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BLOOD RHEOLOGY ALTERATIONS IN PATIENTS WITH CARDIOVASCULAR DISEASES

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Abstract

Blood rheology is an important determinant of blood flow but is probably one of the most neglected areas in clinical literature and practice. Blood viscosity changes according to shear rates and depends on cellular and plasma factors. RBCs' aggregability and deformability are the main determinants of local flow characteristics in areas with lower and higher shear rates, but plasma viscosity is the main regulatory factor of flow resistance in the microcirculation. In individuals with altered blood rheology, the mechanical stress to vascular walls induces endothelial injury and vascular remodelling, and promotes atherosclerosis. Increased values of whole blood viscosity and plasma viscosity are correlated with cardiovascular risk factors and adverse cardiovascular events. The long-term effects of physical exercise can produce a hemorheological fitness that protects against cardiovascular diseases.

Keywords

hemorheology • whole blood viscosity • plasma viscosity • cardiovascular diseases

Introduction

Blood is a non-Newtonian fluid with changing viscosity according to different hemodynamic conditions reflecting its composition (i.e., a suspension of cell in plasma) and the behaviour of red blood cells (RBCs), its main cellular element [1-2]. Whole blood viscosity (WBV) is dependent on shear rate and RBCs' rheological properties [2]. Normal WBV values are usually considered to be between 3.5 and 5.5 cP, but the normal range can vary tremendously, even in physiological conditions, as a result of different flow rates [3]. At low shear rates (<1-10 s^{-1}) in large vessels (i.e., veins), WBV is high (10-25 cP) and reflects RBC aggregation [4], while at high shear rates (>150 s^{-1}) in large vessels (i.e., arteries) RBCs' deformability and dissociation results in low WBV (4-5 cP) [3]. In capillaries, the central migration of RBCs increases the plasma layer in contact with the endothelium. This results in decreased flow resistance, nitric oxide (NO) production and increase of the plasma skimming effect, with lower microcirculatory haematocrit and WBV (i.e., Fahraeus and Fahraeus-Lindqvist effects) [2, 5]. Thus, plasma viscosity (PV) is the major regulatory factor of flow resistance in the microcirculation and capillary perfusion [6-7]. The increase in WBV in physiological or pathological conditions should result in NO-mediated vasodilation [8-9], but this is true only in individuals with intact endothelial function [2]. Otherwise, the increase in WBV can generate further alterations of blood rheology, following vasoconstriction and increased peripheral vascular resistance.

Determinants of whole blood viscosity

Haematocrit

WBV is exponentially related to haematocrit, especially at higher levels of haematocrit. The impact of haematocrit on WBV is more important at low shear rates (as in veins) than at high shear rates (as in arteries) [10]. At the microcirculatory level, lower

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haematocrit values are observed due to axial RBC migration and increased plasma skimming effect phenomena [2, 5].

Plasma viscosity

Plasma is the extracellular matrix of blood cells. Unlike blood, plasma is a Newtonian fluid and its viscosity is not dependent on the shear rate. PV depends on protein content; acute phase reactants, such as fibrinogen, can induce a significant increase in PV following inflammation. The normal value of PV at 37 degrees C is 1.2–1.35 cP, but values are higher in various inflammatory, metabolic or cardiovascular diseases [11]. Values as high as 5 cP are associated with paraproteinemia or multiple myeloma [3]. Large lipoproteins also contribute to the increase in PV values [1].

RBC deformability

RBCs are elastic bodies and exhibit extensive changes of form when moving from large to small vessels, in response to shear rates [1] and suspension in solutions with lower viscosity than the viscosity of their cytosol, such as plasma [12]. The ellipsoid shape observed at low shear rates in large vessels changes into deformed polylobed forms at high shear rates in capillaries [13]. Their deformability is a major determinant of blood flow in microcirculation and the dynamic behaviour is influenced by the cytoskeleton-induced change of shape [14]. Any change in cytosolic viscosity, membrane viscoelasticity, but also in PV can contribute to decreased RBC deformability and pathological flow [2, 13] with increased flow resistance in microcirculation.

RBC aggregation

At low shear rates, RBCs tend to form aggregates, which increase WBV. As shear rates increase, the aggregates disrupt and facilitate RBC passage into the microcirculation and lower WBV. RBC aggregation depends on the RBCs' intrinsic aggregability [15], but also on the macromolecular composition of the surrounding suspending medium. In vivo, fibrinogen is the main component of plasma that promotes RBC aggregation [16]. RBC aggregation influences blood flow, tissue perfusion and vascular resistance [2]. In cases of increased RBC aggregation, there is a significant increase in WBV, especially in low shear rate areas (such as veins or bifurcations) and RBC aggregates can persist even in large arteries. At the microcirculatory level, the abnormal presence of RBC aggregates increases blood flow resistance [17] and contributes to the development of adverse outcomes [18-19]. Other blood constituents, such as leucocytes and platelets, have minimal effects on WBV in normal conditions. However, inflammation-activated rigid leucocytes can block capillaries and alter microvascular resistance and blood flow in septic patients [1]. Increased levels of large lipoproteins also correlate with high WBV values [1].

Blood rheology and the risk of cardiovascular events

Altered blood rheology can initiate endothelial injury and promote vascular remodelling through direct mechanical injury [1, 4]. Alterations in vasodilatory and anti-aggregation mediators following endothelial injury induce a secondary inflammatory state that promotes atherosclerosis [20]. The resulting adaptative process involves arterial wall thickening and loss of compliance and elasticity, as a result of local flow changes and increased turbulence [1].

Hemorheological alterations are correlated with cardiovascular risk factors, arterial hypertension [21], diabetes [22], peripheral arterial disease [23], and dyslipidaemia [1]. The relationship between WBV, PV and major cardiovascular events (i.e., cardiovascular death, myocardial ischemia, need for urgent cardiovascular surgery) has been investigated in large cohorts that demonstrated the increased risk of such events in patients with elevated WBV, independent of other cardiovascular risk factors [24–26]. Increased PV is independently correlated with the risk for myocardial infarction and 40% of coronary events occur in patients with high WBV or with significant changes in low shear rate viscosity [26]. Also, increased PV is an independent predictor of adverse clinical events in patients with unstable angina or stroke [2]. WBV and PV are significantly higher in patients with ischemic heart disease or stroke [26] and high WBV is strongly associated with cardiovascular events in the older population [27]. Physical exercise is a protective factor against cardiovascular diseases through its positive effects on endothelial function [28].

Changes in blood rheology associated with physical exercise

Physical exercise can be considered a rheo-fluidifying therapy [29] and is an effective method for preventing impaired hemorheology [3]. Constant training is associated with better outcomes after surgery [30-31]. Physical exercise can be classified as a triphasic phenomenon, with acute, delayed and chronic effects [29].

Acute effects observed during submaximal or maximal periods of training are related to haemoconcentration and increased PV and WBV. The most important mechanisms underlying these changes are the redistribution of blood from the splanchnic territory and the loss of a part of the intravascular volume due to thermoregulation and redistribution to muscles, with a resultant increase in plasma total protein values [33]. The increase in WBV is also related to increased RBC aggregation, and decreases in deformability induced by

inflammation [33]. The rapid changes in haematocrit and WBV are compensated by local microcirculation changes and vasodilation in metabolically active tissues. However, association between changes in blood rheology, inflammation and absence of adequate peripheral vasodilation in this phase of training can be partially responsible for the adverse cardiac events associated with physical exercise [34].

In the next hours following physical exercise sessions, there is an increase in plasma volume due to hyperhydration, followed by haemodilution and hypoviscosity. This autohaemodilution results in a lower haematocrit and explains the negative correlation between haematocrit and regular physical exercise [33, 35].

The chronic effect of training can be considered a hemorheological fitness [29, 34]. Active individuals exhibit lower fibrinogen values and increase fibrinolytic activity [35] with a consecutive decrease in PV and WBV values. The chronic profile of hyperhydration-haemodilution is also associated with decreased RBC aggregability and increased deformability, particularly in resistance training [36–37]; changes in RBC membrane fluidity can be related to the improved antioxidant defence systems observed in the trained state [3]. The changes in blood rheology associated with long-term exercise are also observed in cardiac rehabilitation programmes and are associated with an increase in functional capacity and a decrease in cardiac-related mortality [38].

Changes of blood rheology in patients with cardiovascular risk factors

Age

The increase in plasma fibrinogen concentration is the most relevant hemorheological alteration with age [3, 39–40]. The age-related decline in the rate of fibrinogen synthesis is compensated by the low-level inflammation present even in healthy older adults, which increases fibrinogen synthesis [41–42]. Fibrinogen glycation results in impaired fibrinolytic activity of plasmin and decreased degradation rates of fibrinogen [43]. This increase in plasma fibrinogen levels explains the higher RBC aggregation and PV and WBV values in the elderly [44–45]. Also, a larger fraction of lower-density RBCs and circulating reticulocytes and a smaller fraction of higher-density RBCs are observed in older humans when compared to younger subjects [46], reflecting a reduced RBC life duration in older individuals. RBC deformability is also reduced as result of enhanced oxidant stress, altered sialic acid content and impaired NA+/K+ATP-ase activity of the cell membrane [3].

Although in some reports there was no association between changes in hemorheological parameters and age [44], most studies confirm an increase in PV, WBV and fibrinogen [47–48] with advanced age, independent of the presence of other risk factors for coronary heart disease [48].

Gender

Gender differences in blood rheology may contribute to the greater cardiovascular risk observed in men. WBV is markedly higher in men than in women, mainly because of higher haematocrit levels, but no difference is observed regarding PV [49–50]. Men also present with higher RBC aggregability and lower RBC deformability [49], and premenopausal women exhibit a larger number of young, highly deformable RBCs than age-matched men [51].

Smoking

Chronic smoking induces various changes in blood rheology that can promote atherothrombosis [1, 52]. In active smokers, there is an increase in haematocrit, PV and WBV [53–54] and inflammatory markers such as fibrinogen and white cell count [52]. The rheological behaviour of RBCs is altered, with an increase in haematocrit and RBC mass due to the conversion of haemoglobin to functionally inactive carboxyhaemoglobin, reduction in RBC deformability and increased RBC aggregation [52]. The increase in fibrinogen levels is related to daily cigarette numbers and the length of active smoking [52, 54]. The increase in PV is related to the rise in fibrinogen levels and to loss of plasma water induced by chronic smoking. Taken together, these changes result in a 10% to 20% increase in WBV [1]. Haematocrit levels decline quickly, but PV and WBV remain high even after long-term smoking cessation [1], because of a persistent inflammatory state [55]. The hemorheological alterations induced by smoking result in increased total peripheral resistance and left ventricular mass [56].

Arterial hypertension

Blood pressure is directly proportional to cardiac output and total peripheral vascular resistance. Changes in blood rheology directly influence peripheral vascular resistance, and maintaining cardiac output in the appropriate range depends on adaptative mechanisms that can alter blood pressure values in the long term. This hypothesis has been confirmed by large cohort studies showing that WBV, PV and haematocrit are associated with blood pressure independent of age, gender, body mass index or smoking status [57–58]. Moreover, WBV corelated with blood pressure independent of the fibrinogen and haematocrit values [57] and is associated with left ventricular hypertrophy and increased left ventricular mass [59]. The mechanisms of the association between WBV and blood pressure are not clearly defined, but decreased RBCs deformability appears to play a significant role [57]. In hypertensive patients treated with dihydropyridine calcium antagonists, RBCs deformability increased with controlled

blood pressure and cardiovascular ischemic events decreased [60].

Although increased WBV can increase blood pressure, it also increases endothelial shear stress and NO release, causing peripheral vasodilation thus counteracting the increase in peripheral vascular resistance due to hyperviscosity [61–62]. Since other findings show that WBV is not a factor in regulating blood pressure in the healthy normal population [61,63], endothelial dysfunction or pathologies that reduce or abolish the endothelial response to shear stress may be the reason for the association between WBV and blood pressure [64]. Altered hemorheology in patients with normal blood pressure can indicate incipient endothelial dysfunction and subsequent development of hypertension [63, 65].

Diabetes

WBV and PV are elevated in diabetic patients because of increased blood osmolarity, low plasma volume and increased haematocrit [66–67]. Changes in RBCs physical properties furthermore contribute to changes in WBV and induce microvascular complications [66, 68]. Elevated glycosylated haemoglobin caused by poor glycaemic control induces reduced RBCs deformability and increased aggregation [69], which are the main determinants of vascular complications in diabetes, since RBCs can no longer reach the capillary network and induce impaired perfusion at tissue level [66]. Increased adhesiveness of RBCs to vascular endothelium [70] also amplifies the risk of atherosclerosis even in large arteries [66].

As a result of RBC alterations, increased WBV can be considered a pathogenic factor of diabetic microangiopathy [66] and is significantly higher in diabetic patients with proliferative retinopathy, nephropathy [71] and atherosclerosis [72]. Improved glycaemic control could lead to beneficial rheological changes and even improve microcirculation in diabetic patients [72].

Dyslipidaemia

WBV and PV positively correlated with total cholesterol, LDL cholesterol and triglyceride concentrations and negatively correlated with HDL cholesterol concentrations [72–74], suggesting that changes in blood rheology may contribute to the increased cardiovascular risk in patients with dyslipidaemia [72].

Conclusions

Changes in blood rheology associated with cardiovascular risk factors could be an integrative mechanism promoting atherosclerosis and cardiovascular diseases [1]. Increased WBV, PV, RBC aggregation and decreased RBC deformability are common in patients with CVD and induce abnormal blood flow patterns in both macro- and microcirculation. Moreover, the damaged endothelium has an impaired response to blood rheological strain, with limited NO production and reduced vasodilatory response [2]. Increased peripheral resistances result in further macrohaemodynamic alterations (such as arterial hypertension) and organ dysfunctions (such as left ventricular hypertrophy or ischemic heart disease) [33]. Rheological measurements could identify subclinical cardiovascular diseases, contribute to cardiovascular risk profiling and help evaluate the effects of pharmacological agents used for treatment [1–2]. Given the scarce literature data addressing the subject of hemorheology in cardiovascular patients, this review highlights the importance of protective and risk factors in cardiovascular diseases and will help in further describing the baseline alterations of blood viscosity in a population of cardiac surgery patients (Emergency Institute for Cardiovascular Diseases, Prof. Dr. C. C. Iliescu ethics committee, registration number 22927/ 01.10.2018).

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