall (i.e., for normalized distance from the center > 0.8).

The variation of shearing conditions over the cross-section of blood vessels is the basic cause of RBC axial migration and the development of a cell-poor region near the vessel wall; migration leads to various physiologically important processes such as plasma skimming and phase separation in the microcirculation, the Fahraeus Effect, and reduced microvascular-tissue hematocrit.²⁶ The axial accumulation of RBC is promoted by enhanced aggregation.^{23,27} As a result of these migration-related processes, blood composition and hence its rheological properties are not constant throughout the vasculature, but depend both on the axial position within a single vessel and the longitudinal position in the circulatory system. It should be noted that the axial migration of RBC has consequences in terms of the distribution of other blood elements such as platelets and white blood cells. Platelets preferentially accumulate in the marginal flow zone close to the vessel wall, with such accumulation beneficial for their function.^{28,29} However, this accumulation in the high-shear marginal flow zone may also have pathological implications in terms of platelet activation and thrombotic tendency (see section “Shear Forces and Platelet Activation”).

Bishop et al demonstrated that enhanced RBC aggregation results in significant blunting of the velocity profile and an increased shear rate in the marginal flow zone; the differences of velocity distribution between parabolic and blunted curves are shown in ▶Fig. 2.²³ These effects of elevated RBC

aggregation are due to enhanced axial migration and, for intense aggregation, the development of a flat profile known as plug-flow.^{30,31} Collectively, these effects have significant implications in terms of interactions between the functions of various blood elements, including RBC and platelets.

Hyperviscosity Syndromes

Alterations in any of the factors described in previous sections (i.e., plasma composition and viscosity, hematocrit, RBC deformability, and RBC aggregation) may lead to an impaired fluidity of blood (i.e., increased blood viscosity). Leukocytes are not among the frequent causes of hyperviscosity, unless they are present in very high numbers such as in leukemia.³² Note that the influence of RBC-related rheological factors strongly depend on the flow conditions, and therefore any alterations of these factors have a site-specific influence on in vivo blood flow. That is, the local shearing conditions in a given segment of the vasculature determine the impact of RBC deformability or aggregation on blood flow in that area; major differences of flow dynamics occur between arterial and venous vessels. The clinical manifestations of a given alteration in these factors might be influenced by their shear-dependence, as described earlier.

In general, the classical manifestations of a hyperviscosity syndrome include symptoms that may reflect circulatory failure (e.g., congestive heart failure). It may also include signs of neurological dysfunction and hemostatic failure. A detailed description and discussion of the hyperviscosity syndromes is beyond the scope of this review; excellent reviews can be found elsewhere.^{33–36}

Shear Forces and Thrombosis

Thrombosis is a complex pathophysiological process, involving factors associated with both the vessel wall and the blood elements. A detailed discussion of this process can be found elsewhere; this section only provides a brief summary of the influence of shear forces on various aspects of thrombosis. Shear stress has direct effects on blood elements involved in thrombosis (e.g., platelets) and on endothelial cell functions that may indirectly affect platelet function and the coagulation cascade. In addition, shear forces have been reported to influence various proteins that are involved in hemostatic-thrombotic events, such as von Willebrand factor.^{37,38}

Shear Forces and Platelet Activation

It is well known that the contribution of platelets to thrombosis is controlled by a variety of humoral and mechanical factors. Exposure of platelets to various experimental shear stress regimes has been reported to induce platelet activation.^{39–43} It is now well known that both the magnitude of shear stress and the exposure time to the stress are important in determining the platelet response.^{43,44} Rubenstein and Yin demonstrated that the integral of a shear stress–time curve predicts alterations in platelet function over a range of magnitude–exposure time combinations.⁴³

The molecular mechanisms of shear-induced platelet activation have not been fully elucidated, although the response

seems to be mediated by various receptors related to platelet activation by biochemical ligands, including purinergic P2X and P2Y receptor families that mediate activation by ATP and ADP, respectively.⁴⁵ An alternative mechanism for platelet activation by shear stress involves the von Willebrand factor interaction with platelet receptor GPIb and integrins, which in turn triggers the release of activating factors such as ADP and thromboxane A₂.^{45,46} The role of increased intracellular calcium concentration in shear stress-related activation response is controversial: such an increase was proposed to be involved in GPIb mediated activation,⁴⁷ but it has been reported that shear stress-induced platelet activation could not be blocked by an intracellular calcium inhibitor, suggesting that a calcium increment does not play a role in shear stress-induced platelet activation.⁴⁸

It is generally accepted that physiological levels of shear stress do not cause platelet activation, but even brief periods of exposure to supra-physiological shear stresses may either activate or sensitize platelets for further activation at lower shear stresses.⁴⁸ Such brief exposures to extreme values of shear stress may occur during flow through a stenotic region of the vasculature or in an artificial environment (e.g., artificial heart valves, extracorporeal circulation). Additionally, platelets may locally be exposed to shear stresses higher than the average levels estimated for a given blood vessel segment due to the radial variations in the shear rate-shear stress distributions (see "Red blood cell properties and the distribution of shear forces in blood vessels"). Shear rate and hence shear stress may be significantly enhanced in the marginal flow zone due to blunting of velocity profiles induced by alterations in the flow properties of blood.³¹ It should be noted that platelets tend to accumulate in this marginal flow zone due to the axial migration of RBCs,^{28,29} increasing the probability of exposure to high local shear stress near the vessel wall.

Shear stress may also influence the plasmatic factors involved in platelet aggregation-activation, such as von Willebrand factor.³⁷ It has been demonstrated that increased shear stress increases the adhesive activity of von Willebrand factor, and may play a role in the development of arterial thrombosis.^{37,38}

Role of Shear Forces in Endothelial Cell Maintenance

Hemodynamic shear stress is a requirement for maintenance of the normal, quiescent status of endothelial cells.^{49,50} The quiescent endothelium has anticoagulant and antithrombotic properties owing to the expression of various factors such as prostaglandin I₂, nitric oxide, and thrombomodulin, which tend to inhibit platelet activation-aggregation and the coagulation cascade.⁵¹⁻⁵⁵ Alterations of shear stress patterns in the vasculature may result from disturbed flow (e.g., shift to turbulent flow in stenotic vascular regions), reduction of average blood flow (e.g., heart failure) or alterations of the flow properties of blood.^{52,54,55} It has been argued that plasma viscosity is a significant determinant of endothelial function and plays an important role in the maintenance of normal vascular resistance.^{56,57} Further, it has been experimentally demonstrated that alterations of RBC aggregation influence endothelial cell function.^{58,59}

Relationship of Hyperviscosity to Thrombosis

There is a well-established body of evidence indicating the relationship of blood hyperviscosity with thrombosis, including clinical correlations and mechanisms of interactions.^{34,35,60,61} The overall pattern of the relationship between blood rheology and hemostatic mechanisms is complex and includes direct influences that are reciprocal. That is, blood rheology alterations affecting hemostatic-thrombotic mechanisms as well as thrombotic events with alterations resulting from disturbances of tissue perfusion affecting rheological factors.^{34,62,63} A limited number of clinical examples illustrating the reciprocal relationship are presented below.

Polycythemia vera is one of the best known examples of clinical conditions with altered hemostatic-thrombotic events together with hyperviscosity. It is a myeloproliferative disease, characterized by increased hematocrit and related hyperviscosity.^{34,64} Thrombosis is the major pathophysiological process leading to morbidity and mortality in polycythemia vera, frequently being the presenting manifestation.⁶⁵ Thrombotic risk in polycythemia vera is especially high in patients with cardiovascular risk factors.³⁴

Kwaan and Wang have listed the factors leading to thrombosis in polycythemia vera, including increased whole blood viscosity resulting from increased RBC mass and hematocrit, as well as increased RBC aggregation, as important contributors to low-shear blood viscosity.³⁴ Their list also includes activation of platelets, leukocytes, and endothelial cells; any alterations of blood rheology factors as discussed in section "Shear Forces and Thrombosis" may enhance these activation processes, which become secondary contributors to hyperviscosity and thrombotic tendency. Increased RBC aggregation has been demonstrated to enhance the axial accumulation of RBCs⁶⁶ and alter the wall shear stress in the vasculature, resulting in lower local nitric oxide bioavailability.^{58,59} This alteration of wall shear stress may be expected to influence platelet functions and hemostatic mechanisms because of the role of nitric oxide in maintaining the quiescent status of endothelial cells and platelets.⁶⁷

Enhanced hematocrit in polycythemia vera may have a direct influence on flow distribution, with different hemodynamic results depending on the location in the vasculature. Blood flow is expected to be significantly reduced, especially in low-shear regions (e.g., in venous vessels, venous valves) due to the exponential increase in viscosity at hematocrit values above the physiological range.² This effect is further enhanced by RBC aggregation, which is also favored at high hematocrits¹²; the slow flowing aggregated blood, often termed *blood sludge*, has been accepted as one of the reasons for increased thrombotic tendency. Further, high hematocrits amplify the influence of RBC axial migration on the margination of platelets and increase the bluntness of the velocity profile (see section "Red Blood Cell Properties and the Distribution of Shear Forces in Blood Vessels" and **Fig. 2**). Combined, these two consequences of enhanced hematocrit result in exposure of platelets to higher shear forces and hence

activation (see section "Shear Forces and Platelet Activation"). Reducing the hematocrit to physiological levels significantly decreases thrombotic risk; common practice aims at reducing hematocrit to 44% by phlebotomy and/or cytoreductive therapy as needed.^{34,64,68} It should be noted that there are factors, independent from hyperviscosity, that affect hemostatic mechanisms in polycythemia vera and that are associated with the thrombotic risk and bleeding tendency seen in some patients.^{34,62}

Other clinical examples of hyperviscosity that might be associated with enhanced thrombotic risk include malignancies. It is widely accepted that there is a very significant increase of thrombotic events in patients with various types of cancer.^{69–72} A number of tumor cells, including breast and ovarian cancer cells, have been shown to express procoagulant activity, thus explaining the activation of coagulation cascade in cancer patients.⁶⁰ Although this hemostatic tendency can be kept under control with adequate blood flow in the vasculature, impaired blood fluidity and reduced blood flow shifts the critical balance toward manifestations of clinical thrombosis by reducing the wash-out of activated coagulation factors.⁶⁰ The reduced wash-out of emboli due to hemorheologic impairment has been proposed to be an important mechanisms for the serious complications of hyperviscosity syndromes.^{73,74} In an analysis of data from a relatively large group of patients with gynecological cancers, von Tempelhoff reported a significant relationship between the determinants of blood fluidity and thrombotic risk.⁶¹

Drug-Induced Hyperviscosity Syndromes

Oral Contraceptives

The absolute rate of venous thromboembolism in young women is low, but the use of combined oral contraceptives (OCs) increases this rate three- to five-fold; several studies have explored the effects of these agents on hemorheologic parameters, yet results are not always concordant. Plasma viscosity and fibrinogen levels were significantly higher in a study of 841 pre-menopausal women taking contraceptives containing desogestrel or gestodene,⁷⁵ whereas in postmenopausal women receiving methyl testosterone, plasma viscosity decreased but fibrinogen was elevated.^{76,77} Both blood viscosity and RBC aggregation can be elevated by OCs⁷⁸; low-dose triphasic OCs containing ethinyl estradiol plus gestodene either have no effect on blood rheology⁷⁹ or elevate plasma viscosity but not blood viscosity or fibrinogen.⁸⁰ Ethinyl estradiol plus desogestrel significantly increases hematocrit, yet interestingly, blood viscosity does not differ from control.⁸¹ Studies in which women took estrogen OCs report significant increases of hematocrit, blood viscosity, and fibrinogen but no alteration of plasma viscosity; the elevation of blood viscosity remained significant after an adjustment for hematocrit.⁸² OCs abolish cyclical changes of hematocrit, RBC deformability, fibrinogen, and plasma and whole blood viscosity, and increases these parameters by an amount potentially predisposing to thrombosis⁸³; OCs appear to have no effect on RBC deformability and surface charge.⁸⁴

Radio-Opaque Contrast Media

The effects of radio-opaque contrast media (CM) on blood rheology, tissue perfusion, and renal function have been extensively studied, with the results highly dependent on CM viscosity, osmolality, ionic strength, concentration, and whether in vitro mixtures or ex vivo samples were studied. Although not very common, there are reports of thrombotic complications associated with radiological interventions involving the usage of CM.⁸⁵ Mixtures of CM and blood exhibit elevated high shear blood viscosity, higher plasma viscosity and, depending on the specific CM, echinocytic RBC^{86–89}; low shear viscosity is reduced presumably due to reduced RBC aggregation.^{86,87} Studies in which blood is sampled following CM injection generally indicate that hematocrit, plasma viscosity, and RBC aggregation are reduced,⁹⁰ with the extent of these changes greater with larger infusion volumes and higher viscosity CM. Nail-bed capillary perfusion (i.e., RBC velocity) is significantly reduced at 10 seconds postinjection and persists for up to 6 minutes when using high-viscosity media but is unaltered for low-viscosity CM.⁹¹

Diuretics

In theory, use of diuretics in hypertension therapy has several potential adverse rheological effects: (1) increased hematocrit; (2) increased blood viscosity; (3) increased plasma viscosity due to elevated levels of plasma proteins; and (4) enhanced RBC aggregation caused by higher plasma levels of pro-aggregating proteins (e.g., fibrinogen). Literature reports in this area do not agree, most likely due to differences of protocol and/or data analysis. Studies involving thiazides have indicated: unchanged hemorheologic parameters⁹²; no difference in plasma viscosity, hematocrit, and RBC aggregation⁹³; increased blood viscosity after 2 months of therapy⁹⁴; unchanged hematocrit, plasma viscosity, and blood filterability; a tendency for higher blood viscosity and faster and stronger RBC aggregation⁹⁵; and increased plasma viscosity, fibrinogen, and RBC rigidity.⁹⁶ Mannitol causes a transient fall of blood viscosity and hematocrit that returns to control at 2 to 4 hours postinfusion.⁹⁷

Studies by Muravyov and coworkers appear useful in understanding the diverse effects of diuretics.⁹⁸ In their study, 82 subjects were classified as having high (H) or low (L) high shear blood viscosity, following which subjects in the two groups were randomly assigned to a thiazide, ACE-inhibitor, calcium antagonist, or a beta-1-blocker; various parameters were measured prior to and following 6 weeks of therapy. Their results indicate that the hemorheologic effects of these agents strongly depend on the initial, pre-treatment status of the subject. In the L group, therapy resulted in significantly increased plasma and whole blood viscosity, whereas in the H group, there was a significant reduction of these two viscosity parameters. Fibrinogen levels and RBC aggregation decreased in both groups, and hematocrit did not change. Their results indicate that pooling of subject data without regard to initial findings is inappropriate, and that for some subjects, antihypertensive therapy can result in adverse hemorheologic alterations.

Administration of diuretics has been reported to cause changes in the coagulation system that could favor

thrombosis. Bird and Carmona report a case in which the addition of the loop diuretic torsemide to the therapeutic regimen of an individual effectively anticoagulated with warfarin caused a twofold increase in the subject's INR and required a substantial reduction of warfarin dosage.⁹⁹ Conversely, the initiation of furosemide dosing in a patient receiving a stable dose of warfarin decreased the INR by about 30%, possibly suggesting a diuretic-specific effect with warfarin therapy.¹⁰⁰ Thiazides can adversely affect endogenous fibrinolytic activity, although their use in combination with an aldosterone antagonist decreases the hypofibrinolytic side effects.¹⁰¹ Alterations of fibrinolytic function in diuretic-induced volume depletion have been reported: 10 days of treatment with hydrochlorothiazide significantly increased plasminogen activator inhibitor-1 (PAI-1) antigen as well as PAI-1 activity.¹⁰²

Intravenous Immunoglobulin

Intravenous immunoglobulin (Ig) is a commonly used therapy for autoimmune disease and, in some reports, is associated with cardiovascular or cerebrovascular events.^{103,104} The rheological effects of infused Ig are twofold: (1) increased plasma, serum, and blood viscosity; and (2) enhanced RBC aggregation. The magnitude of these changes depends on the therapy protocol, sampling time (i.e., acute or chronic), and plasma levels of Ig.¹⁰⁵ Several reports have demonstrated both the acute and cumulative increases of plasma and/or serum viscosity³⁶; given unchanged hematocrits, increases of high shear blood viscosity are proportionately related to the rise of plasma viscosity. Low shear blood viscosity is elevated due to increases of plasma viscosity and to enhanced RBC aggregation.^{103,106} Interestingly, RBC aggregation appears to be determined by the plasma levels of albumin and fibrinogen as well as that of Ig.^{107,108} Associations between Ig levels and thrombotic events have been shown, and it has been suggested that there is a symptomatic threshold for plasma viscosity beyond which such events become more frequent.¹⁰⁴

Stimulation of Erythropoiesis

Erythropoietin (Epo) is frequently used to stimulate RBC production in anemic patients, particularly those with renal disease who are on chronic dialysis. The goal is to increase hematocrit and hemoglobin and thus to increase arterial oxygen content. Hematocrit is a major determinant of blood viscosity: there is an exponential increase at high shear and greater sensitivity at low shear and stasis.^{109,110} Several studies have shown the expected influence of increased hematocrit,^{111,112} whereas some indicate increased hematocrit but lower viscosity.^{109,112,113} Such reports suggest or demonstrate that RBC in Epo therapy have improved deformability¹¹⁴ and that the improvement counters the effect of increased hematocrit. However, detailed analyses of RBC viscoelastic properties during Epo therapy do not appear to support this suggestion; a study in rats with EPO treatment indicated no change in the mean pore transit times of RBC, whereas the 5th percentile of transit times increased significantly, indicating the presence of a rigid subpopulation of

RBCs.¹¹⁵ Plasma viscosity can be elevated¹¹⁶ or unaltered.¹¹⁰ Relatively few investigations have explored total peripheral resistance (TPR) in Epo therapy; blood pressure and TPR have been reported to increase, yet it appears that not all of the TPR change is due to either increased viscosity or the loss of hypoxic vasodilation.¹¹⁷ In dialysis, mass transport of some clinically important solutes can be impaired due to elevated blood and/or plasma viscosity and to physical interference of solute transfer by RBCs.¹¹⁷ Treatment with erythropoiesis-stimulating agents has been considered to involve risks related to thrombotic complications and various other side effects, thus limiting their wider usage in clinical conditions.¹¹⁸

Chemotherapy

It is well known that there is higher thrombotic tendency in patients with malignant tumors and that this is associated with altered blood rheology^{60,70} as discussed in the section "Relationship of Hyperviscosity to Thrombosis." Cancer treatment, including chemotherapy, increases the thrombotic risk,^{61,119} and chemotherapy and radiotherapy are both associated with an increased rate of deep vein thrombosis.⁶¹ Such findings include breast cancer, uterine cancer, and ovarian cancer patients, and also in vitro effects of chemotherapeutic agents on factors that are relevant to hyperviscosity and thrombosis.⁶¹ von Tempelhoff proposed that chemotherapy may induce alterations in RBC deformability, aggregation, and plasma viscosity, mainly due to an increased rate of fibrinogen turnover.⁶⁰ It has been suggested that the activation of clotting factors alone may not cause thrombosis because under normal blood flow conditions, the activated factors are diluted, yet in the presence of hyperviscosity and decreased blood flow, the thrombotic risk would be significantly enhanced.⁶⁰

It should also be noted that hyperviscosity may in turn interfere with the efficiency of cancer therapy, due to decreased susceptibility of cancer cells to the therapeutic as a result of reduced oxygenation.^{61,120} Furthermore, behavior of circulating cancer cells might be affected by blood rheology factors; hyperviscosity may result in flow reduction, increasing the probability for extravasation of the cancer cell. This behavior of tumor cells might be further promoted by enhanced RBC aggregation, displacing them to the peripheral flow zone of the blood vessels as axial accumulation of RBCs will be promoted.⁶¹ Therefore, it has been discussed that the efficiency of the cancer therapy and prognosis are significantly influenced by hyperviscosity, if present.¹²⁰

Other Iatrogenic Hyperviscosity Syndromes

Artificial Organs and Extracorporeal Devices in Contact with Blood

There are a variety of biomedical devices that come into contact with blood to perform their function, including hemodialysis equipment, cardiopulmonary bypass systems, ventricular assist devices, and heart valves.¹²¹⁻¹²⁴ It is well known that blood is exposed to nonphysiologic shearing

environments in such devices and encounters mechanical damage.¹²¹ The mechanical damage has a spectrum ranging from sub-lethal cellular damage to cell rupture and hemolysis; such damage can be detected in terms of alterations of RBC mechanical properties, leukocyte activation, or enhanced thrombotic tendency.¹²¹

Hemodialysis is known to cause hemoconcentration and increased hematocrit, as well as increased plasma viscosity, which is a manifestation of increased plasma protein concentration.¹²⁵ This alteration of plasma proteins also results in enhanced RBC aggregation.^{125,126} Impaired RBC deformability has been reported by various groups,^{127,128} with similar alterations of RBC mechanical properties observed in patients undergoing cardiopulmonary bypass.¹²¹

The use of artificial organs and extracorporeal devices causes a significant increase of risk for thrombotic events.¹²⁹ Ocak, et al reported that the incidence of venous thrombosis was 5.6 times higher in hemodialysis patients, and was associated with a 11.9 times higher incidence of myocardial infarction and a 9.6 times higher incidence of ischemic stroke.¹²⁹ Hemolysis contributes to the enhanced thrombotic tendency of blood exposed to nonphysiological shear stresses in artificial organs, mainly due to the activation of platelets by the free hemoglobin in plasma.¹³⁰ Free hemoglobin also affects endothelial function and influences nitric oxide bioavailability,¹²¹ which in turn contributes to the activation of endothelium and platelets and hence greater thrombotic risk. Altered RBC rheological properties (e.g., enhanced RBC aggregation) also influence platelet distribution and activation by changing intravascular hemodynamics (see section "Red Blood Cell Properties and the Distribution of Shear Forces in Blood Vessels").

Although hemolytic mechanical damage to blood has been reduced by improved designs of modern artificial organs and equipment, sub-hemolytic blood trauma may still play a significant role in the complications (e.g., thrombotic risk) that adversely affect the safety and efficacy of such devices.¹²¹ This possibility should be considered when reviewing regulations for testing biomedical equipment that have contact with blood.

Physical Exercise and Sports

Regular physical exercise is widely recommended for reducing the risk of thrombotic events and thus the associated morbidity and mortality. However, acute strenuous exercise is also known to induce alterations of blood viscosity factors, even in healthy individuals.^{131,132} Acute dehydration and consequent reduction in plasma volume and increased hematocrit,¹³³ impaired RBC deformability,^{133,134} and altered RBC aggregation^{135,136} have been reported in human subjects undergoing exercise. Thrombotic events have been reported to be associated with such rheologic alterations following episodes of exercise.^{137–139} Hemostatic-thrombotic mechanisms affected by physical exercise have been studied in detail, and excellent reviews exist.^{138–140} It has been demonstrated that fluid mechanical factors may play significant roles in exercise-related activation of hemostatic mechanisms.¹³⁹

It has been suggested that in some cases, sudden death events during and/or following heavy exercise might be related to thrombotic events,^{137,141} although evidence supporting hyperviscosity in such cases is usually not available. The risk of exercise-induced hyperviscosity and related thrombosis may be higher in subjects with conditions such as sickle-cell trait.¹⁴² Adequate hydration during exercise has been demonstrated to be effective in limiting hemorheologic alterations, and has the potential to prevent subsequent risk in such subject groups.¹³⁹ Exercise training has also been reported to reduce the risk of acute exercise-induced morbidity and mortality.^{131,138} Exercise-related morbidity and mortality may occasionally be encountered in professional sports activities.

A serious source of health problems in sports is related to the hyperviscosity and enhanced thrombosis potential consequent to an intervention known as "blood doping."^{143,144} This is a widely used method for increasing circulating RBC mass, with the goal of increasing blood's oxygen-carrying capacity.¹⁴⁴ Self-transfusion of previously obtained and stored blood (i.e., blood doping) was one of the preferred methods in the past due to the lack of proper methods to detect the transfusion, but recent developments have allowed detection.¹⁴⁵ Blood doping has serious cardiovascular complications, mainly resulting from the hyperviscosity.¹⁴⁶ Additional treatments to increase hematocrit include injections of erythropoiesis-stimulating agents (i.e., erythropoietin derivatives; see section "Stimulation of Erythropoiesis") and androgenic anabolic steroids, both of which have the potential for inducing hyperviscosity and thrombotic events.

Conclusion

It is obvious from the discussion in the first four sections of this review that the factors determining fluid mechanical properties of blood and hemostatic/thrombotic mechanisms are interrelated. Therefore, any alterations in blood rheology factors (e.g., increased plasma and whole blood viscosity, decreased RBC deformability, greater RBC aggregation) should be expected to increase the risk of thrombotic events. Rheologic factors may be altered in a wide variety of physiological and pathological conditions and during medical therapy, and thus such possible alterations should be considered even in the absence of overt signs of hyperviscosity.

References

- 1 Cokelet GR. Hemorheology and Hemodynamics. San Francisco, CA: Morgan & Claypool Life Sciences; 2011
- 2 Cokelet GR, Meiselman HJ. Macro- and micro-rheological properties of blood. In: Baskurt OK, Hardeman MR, Rampling MW, Meiselman HJ, eds. Handbook of Hemorheology and Hemodynamics. Amsterdam, Netherlands: IOS Press; 2007:45–71
- 3 Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. *Semin Thromb Hemost* 2003;29(5):435–450
- 4 Mohandas N, Chasis JA. Red blood cell deformability, membrane material properties and shape: regulation by transmembrane, skeletal and cytosolic proteins and lipids. *Semin Hematol* 1993;30(3):171–192

- 5 Takakuwa Y, Ishibashi T, Mohandas N. Regulation of red cell membrane deformability and stability by skeletal protein network. *Biorheology* 1990;27(3-4):357-365
- 6 Chien S. Red cell deformability and its relevance to blood flow. *Annu Rev Physiol* 1987;49:177-192
- 7 Alexy T, Sangkatumvong S, Connes P, et al. Sick cell disease: selected aspects of pathophysiology. *Clin Hemorheol Microcirc* 2010;44(3):155-166
- 8 Vayá A, Iborra J, Falcó C, et al. Rheological behaviour of red blood cells in beta and deltabeta thalassemia trait. *Clin Hemorheol Microcirc* 2003;28(2):71-78
- 9 Baskurt OK. Mechanisms of blood rheology alterations. In: Baskurt OK, Hardeman MR, Rampling MW, Meiselman HJ, eds. *Handbook of Hemorheology and Hemodynamics*. Amsterdam, Netherlands: IOS Press; 2007:170-190
- 10 Baskurt OK, Temiz A, Meiselman HJ. Effect of superoxide anions on red blood cell rheologic properties. *Free Radic Biol Med* 1998;24(1):102-110
- 11 Hebbel RP, Leung A, Mohandas N. Oxidation-induced changes in microrheologic properties of the red blood cell membrane. *Blood* 1990;76(5):1015-1020
- 12 Baskurt OK, Neu B, Meiselman HJ. *Red Blood Cell Aggregation*. Boca Raton, Florida: CRC Press; 2011
- 13 Rampling MW, Meiselman HJ, Neu B, Baskurt OK. Influence of cell-specific factors on red blood cell aggregation. *Biorheology* 2004;41(2):91-112
- 14 Alt E, Amann-Vesti BR, Madl C, Funk G, Koppensteiner R. Platelet aggregation and blood rheology in severe sepsis/septic shock: relation to the Sepsis-related Organ Failure Assessment (SOFA) score. *Clin Hemorheol Microcirc* 2004;30(2):107-115
- 15 Baskurt OK, Temiz A, Meiselman HJ. Red blood cell aggregation in experimental sepsis. *J Lab Clin Med* 1997;130(2):183-190
- 16 Berliner AS, Shapira I, Rogowski O, et al. Combined leukocyte and erythrocyte aggregation in the peripheral venous blood during sepsis. An indication of commonly shared adhesive protein(s). *Int J Clin Lab Res* 2000;30(1):27-31
- 17 Chong-Martinez B, Buchanan TA, Wenby RB, Meiselman HJ. Decreased red blood cell aggregation subsequent to improved glycaemic control in Type 2 diabetes mellitus. *Diabet Med* 2003;20(4):301-306
- 18 Zilberman-Kravits D, Harman-Boehm I, Shuster T, Meyerstein N. Increased red cell aggregation is correlated with HbA1C and lipid levels in type 1 but not type 2 diabetes. *Clin Hemorheol Microcirc* 2006;35(4):463-471
- 19 Cicco G, Pirrelli A. Red blood cell (RBC) deformability, RBC aggregability and tissue oxygenation in hypertension. *Clin Hemorheol Microcirc* 1999;21(3-4):169-177
- 20 Lebensohn N, Re A, Carrera L, Barberena L, D'Arrigo M, Foresto P. [Serum sialic acid, cellular anionic charge and erythrocyte aggregation in diabetic and hypertensive patients]. *Medicina (B Aires)* 2009;69(3):331-334
- 21 Reneman RS, Arts T, Hoeks APG. Wall shear stress—an important determinant of endothelial cell function and structure—in the arterial system in vivo. Discrepancies with theory. *J Vasc Res* 2006;43(3):251-269
- 22 Katritsis D, Kaiktsis L, Chaniotis A, Pantos J, Efstathiopoulos EP, Marmarelis V. Wall shear stress: theoretical considerations and methods of measurement. *Prog Cardiovasc Dis* 2007;49(5):307-329
- 23 Bishop JJ, Popel AS, Intaglietta M, Johnson PC. Effects of erythrocyte aggregation and venous network geometry on red blood cell axial migration. *Am J Physiol Heart Circ Physiol* 2001;281(2):H939-H950
- 24 Bishop JJ, Popel AS, Intaglietta M, Johnson PC. Effect of aggregation and shear rate on the dispersion of red blood cells flowing in venules. *Am J Physiol Heart Circ Physiol* 2002;283(5):H1985-H1996
- 25 Gaehtgens P, Meiselman HJ, Wayland H. Velocity profiles of human blood at normal and reduced hematocrit in glass tubes up to 130 diameter. *Microvasc Res* 1970;2(1):13-23
- 26 Goldsmith HL, Cokelet GR, Gaehtgens P. Robin Fåhræus: evolution of his concepts in cardiovascular physiology. *Am J Physiol* 1989;257(3 pt 2):H1005-H1015
- 27 Ong PK, Jain S, Kim S. Temporal variations of the cell-free layer width may enhance NO bioavailability in small arterioles: effects of erythrocyte aggregation. *Microvasc Res* 2011;81(3):303-312
- 28 Goldsmith HL, Bell DN, Spain S, McIntosh FA. Effect of red blood cells and their aggregates on platelets and white cells in flowing blood. *Biorheology* 1999;36(5-6):461-468
- 29 Nash GB, Watts T, Thornton C, Barigou M. Red cell aggregation as a factor influencing margination and adhesion of leukocytes and platelets. *Clin Hemorheol Microcirc* 2008;39(1-4):303-310
- 30 Bishop JJ, Popel AS, Intaglietta M, Johnson PC. Rheological effects of red blood cell aggregation in the venous network: a review of recent studies. *Biorheology* 2001;38(2-3):263-274
- 31 Bishop JJ, Nance PR, Popel AS, Intaglietta M, Johnson PC. Effect of erythrocyte aggregation on velocity profiles in venules. *Am J Physiol Heart Circ Physiol* 2001;280(1):H222-H236
- 32 Rampling MW. Hyperviscosity as a complication in a variety of disorders. *Semin Thromb Hemost* 2003;29(5):459-465
- 33 Isbister JP. Hyperviscosity: clinical disorders. In: Baskurt OK, Hardeman MR, Rampling MW, Meiselman HJ, eds. *Handbook of Hemorheology and Hemodynamics*. Amsterdam, Netherlands: IOS Press; 2007:371-391
- 34 Kwaan HC, Wang J. Hyperviscosity in polycythemia vera and other red cell abnormalities. *Semin Thromb Hemost* 2003;29(5):451-458
- 35 Kwaan HC, Bongu A. The hyperviscosity syndromes. *Semin Thromb Hemost* 1999;25(2):199-208
- 36 Kwaan HC. Role of plasma proteins in whole blood viscosity: a brief clinical review. *Clin Hemorheol Microcirc* 2010;44(3):167-176
- 37 Tsai HM. Shear stress and von Willebrand factor in health and disease. *Semin Thromb Hemost* 2003;29(5):479-488
- 38 Di Stasio E, De Cristofaro R. The effect of shear stress on protein conformation: physical forces operating on biochemical systems: the case of von Willebrand factor. *Biophys Chem* 2010;153(1):1-8
- 39 Anderson GH, Hellums JD, Moake J, Alfrey CP Jr. Platelet response to shear stress: changes in serotonin uptake, serotonin release, and ADP induced aggregation. *Thromb Res* 1978;13(6):1039-1047
- 40 Colantuoni G, Hellums JD, Moake JL, Alfrey CP Jr. The response of human platelets to shear stress at short exposure times. *Trans Am Soc Artif Intern Organs* 1977;23:626-631
- 41 Jesty J, Yin W, Perrotta P, Bluestein D. Platelet activation in a circulating flow loop: combined effects of shear stress and exposure time. *Platelets* 2003;14(3):143-149
- 42 Nobili M, Sheriff J, Morbiducci U, Redaelli A, Bluestein D. Platelet activation due to hemodynamic shear stresses: damage accumulation model and comparison to in vitro measurements. *ASAIO J* 2008;54(1):64-72
- 43 Rubenstein DA, Yin W. Quantifying the effects of shear stress and shear exposure duration regulation on flow induced platelet activation and aggregation. *J Thromb Thrombolysis* 2010;30(1):36-45
- 44 Hellums JD. 1993 Whitaker Lecture: biorheology in thrombosis research. *Ann Biomed Eng* 1994;22(5):445-455
- 45 Nesbitt WS, Mangin P, Salem HH, Jackson SP. The impact of blood rheology on the molecular and cellular events underlying arterial thrombosis. *J Mol Med (Berl)* 2006;84(12):989-995
- 46 Kroll MH, Hellums JD, McIntire LV, Schafer AI, Moake JL. Platelets and shear stress. *Blood* 1996;88(5):1525-1541
- 47 Nesbitt WS, Kulkarni S, Giuliano S, et al. Distinct glycoprotein Ib/V/IX and integrin alpha IIb beta 3-dependent calcium signals

- cooperatively regulate platelet adhesion under flow. *J Biol Chem* 2002;277(4):2965–2972
- 48 Sherif J, Bluestein D, Girdhar G, Jesty J. High-shear stress sensitizes platelets to subsequent low-shear conditions. *Ann Biomed Eng* 2010;38(4):1442–1450
 - 49 Michiels C. Endothelial cell functions. *J Cell Physiol* 2003;196(3):430–443
 - 50 Toborek M, Kaiser S. Endothelial cell functions. Relationship to atherogenesis. *Basic Res Cardiol* 1999;94(5):295–314
 - 51 Chien S. Molecular basis of rheological modulation of endothelial functions: importance of stress direction. *Biorheology* 2006;43(2):95–116
 - 52 Chiu JJ, Chien S. Effects of disturbed flow on vascular endothelium: pathophysiological basis and clinical perspectives. *Physiol Rev* 2011;91(1):327–387
 - 53 Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. *JAMA* 1999;282(21):2035–2042
 - 54 Traub O, Berk BC. Laminar shear stress: mechanisms by which endothelial cells transduce an atheroprotective force. *Arterioscler Thromb Vasc Biol* 1998;18(5):677–685
 - 55 Varin R, Mulder P, Richard V, et al. Exercise improves flow-mediated vasodilatation of skeletal muscle arteries in rats with chronic heart failure. Role of nitric oxide, prostanoids, and oxidant stress. *Circulation* 1999;99(22):2951–2957
 - 56 Tsai AG, Friesenecker B, McCarthy M, Sakai H, Intaglietta M. Plasma viscosity regulates capillary perfusion during extreme hemodilution in hamster skinfold model. *Am J Physiol* 1998;275(6 pt 2):H2170–H2180
 - 57 Tsai AG, Acero C, Nance PR, et al. Elevated plasma viscosity in extreme hemodilution increases perivascular nitric oxide concentration and microvascular perfusion. *Am J Physiol Heart Circ Physiol* 2005;288(4):H1730–H1739
 - 58 Baskurt OK, Yalcin O, Ozdem S, Armstrong JK, Meiselman HJ. Modulation of endothelial nitric oxide synthase expression by red blood cell aggregation. *Am J Physiol Heart Circ Physiol* 2004;286(1):H222–H229
 - 59 Yalcin O, Ulker P, Yavuzer U, Meiselman HJ, Baskurt OK. Nitric oxide generation by endothelial cells exposed to shear stress in glass tubes perfused with red blood cell suspensions: role of aggregation. *Am J Physiol Heart Circ Physiol* 2008;294(5):H2098–H2105
 - 60 von Tempelhoff GF, Nieman F, Heilmann L, Hommel G. Association between blood rheology, thrombosis and cancer survival in patients with gynecologic malignancy. *Clin Hemorheol Microcirc* 2000;22(2):107–130
 - 61 von Tempelhoff GF, Heilmann L, Hommel G, Pollow K. Impact of rheological variables in cancer. *Semin Thromb Hemost* 2003;29(5):499–513
 - 62 Cao M, Olsen RJ, Zu Y. Polycythemia vera: new clinicopathologic perspectives. *Arch Pathol Lab Med* 2006;130(8):1126–1132
 - 63 Tefferi A, Spivak JL. Polycythemia vera: scientific advances and current practice. *Semin Hematol* 2005;42(4):206–220
 - 64 Landolfi R, Nicolazzi MA, Porfida A, Di Gennaro L. Polycythemia vera. *Intern Emerg Med* 2010;5(5):375–384
 - 65 Barbui T, Finazzi G. Evidence-based management of polycythemia vera. *Best Pract Res Clin Haematol* 2006;19(3):483–493
 - 66 Fahraeus R. The influence of the rouleau formation of the erythrocytes on the rheology of the blood. *Acta Med Scand* 1958;161(2):151–165
 - 67 Loscalzo J. Nitric oxide insufficiency, platelet activation, and arterial thrombosis. *Circ Res* 2001;88(8):756–762
 - 68 Landolfi R, Cipriani MC, Novarese L. Thrombosis and bleeding in polycythemia vera and essential thrombocythemia: pathogenetic mechanisms and prevention. *Best Pract Res Clin Haematol* 2006;19(3):617–633
 - 69 Garcia D, Quintana D. Thrombosis and malignancy: a case-based review. *Semin Hematol* 2011;48(4):259–263
 - 70 Zahra S, Anderson JAM, Stirling D, Ludlam CA. Microparticles, malignancy and thrombosis. *Br J Haematol* 2011;152(6):688–700
 - 71 Contrino J, Hair G, Kreutzer DL, Rickles FR. In situ detection of tissue factor in vascular endothelial cells: correlation with the malignant phenotype of human breast disease. *Nat Med* 1996;2(2):209–215
 - 72 Zacharski LR, Memoli VA, Ornstein DL, Rousseau SM, Kisiel W, Kudryk BJ. Tumor cell procoagulant and urokinase expression in carcinoma of the ovary. *J Natl Cancer Inst* 1993;85(15):1225–1230
 - 73 Caplan LR, Hennerici M. Impaired clearance of emboli (washout) is an important link between hypoperfusion, embolism, and ischemic stroke. *Arch Neurol* 1998;55(11):1475–1482
 - 74 Sedlaczek O, Caplan L, Hennerici M. Impaired washout—embolism and ischemic stroke: further examples and proof of concept. *Cerebrovasc Dis* 2005;19(6):396–401
 - 75 Döring A, Fröhlich M, Löwel H, Koenig W. Third generation oral contraceptive use and cardiovascular risk factors. *Atherosclerosis* 2004;172(2):281–286
 - 76 Basaria S, Nguyen T, Rosenson RS, Dobs AS. Effect of methyl testosterone administration on plasma viscosity in postmenopausal women. *Clin Endocrinol (Oxf)* 2002;57(2):209–214
 - 77 El Bouhmedi A, Laffargue F, Raspal N, Brun JF. 100 mg acetylsalicylic acid acutely decreases red cell aggregation in women taking oral contraceptives. *Clin Hemorheol Microcirc* 2000;22(2):99–106
 - 78 Ernst E, Schmölzl C, Matrai A, Schramm W. Hemorheological effects of oral contraceptives. *Contraception* 1989;40(5):571–580
 - 79 Solerte SB, Fioravanti M, Spinillo A, Ferrari E, Guaschino S. Influence of triphasic oral contraceptives on blood rheology and hemostatic and metabolic patterns in young women. Results of a three-year study. *J Reprod Med* 1992;37(8):725–732
 - 80 Coata G, Ventura F, Lombardini R, Ciuffetti G, Cosmi EV, Di Renzo GC. Effect of low-dose oral triphasic contraceptives on blood viscosity, coagulation and lipid metabolism. *Contraception* 1995;52(3):151–157
 - 81 Ishak R, Khim LC. Effect of combined low-dose oral contraceptives on blood viscosity and haematocrit. *Malays J Reprod Health* 1991;9(1):5–8
 - 82 Lowe GDO, Drummond MM, Forbes CD, Barbenel JC. Increased blood viscosity in young women using oral contraceptives. *Am J Obstet Gynecol* 1980;137(7):840–842
 - 83 Buchan PC, Macdonald HN. Altered haemorheology in oral contraceptive users. *BMJ* 1980;280(6219):978–979
 - 84 Durocher JR, Weir MS, Lundblad EG, Patow WE, Conrad ME. Effect of oral contraceptives and pregnancy on erythrocyte deformability and surface charge. *Proc Soc Exp Biol Med* 1975;150(2):368–370
 - 85 Reiner JS. Contrast media and clotting: what is the evidence? *Catheter Cardiovasc Interv* 2010;75(Suppl 1):S35–S38
 - 86 Hardeman MR, Goedhart P, Koen IY. The effect of low-osmolar ionic and nonionic contrast media on human blood viscosity, erythrocyte morphology, and aggregation behavior. *Invest Radiol* 1991;26(9):810–819
 - 87 Laurent A, Durussel JJ, Dufaux J, et al. Effects of contrast media on blood rheology: comparison in humans, pigs, and sheep. *Cardiovasc Intervent Radiol* 1999;22(1):62–66
 - 88 Reinhart WH, Pleisch B, Harris LG, Lütolf M. Influence of contrast media (iopromide, ioxaglate, gadolinium-DOTA) on blood viscosity, erythrocyte morphology and platelet function. *Clin Hemorheol Microcirc* 2005;32(3):227–239
 - 89 Smedby O. Viscosity of some contemporary contrast media before and after mixing with whole blood. *Acta Radiol* 1992;33(6):600–605
 - 90 Scheller B, Hennen B, Thünenkötter T, et al. Effect of X-ray contrast media on blood flow properties after coronary angiography. *Thromb Res* 1999;96(4):253–260

- 91 Spitzer S, Münster W, Sternitzky R, Bach R, Jung F. Influence of Iodixanol-270 and Iopentol-150 on the microcirculation in man: influence of viscosity on capillary perfusion. *Clin Hemorheol Microcirc* 1999;20(1):49–55
- 92 Spencer CG, Felmeden DC, Blann AD, Lip GY. Effects of “newer” and “older” antihypertensive drugs on hemorrheological, platelet, and endothelial factors. A substudy of the Anglo-Scandinavian Cardiac Outcomes Trial. *Am J Hypertens* 2007;20(6):699–704
- 93 Muravyov AV, Yakusevich VV, Kabanov AV, Petrochenko AS. The effect of diuretics on red blood cell microrheological parameters in female hypertensive patients. *Clin Hemorheol Microcirc* 2005;33(2):121–126
- 94 Khder Y, Bray des Bosc L, el Ghawi R, et al. Calcium antagonists and thiazide diuretics have opposite effects on blood rheology and radial artery compliance in arterial hypertension: a randomized double-blind study. *Fundam Clin Pharmacol* 1998;12(4):457–462
- 95 Zannad F, Bray-Desbosc L, el Ghawi R, Donner M, Thibout E, Stoltz JF. Effects of lisinopril and hydrochlorothiazide on platelet function and blood rheology in essential hypertension: a randomly allocated double-blind study. *J Hypertens* 1993;11(5):559–564
- 96 Koenig W, Sund M, Ernst E, et al. Effects of felodipine ER and hydrochlorothiazide on blood rheology in essential hypertension—a randomized, double-blind, crossover study. *J Intern Med* 1991;229(6):533–538
- 97 Andrews RJ, Bringas JR, Muto RP. Effects of mannitol on cerebral blood flow, blood pressure, blood viscosity, hematocrit, sodium, and potassium. *Surg Neurol* 1993;39(3):218–222
- 98 Muravyov AV, Meiselman HJ, Yakusevich VV, Zamishlayev AV. Effects of antihypertensive therapy on hemorrheological profiles in female hypertensive patients with initially low or high whole blood viscosity. *Clin Hemorheol Microcirc* 2002;26(2):125–135
- 99 Bird J, Carmona C. Probable interaction between warfarin and torsemide. *Ann Pharmacother* 2008;42(12):1893–1898
- 100 Laizure SC, Madlock L, Cyr M, Self T. Decreased hypoprothrombinemic effect of warfarin associated with furosemide. *Ther Drug Monit* 1997;19(3):361–363
- 101 Kaşifoğlu T, Yalçın AU. The effects of thiazide and thiazide-potassium sparing diuretics on fibrinolytic system parameters. *Anadolu Kardiyol Derg* 2006;6(2):143–147
- 102 Lottermoser K, Hertfelder HJ, Vetter H, Düsing R. Fibrinolytic function in diuretic-induced volume depletion. *Am J Hypertens* 2000;13(4 Pt 1):359–363
- 103 Bentley P, Rosso M, Sadnicka A, Israeli-Korn S, Laffan M, Sharma P. Intravenous immunoglobulin increases plasma viscosity without parallel rise in blood pressure. *J Clin Pharm Ther* 2012;37(3):286–290
- 104 Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. *Neurology* 1994;44(2):223–226
- 105 Kowal P, Zmyślony A. Hemorrheological changes after intravenous gammaglobulin administration in patients with neurological disorders. *Clin Hemorheol Microcirc* 2008;40(3):229–234
- 106 Baba R, Shibata A, Tsurusawa M. Single high-dose intravenous immunoglobulin therapy for kawasaki disease increases plasma viscosity. *Circ J* 2005;69(8):962–964
- 107 Ben-Ami R, Barshtein G, Mardi T, et al. A synergistic effect of albumin and fibrinogen on immunoglobulin-induced red blood cell aggregation. *Am J Physiol Heart Circ Physiol* 2003;285(6):H2663–H2669
- 108 Game L, Voegel JC, Schaaf P, Stoltz JF. Do physiological concentrations of IgG induce a direct aggregation of red blood cells: comparison with fibrinogen. *Biochim Biophys Acta* 1996;1291(2):138–142
- 109 Macdougall IC, Davies ME, Hutton RD, Coles GA, Williams JD. Rheological studies during treatment of renal anaemia with recombinant human erythropoietin. *Br J Haematol* 1991;77(4):550–558
- 110 Nowicki M. Erythropoietin and hypertension. *J Hum Hypertens* 1995;9(2):81–88
- 111 Crowley JP, Chazan JA, Metzger JB, Pono L, Valeri CR. Blood rheology and 2,3-diphosphoglycerate levels after erythropoietin treatment. *Ann Clin Lab Sci* 1993;23(1):24–32
- 112 Delamaire M, Durand F, Hamel D, Joyeux V, Lepogamp P, Genetet B. [Improvement of hemorrheologic parameters in hemodialyzed patients treated with human recombinant erythropoietin]. *J Mal Vasc* 1991;16(3):289–294
- 113 Hassan K, Roguin N, Kaganov Y, Hasan S, Kristal B. Effect of erythropoietin therapy on red cells filterability and left ventricular mass in predialysis patients. *Ren Fail* 2005;27(2):177–182
- 114 Singh A, Eckardt KU, Zimmermann A, et al. Increased plasma viscosity as a reason for inappropriate erythropoietin formation. *J Clin Invest* 1993;91(1):251–256
- 115 Bor-Kucukay M, Yalcin O, Meiselman HJ, Baskurt OK. Erythropoietin-induced rheological changes of rat erythrocytes. *Br J Haematol* 2000;110(1):82–88
- 116 Vaziri ND, Ritchie C, Brown P, et al. Effect of erythropoietin administration on blood and plasma viscosity in hemodialysis patients. *ASAIO Trans* 1989;35(3):505–508
- 117 Shinaberger JH, Miller JH, Gardner PW. Erythropoietin alert: risks of high hematocrit hemodialysis. *ASAIO Trans* 1988;34(3):179–184
- 118 Lippi G, Franchini M, Favaloro EJ. Thrombotic complications of erythropoiesis-stimulating agents. *Semin Thromb Hemost* 2010;36(5):537–549
- 119 von Tempelhoff GF, Niemann F, Schneider DM, Kirkpatrick CJ, Hommel G, Heilmann L. Blood rheology during chemotherapy in patients with ovarian cancer. *Thromb Res* 1998;90(2):73–82
- 120 von Tempelhoff GF, Heilmann L, Pollow K, Hommel G. Monitoring of rheologic variables during postoperative high-dose brachytherapy for uterine cancer. *Clin Appl Thromb Hemost* 2004;10(3):239–248
- 121 Kameneva MV, Antaki JF. Mechanical trauma to blood. In: Baskurt OK, Hardeman MR, Rampling MW, Meiselman HJ, eds. *Handbook of Hemorrheology and Hemodynamics*. Amsterdam, Netherlands: IOS Press; 2007:206–227
- 122 Hirayama T, Roberts D, William-Olsson G. Mechanical trauma to red blood cells caused by Björk-Shiley and Carpentier-Edwards heart valves. *Scand J Thorac Cardiovasc Surg* 1985;19(3):253–256
- 123 Hirayama T, Yamaguchi H, Allers M, Roberts D, William-Olsson G. Changes in red cell deformability associated with anaesthesia and cardiopulmonary bypass in open-heart surgery. *Scand J Thorac Cardiovasc Surg* 1985;19(3):257–262
- 124 Vaisman S, Kensey K, Cho YI. Effect of hemodialysis on whole blood viscosity. *Int J Artif Organs* 2009;32(6):329–335
- 125 Martínez M, Vayá A, Alvario J, et al. Hemorrheological alterations in patients with chronic renal failure. Effect of hemodialysis. *Clin Hemorheol Microcirc* 1999;21(1):1–6
- 126 Dhar P, Eadon M, Hallak P, Munoz RA, Hammes M. Whole blood viscosity: effect of hemodialysis treatment and implications for access patency and vascular disease. *Clin Hemorheol Microcirc* 2012. In press
- 127 Ibrahim FF, Ghannam MM, Ali FM. Effect of dialysis on erythrocyte membrane of chronically hemodialyzed patients. *Ren Fail* 2002;24(6):779–790
- 128 Kameneva MV, Marad PF, Brugger JM, et al. In vitro evaluation of hemolysis and sublethal blood trauma in a novel subcutaneous vascular access system for hemodialysis. *ASAIO J* 2002;48(1):34–38
- 129 Ocak G, Vossen CY, Rotmans JJ, et al. Venous and arterial thrombosis in dialysis patients. *Thromb Haemost* 2011;106(6):1046–1052
- 130 Minneci PC, Deans KJ, Zhi H, et al. Hemolysis-associated endothelial dysfunction mediated by accelerated NO inactivation by decompartmentalized oxyhemoglobin. *J Clin Invest* 2005;115(12):3409–3417

- 131 Connes P, Brun JF, Baskurt OK. Blood rheology and exercise. In: Connes P, Hue O, Perrey S, eds. *Exercise Physiology: From a Cellular to an Integrative Approach*. Amsterdam, Netherlands: IOS Press; 2010:213–229
- 132 Vandewalle H, Lacombe C, Lelièvre JC, Poirot C. Blood viscosity after a 1-h submaximal exercise with and without drinking. *Int J Sports Med* 1988;9(2):104–107
- 133 Yalcin O, Erman A, Muratli S, Bor-Kucukatay M, Baskurt OK. Time course of hemorheological alterations after heavy anaerobic exercise in untrained human subjects. *J Appl Physiol* 2003;94(3):997–1002
- 134 Ernst E, Daburger L, Saradeth T. The kinetics of blood rheology during and after prolonged standardized exercise. *Clin Hemorheol* 1991;11:429–439
- 135 Brun JF, Belhabas H, Granat MCh, et al. Postexercise red cell aggregation is negatively correlated with blood lactate rate of disappearance. *Clin Hemorheol Microcirc* 2002;26(4):231–239
- 136 Gaudard A, Varlet-Marie E, Monnier JF, et al. Exercise-induced central retinal vein thrombosis: possible involvement of hemorheological disturbances. A case report. *Clin Hemorheol Microcirc* 2002;27(2):115–122
- 137 Connes P, Tripette J, Chalabi T, et al. Effects of strenuous exercise on blood coagulation activity in sickle cell trait carriers. *Clin Hemorheol Microcirc* 2008;38(1):13–21
- 138 El-Sayed MS, Nagia A. Blood hemostasis in exercise and training. In: Connes P, Hue O, Perrey S, eds. *Exercise Physiology: From a Cellular to an Integrative Approach*. Amsterdam, Netherlands: IOS Press; 2010:259–281
- 139 Lippi G, Maffulli N. Biological influence of physical exercise on hemostasis. *Semin Thromb Hemost* 2009;35(3):269–276
- 140 Ikarugi H, Shibata M, Shibata S, Ishii H, Taka T, Yamamoto J. High intensity exercise enhances platelet reactivity to shear stress and coagulation during and after exercise. *Pathophysiol Haemost Thromb* 2003;33(3):127–133
- 141 Connes P, Machado R, Hue O, Reid H. Exercise limitation, exercise testing and exercise recommendations in sickle cell anemia. *Clin Hemorheol Microcirc* 2011;49(1–4):151–163
- 142 Tripette J, Loko G, Samb A, et al. Effects of hydration and dehydration on blood rheology in sickle cell trait carriers during exercise. *Am J Physiol Heart Circ Physiol* 2010;299(3):H908–H914
- 143 Lippi G, Banfi G. Doping and thrombosis in sports. *Semin Thromb Hemost* 2011;37(8):918–928
- 144 Leigh-Smith S. Blood boosting. *Br J Sports Med* 2004;38(1):99–101
- 145 Segura J, Ventura R, Pascual JA. Current strategic approaches for the detection of blood doping practices. *Forensic Sci Int* 2011;213(1–3):42–48
- 146 Gauthier J. [Blood doping and cardiovascular consequences]. *Presse Med* 2002;31(40):1904–1908