

Regulation of blood viscosity in disease prevention and treatment

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Blood viscosity plays an important role in maintaining vascular homeostasis. Under normal physiological conditions, blood viscosity is kept at a relatively stable level by a variety of regulatory mechanisms. However, under pathological conditions, disorders in these regulatory mechanisms mediated by endothelial cell dysfunction result in the pathogenesis and development of certain diseases, such as cardio-cerebrovascular diseases, diabetes mellitus, and hemorrhagic shock. Therefore, monitoring and regulating blood viscosity are important for the diagnosis, treatment, and prognosis of disease. This article reviews the role of blood viscosity regulation and its importance in disease prevention and treatment.

blood viscosity, cardio-cerebrovascular diseases, diabetes mellitus, hemorrhagic shock, endothelial dysfunction

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Viscosity, a basal parameter in rheology, is a major determinant of the shear stress imparted by blood flow, and plays an important role in maintaining vascular homeostasis. Blood viscosity is mainly determined by hematocrit levels, plasma viscosity, and the deformability and aggregation of red blood cells (RBCs). Blood viscosity varies under normal physiological conditions due to differences in heredity, sex, and geography. Under pathological conditions, changes in blood viscosity usually correlate with endothelial cell dysfunction and changes in the shear stress imparted by blood flow, which can damage the circulatory system and related tissues and organs. Abnormal blood viscosity plays an important role in the development of cardio-cerebrovascular disease, diabetes, hemorrhagic shock, and renal disease. When treating these diseases, much attention is paid to the regulation of blood viscosity, which is pivotal to successful treatment and avoiding undesirable syndromes. Since the 1970s, researchers have paid greater attention to the role of hemorheological parameters, including blood viscosity, in the diagnosis and treatment of diseases [1]. In the 1980s, the

relationship between hemorheology and disease was intensively investigated and several monographs were published [2,3]. Therefore, this article will review recent progress regarding the manipulation of blood viscosity for disease prevention and treatment.

1 Blood viscosity under physiological conditions

Within the physiological range of shear rates, blood viscosity is primarily determined by hematocrit levels and plasma viscosity [4]. The deformability and aggregation of erythrocytes and the interaction between blood cells are also important contributing factors. The viscosity of plasma, which has similar properties to those of a Newtonian fluid, is determined mainly by the concentration of plasma proteins, but the erythrocyte deformability and aggregation vary with different blood shear rates. Therefore, blood has the properties of a pseudoplastic non-Newtonian fluid. In addition to plasma and hematocrit, erythrocyte deformability at high shear rates ($>200 \text{ s}^{-1}$) is a major determinant of blood viscosity. At low shear rates, blood viscosity is affected by

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deformability and aggregation of erythrocytes and by platelet aggregation [5,6].

#4 Epidemiological studies show that blood viscosity is affected by many factors. A study conducted in apparently normal adults by De Simone et al. [7] found that cholesterol and triglyceride levels were positively related to blood viscosity; obesity, high sodium intake and aging also increased blood viscosity. Mental stress may also induce the decrease in erythrocyte deformability and an acute elevation in hematocrit levels [6,8,9]. Blood viscosity is also influenced by gender. Men have a significantly higher blood viscosity than women due to differences in hematocrit and the deformability and aggregation of erythrocytes [7,8,10]. Geographical factors also affect blood viscosity. Compared with low-altitude residents, high altitude-residents have higher levels of hematocrit, blood viscosity [11–13], blood flow, and circulating nitric oxide (NO) products [14]. A study by Cheng et al. [15] indicates that, although hematocrit is higher among high-altitude residents, compensatory regulation can prevent excessive increases in blood viscosity via increased erythrocyte deformability and decreased erythrocyte aggregation. Martini et al. [16] suggest that high altitudes cause increased hematocrit levels and, therefore, increased blood viscosity, which results in increased shear stress on the endothelium; this, in turn, causes the release of stress-mediated vasodilators, leading to a reduction in blood pressure. This may be one of the explanations for the low mortality from coronary heart disease and stroke observed in high altitude residents [17].

Under normal physiological conditions, variations in blood viscosity directly affect the endothelium, which then regulates blood viscosity and blood vessel diameter by releasing vasoactive factors to keep the vascular wall shear stress relatively stable. Because of these endothelium-dependent regulatory mechanisms, increased blood viscosity does not result in increases vascular resistance. In a large-scale epidemiological study, De Simone et al. [18] found that blood viscosity was negatively related to pulse pressure in apparently normal adults. A study by Salazar Vázquez et al. [19,20] showed that mean arterial blood pressure (MAP), which reflects peripheral vascular resistance, was negatively correlated with blood viscosity in healthy children and premenopausal women, but this was not significant. However, some research suggests that, hematocrit levels and blood viscosity in normal adults do not correlate with MAP [21].

#5 2 Abnormalities in blood viscosity and disease

Abnormal changes in blood viscosity play an important role in the pathogenesis and development of many diseases, including cardio-cerebrovascular diseases, diabetes mellitus, and hemorrhagic shock. Abnormal changes in blood viscosity and endothelial dysfunction promote each other, forming a vicious circle. Endothelial cell dysfunction, a key link in

the pathogenesis of many diseases, is associated with imbalances in the production and release of vasoactive factors, such as vasoconstrictors and vasodilators, pro-coagulant and anti-coagulant factors, and inhibitors and promoters of proliferation [22].

2.1 Abnormalities in blood viscosity and cardio-cerebrovascular diseases

Increased blood viscosity is associated with cardio-cerebrovascular diseases. In a 5-year follow-up study, Lowe et al. [23] found that blood viscosity and plasma viscosity were significantly higher in patients who experienced cardiovascular events than in those who did not, and that was because of increases in fibrinogen concentration and hematocrit. In a similar study, Lee et al. [24] showed that increased blood viscosity was associated with the early stages of atherosclerosis. In addition, hyperviscosity may play a role in the occurrence of cerebral ischemic complications in patients with atrial fibrillation (AF). AF patients who had experienced previous cerebral ischemic events had a higher blood viscosity than AF patients who had not experienced such events [25].

Abnormal increases in blood viscosity are associated with the development and prognosis of cardio-cerebrovascular diseases. Increasing hematocrit, abnormal increases in fibrinogen concentration, and blood viscosity can all make cardio-cerebrovascular diseases worse and increase the long term risk of mortality [26,27]. Cecchi et al. [28] found that blood viscosity was independently and positively associated with infarct size. It is possible that increased blood viscosity may contribute to a lack of myocardial perfusion, which may then result in an increased infarct size. Malinova et al. [29] undertook a 7-year follow-up study in patients with ischemic heart disease and suggested that blood viscosity and blood flow change with the severity of coronary artery disease. In hypertensive men, increased blood viscosity at low shear rates is a predictor of cardiovascular events, including acute myocardial infarction, unstable angina, or stroke [30].

In cardio-cerebrovascular diseases, abnormal increases in blood viscosity caused by factors such as an increase in oxygen/nitrogen free radicals, fibrinogen, and oxidized low density lipoprotein will not only increase platelet adhesion, but also alter vascular wall shear stress. This leads to endothelial dysfunction, increased inflammation, and hypertrophy of smooth muscle cells [31], as well as vascular stenosis and insufficient blood flow, which can lead to myocardial infarction and stroke.

2.2 Abnormalities in blood viscosity associated with diabetes mellitus

#6 Increased blood viscosity is closely related to the occurrence and development of diabetes mellitus. Insulin resistance and hyperinsulinemia predispose to diabetes mellitus. Increased

blood viscosity will, in turn, impair blood flow within the tissues and limit the delivery of insulin, glucose, and oxygen to metabolically active tissue [32], ultimately resulting in increased insulin resistance [33]. Hyperinsulinemic obese female patients show significantly higher plasma viscosities than normoinsulinemic patients [34]. Increased blood viscosity in patients with diabetes mellitus is an important factor that contributes to diabetic macrovascular complications [19,35,36]. Blood viscosity in diabetic patients is also positively correlated with the severity of retinopathy [37,38]. Diabetic patients with retinopathy show higher blood viscosity than diabetics without retinopathy at both high and low shear rates [37]. However, another study came to the opposite conclusion [39]. Blood viscosity in diabetic patients who have experienced complications, such as microalbuminuria and nephropathy, is also higher than that in patients without such complications [40,41]. Measurements of blood viscosity at low shear rates in diabetic patients have prognostic value. Compared with those who were either asymptomatic or had mild peripheral vascular disease, patients with critical limb ischemia showed higher blood viscosity and RBC aggregation at low shear rates [42].

Diabetes mellitus is accompanied by decreased production of the vasodilators, NO, and prostacyclin, and increased formation of vasoconstrictor eicosanoids [43], leading to increased peripheral vascular resistance and abnormal blood pressure. This is due to impairment of endothelial vasodilator mechanisms. Salazar Vázquez et al. [21] found a correlation between MAP and hematocrit in patients with a previous diagnosis of type 2 diabetes. MAP levels decrease significantly as hematocrit levels increase within the low hematocrit range (<43%), but increase as hematocrit levels increase within the high hematocrit range (>43%). Nevertheless, blood viscosity in children with type 1 diabetes is positively correlated with MAP, indicating endothelial dysfunction [19].

Many factors contribute to increased blood viscosity in diabetic patients. First, increased glucose causes endothelial dysfunction and, therefore, disorders in the feedback mechanisms that regulate blood viscosity. Second, high glucose levels increase the generation of active oxygen species in erythrocytes and endothelial cells, leading to reduced RBC deformability and increased blood viscosity. Third, increased RBC aggregation [44] and fibrinogen levels also contribute to increased blood viscosity in diabetic patients. Microcirculatory disturbances caused by abnormal changes in blood viscosity may worsen the complications associated with diabetes mellitus [45,46].

2.3 Abnormalities in blood viscosity associated with other diseases

Increased blood viscosity is also observed in other diseases. Plasma viscosity, fibrinogen concentration, and RBC aggregation in renal transplant recipients are all significantly

higher than those in control subjects [47]. Elevated blood viscosity in patients with systemic lupus erythematosus may be associated with atherothrombotic disease [48]. In addition, increased blood viscosity is an important factor that impacts upon prognosis [49]. As a marker of vasculopathy, increased blood viscosity may accelerate disease progression in Alzheimer's disease patients by worsening vasculopathy [50].

In some diseases, such as chronic anemia and liver disease, plasma and blood viscosity show a long term decline because of low concentration of plasma proteins rather than an abnormal increase in blood viscosity [51–53], leading to disorders in endothelial shear response mechanisms. This may also occur in hemoglobin or RBC diseases [54]. During the early stage of severe hemorrhagic shock, a sharp decline plasma and blood viscosity occurs resulting from the loss of RBCs and plasma proteins [55]. With respect to the microcirculation, a rapid decrease in arteriolar blood flow and functional capillary density during hemorrhagic shock may give rise to microcirculatory disturbances [56,57].

3 Regulation of blood viscosity and treatment of disease

As previously mentioned, abnormal changes in blood viscosity are closely related to the pathogenesis and development of many diseases. There is growing evidence to suggest that regulation of blood viscosity is beneficial for disease treatment. Hemodilution can be used to treat diseases resulting from abnormal increases in blood viscosity. However, under a severe decrease in blood viscosity, e.g. hemorrhagic shock and extreme hemodilution, the appropriate increase in blood viscosity can maintain the shear stress on endothelium and maintain vasodilatation, thereby improve microcirculation and increase cardiac output [58].

3.1 Treatments that reduce blood viscosity

For diseases associated with abnormal increases in blood viscosity, such as cardio-cerebrovascular diseases and diabetes mellitus, two methods are currently used to reduce viscosity: direct and indirect. Direct methods include plasma exchange, phlebotomy, and rheopheresis. Plasma exchange uses plasma substitutes to replace plasma to reduce blood viscosity without affecting the packed cell volume. In the short term, it reduces blood viscosity, the concentration of fibrinogen, and the levels of triglycerides and cholesterol, and improves local blood flow [59,60]. Phlebotomy, which is used to treat patients with polycythemia vera and hemochromatosis, reduces hematocrit levels, and plasma and blood viscosity via controlled bleeding [61,62]. The combination of phlebotomy and fluid therapy has been used to treat diseases such as ischemic stroke and myocardial infarction. Strand et al. [63] used phlebotomy and repeated

low-molecular weight dextran infusions to treat the early phase of ischemic stroke. During the 3-month follow-up, the treatment significantly reduced blood viscosity and improved the overall clinical outcome of patients. Rheopheresis therapy improves hemorheological parameters by reducing fibrinogen levels, low-density lipoprotein cholesterol, and alpha-2-macroglobulin and improves the treatment of microvascular diseases, and relieves the symptoms of age-related macular degeneration and peripheral arterial occlusive disease [64].

Indirect therapy reduces blood viscosity by regulating the factors that influence blood viscosity, such as erythrocytes, platelets, and endothelial cells. For example, antioxidant therapy uses vitamins E and C to reduce oxidative stress *in vivo*, increase RBC deformability, improve endothelial dysfunction, and lower blood viscosity [65–67]. In a 6-month follow-up study, Galduroz et al. [10] found that the extract of *Ginkgo biloba* significantly reduced blood viscosity. Nitroglycerin can also reduce blood viscosity, the decrease being associated with an increase in myocardial blood flow and a decrease in vascular resistance [68]. In addition, the essence of stimulating the circulation to end stasis in Chinese Medicine is similar to reducing blood viscosity to improve microcirculation. Traditional Chinese medicines, such as *Salvia miltiorrhiza* Bunge and *Ligusticum chuanxiong* Hort, effectively regulate blood viscosity by protecting the endothelium and inhibiting platelet aggregation [69–73].

3.2 Treatments that increase blood viscosity

Blood viscosity shall be increased moderately when treating diseases that extremely reduce viscosity. Transfusion is commonly used to restore blood volume and improve the delivery of oxygen and nutrients. Recent studies interpreted the effects of transfusion in terms of maintaining blood viscosity. The studies concluded that transfusion works by maintaining viscosity and restoring oxygen-carrying capacity. Transfusion restores blood viscosity, and maintains the shear stress on the endothelium and microvascular perfusion such that oxygen delivery and removal of metabolites can be maintained [58,74–76]. Martini et al. [77] studied exchange transfusions of homologous packed red blood cells using the awake hamster window chamber model, and observed a moderate elevation of hematocrit (10% above baseline), which causing an increased cardiac index, increased oxygen transport and consumption, and a reduction in total peripheral vascular resistance.

Maintenance of blood viscosity should also be taken into consideration when developing blood substitutes. Researchers found that some hemoglobin-based oxygen carriers caused transient systemic hypertension [78,79] and reduced cardiac output [80]. This is because large infusions of blood substitutes lower blood viscosity and the shear stress on the endothelium, which down-regulates the production of vasodilators by endothelial cells, causing vasoconstriction and

increasing total peripheral vascular resistance [81]. In the hemorrhagic shock model, viscous blood substitutes limit vasoconstriction [82,83] and improve functional capillary density and oxygen content.

Maintenance of plasma viscosity is critically important when rapid infusion of erythrocytes and increased blood viscosity cannot be performed. Tsai et al. [84,85] showed that the use of high viscosity plasma expanders during extreme hemodilution could maintain functional capillary density and significantly improve capillary perfusion. The researchers concluded that increased production of vasodilators by the endothelium (e.g. NO) might be the major reason for improvements in the microcirculation. Using the severe experimental hemorrhagic shock model based on the infusion of hypertonic saline, Golden Syrian Hamsters were randomly infused with Hextend (6% Hetastarch in lactated electrolyte solution, 4 mPa s) or viscosity-enhanced Hextend (Hextend + 0.4% alginate, 8 mPa s). Resuscitation with Hextend resulted in higher MAP, but viscosity-enhanced Hextend showed better results in terms of improved functional capillary density, microvascular perfusion, and the restoration of acid-base balance [86].

4 Regulation of blood viscosity

Although blood viscosity plays an important role in disease prevention and treatment, research into the mechanisms that regulate blood viscosity is still lacking. Previous studies show that the endothelium plays a key role in regulating blood viscosity. Endothelium, as both the sensor and effector of blood viscosity, not only is regulated by blood viscosity [87], but also plays a vital role in the feedback regulation mechanisms that control it. The effects of blood viscosity on an organism depend on endothelial cell function. Under normal physiological conditions, increased blood viscosity leads to increased vascular wall shear stress and increased production of endothelial-derived relaxing factors, such as NO and prostacyclin. These vasoactive substances not only cause vasodilatation and, therefore, lower MAP, but also reduce blood viscosity by improving RBC deformability, thereby suppressing RBC aggregation and platelet aggregation and adhesion [88–90]. Under pathological conditions, many harmful factors, such as mental stress, inflammation [27] and high glucose levels, result in increased production of reactive oxygen species, fibrinogen, immunoglobulins, and hematocrit, which lead to abnormally increased blood viscosity. Furthermore, they may both directly and indirectly cause endothelial dysfunction and feedback regulation mechanism disorders. Therefore, abnormal changes in blood viscosity and endothelial dysfunction promote each other and form a vicious circle.

Blood viscosity is closely related to endothelial cell function. Malek et al. [91] found that a constant, high level of shear stress which generated by the flow and viscosity could

THAT'S WHAT
YOU THINK!!

suppress the expression of endothelin-1 in bovine aortic endothelial cells. Koller et al. [92] varied the viscosity of the perfusate in isolated arterioles from the cremaster muscle by adding dextran, and found that, at a constant flow rate, increases in the viscosity of the perfusate caused gradual vasodilation. Viscosity-induced dilation was eliminated by removing the endothelium from the arterioles, confirming that viscosity-induced dilation is endothelium-dependent. They concluded that increased perfusate viscosity increased shear stress and, thus, induced prostacyclin release by the endothelium, resulting in vasodilation. Using the severe hemodilution model, Bertuglia [93] found that hyperviscous infusions preserved both the endothelium and capillary perfusion.

As mentioned previously, viscosity can affect endothelial cell function by altering shear stress. Furthermore, substrate stiffness and micro- and nano-structural surfaces can directly modulate cell shape, stiffness, gene expression, and adhesion molecule distribution [94–96]. It is interesting to speculate whether blood viscosity, as one determinant of the viscoelasticity of the material that contacts the endothelium, may modulate endothelial cell shape, stiffness, gene expression, adhesion molecule distribution and, therefore, overall health status, in addition to directly affecting endothelial cells through shear stress. This would constitute an important additional endothelium-dependent regulatory mechanism of blood viscosity and needs further study.

5 Conclusions and expectations

Blood viscosity is an important parameter to be considered during drug evaluation and research into their mechanisms of action as it correlates closely with the pathogenesis, development, and prognosis of cardio-cerebrovascular diseases, diabetes and other diseases. More interest is now being paid to treatments that manipulate blood viscosity. However, the bio-effectiveness of viscosity is sometimes overlooked in the clinic. The role of hemorheology in the pathogenesis, development, and prognosis of disease needs more attention. Future investigations should include the following: (1) The relationship between hemorheological parameters and the correlation between abnormal blood viscosity and endothelial cell dysfunction, such as blood viscosity, and the pathogenesis, development and prognosis of diseases; (2) the benefits of treatments that control blood viscosity at different stages of disease; and (3) the correlations between hemorheological parameters and other clinical parameters. A general system of diagnosis and monitoring of the effectiveness of treatments should also be established.

Research on blood viscosity has facilitated the development of Biomechanopharmacology [97], a new borderline discipline that considers the effect of pharmacological interventions on biomechanical factors and the biomechanical influence of pharmacokinetics and pharmacodynamics. Me-

chanical impacts on endothelial cell functions are an important concern of Biomechanopharmacology. Shear stress results from flow flux and hydro-viscosity, and regulates endothelial cell structure and function; however, the relationship between flow flux and hydro-viscosity has not been comprehensively investigated. Many studies merely focus on changes in shear stress caused by altering the flow flux without considering hydro-viscosity, which is also a major determinant of shear stress [98]. Further intensive studies on blood viscosity will promote the development of Biomechanopharmacology.

Studies of the pathogenesis of hemorrhagic shock and strategies for resuscitation have identified changes in hemorheology during the early stages of hemorrhagic shock [99]. Different plasma volume expanders cause different changes in blood viscosity and the rheological parameters of RBCs, which further affects perfusion of the microcirculation [100,101]. In future, we intend to establish both *in vitro* and *in vivo* research systems to investigate the mechanisms that regulate blood and plasma viscosity. The influence of blood viscosity on the mechano-properties of endothelial cells will be one focus of our future studies.

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