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The role of blood rheology in sickle cell disease

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Abstract

Studies performed in the last decades have highlighted the need to better understand the contribution of the endothelium, vascular function, oxidative stress, inflammation, coagulation, hemolysis and vascular adhesion mechanisms to the pathophysiology of acute vaso-occlusive like events and chronic organ damages in sickle cell disease (SCD). Although SCD is a hemorheological disease, a few works focused on the contribution of blood viscosity, plasma viscosity, red blood cell deformability and aggregation in the pathophysiology of SCD. After a brief description of basic hemorheology, the present review focuses on the role of the hemorheological abnormalities in the causation of several SCD complications, mainly in sickle cell anemia and hemoglobin (Hb) SC disease. Several genetic and cellular modulators of blood rheology in SCD are discussed, as well as unresolved questions and perspectives.

Keywords

Sickle cell disease; Blood viscosity; Red blood cell deformability; Red blood cell aggregation; Vaso-occlusive crises

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Conflict of interest statement

None.

1. Introduction

Sickle cell disease (SCD) is the most frequent genetic disease in the world, with sickle cell anemia (SCA; i.e. homozygous sickle cell disease or HbSS), and to a lesser extent hemoglobin SC disease (SC), reaching the highest prevalence [1]. It is estimated that over 300,000 children are born each year with a severe inherited hemoglobinopathy, over 80% of these in low-or middle-income countries, and approximately 220,000 newborns are affected by SCA [1].

SCA is characterized by a single nucleotide mutation (adenine–thymine) in exon I of the beta globin gene that leads to the presence of sickle hemoglobin (HbS) resulting from the substitution of valine for glutamic acid at the sixth position of the β-globin chain. The hydrophobic residue of valine associates with other hydrophobic residues causing HbS molecules to aggregate, forming fibrous precipitates when hemoglobin is deoxygenated. This phenomenon is called “HbS polymerization” and is responsible for the characteristic shape change termed “sickling” of red blood cells (RBCs). Sickle RBCs are rigid and do not easily flow through the microcirculation, causing frequent vaso-occlusive episodes in affected patients. Recurrent HbS polymerization leads to numerous RBC and systemic physiological abnormalities with variable phenotypic severity [2].

Hemoglobin C (HbC) is a variant in which lysine is substituted for glutamic acid at position 6 of the β-globin chain. HbC has a tendency to crystallize in oxy-configuration [3]. When HbC and HbS are present together (HbSC disease), this may lead to an acceleration of HbC crystallization [4], which promotes RBC dehydration. As a consequence, mean corpuscular Hb concentration (MCHC) increases, inducing HbS polymerization, and reducing RBC deformability [5,6]. Thereby, as well as RBCs from SCA patients, RBCs from SC patients are also characterized by a loss of deformability. SC patients are marked by milder anemia than SCA patients with an over-representation of chronic organ complications such as retinopathy, otologic disorders or osteonecrosis [7].

At its core, SCD is a hemorheological disease [8], with HbS polymerization leading to the loss of RBC deformability considered to be the primary factor responsible for the vaso-occlusive crises (VOC) and all downstream progressive organ dysfunctions. While the underlying genetic mutations described above are well known, the exact pathophysiological mechanisms responsible for the individual phenotypic manifestations and long term complications are not yet fully elucidated. After a brief description of basic hemorheology, the present review focuses on the role of the hemorheological abnormalities in the occurrence of several SCD complications.

2. Basic hemorheology

Hemorheology focuses on blood flow as well as the properties and interaction of blood cells. The specific flow behavior of blood is mainly determined by its structure. Blood is a two-phase liquid and its rheological properties are determined by the flow properties of both phases and the relative contribution of these phases to the total volume of blood. The two phases are 1) plasma and 2) cellular components.

2.1. Blood viscosity

Blood viscosity is an important determinant of local flow characteristics. Blood exhibits shear thinning behavior: its viscosity decreases exponentially with increasing shear rates. Therefore, no single viscosity value exists to characterize blood viscosity, it should rather be expressed as a function of shear rate, which mainly depends on the blood flow rate and the vessel radius (Fig. 1) [9]. In addition, blood has visco-elastic and thixotropic properties also affecting local hemodynamics. A thixotropic fluid is a fluid whose viscosity is a function not only of the shearing condition, but also of the previous history of motion within the fluid [10]. Indeed, for a given flow/shear rate, blood viscosity usually decreases with the length of time the fluid has been in motion (Fig. 2). The relative contribution of RBCs (the most significant cellular element) is represented by the hematocrit (Hct) value. A rise in Hct increases blood viscosity at all shear rates and thixotropy, more particularly at low shear rate, like in veins and venules [9,10].

Plasma is a Newtonian fluid, with its viscosity being independent of shear rate and dependent mainly on the concentration of fibrinogen. Increased plasma viscosity affects blood viscosity and is also an important modulator of endothelial nitric oxide synthase activity through its effects on wall shear stress [11].

2.2. RBC deformability and aggregation in normal blood

The shear thinning characteristics of blood are determined primarily by the mechanical properties of circulating erythrocytes. There are two unique RBC characteristics that are primarily responsible for this non-Newtonian behavior. At high shear rates (characterized by high shear forces), RBCs undergo an extensive passive shape change (RBC deformability) forcing them to align parallel with laminar flow streamlines [9]. As a consequence, blood viscosity and the internal resistance of blood to flow decrease [9]. RBC deformability is determined by cell geometry, cytoplasmic composition, internal viscosity and membrane characteristics [12]. At low flow rates and under low shear forces, normal RBCs have a biconcave disk shape and they lose their parallel orientation with the flow streamlines [9].

In addition, RBCs tend to form aggregates at low shear rates (i.e., in veins) contributing to the observed exponential increase in blood viscosity. RBC aggregation is a physiological process under low shear conditions or stasis and is characterized by the formation of three-dimensional structures called “Rouleaux” similar to a stack of coins. This unique process requires low energy and is reversible: RBC aggregates may disaggregate, at least partly, in vascular regions where shear rate is high, such as in arteries, arterioles or capillaries [13]. RBC aggregation depends on the presence of macromolecules in the suspending medium with molecular weight above a well-defined cutoff [14]. Fibrinogen is the most physiologically relevant macromolecule to promote RBC aggregation in the blood. In addition, RBC surface properties, including surface charge and glycocalyx depth, also play an important role in this process [14].

3. Hemorheological profile in SCD at steady state

Owing to the chronic severe anemia, patients with SCA have lower blood viscosity at native Hct under oxygenated conditions than individuals with normal hemoglobin [15]. As a consequence, there is a decrease in the Hct/blood viscosity ratio reflecting RBC oxygen transport effectiveness [15–17], a parameter that correlates well with the level of tissue oxygenation in combined SCA and SC patients [18]. However, when adjusted to a normal Hct levels (40–45%), SCA patients have blood viscosity that is above the controls under oxygenated conditions (Fig. 3) due to the presence of irreversibly sickled cells (ISCs). When de-oxygenated, the sickling of RBCs causes a further rise in blood viscosity at all shear rates [8]. Plasma viscosity has also been shown to be slightly increased in SCA patients at steady state [19] likely due to the increased concentration of circulating fibrinogen and other acute phase reactant proteins.

In contrast to SCA individuals, patients with HbSC disease have higher blood viscosity than healthy controls at native Hct [15] as the milder anemia in these patients is unable to fully offset the rheological effects of abnormal RBCs. Both SC and SCA patients have decreased RBC deformability in comparison to healthy individuals but the situation is worse for SCA patients [15]. RBC aggregation properties have been poorly studied in SCD but several studies reported that RBC aggregation (which depends on the number of RBC aggregates and time for RBC aggregates formation) is rather decreased in both SCA and SC patients compared to healthy individuals. In contrast, once formed, sickle RBC aggregates are 2 to 3 folds more robust than healthy RBC aggregates [15,20]. The lower RBC aggregation seems to be due to the low ability of the rigid ISCs to form aggregates [8,21]. Deoxygenating sickle cell blood in vitro results in a further decrease of RBC deformability and RBC aggregation [22].

4. Hemorheological profile in SCD during vaso-occlusive crisis (VOC)

Very few studies have investigated the hemorheological changes during acute VOC but it seems clear that overall RBC deformability decreases due to massive sickling and RBC dehydration [23,24]. Rieber et al. [25] described a uniform pattern in RBC rheology during the evolution of VOC in 8 SCA patients. Comparison of data on the first and last day of hospitalization showed decreased percentage of circulating sickled cells associated with increased overall RBC filterability upon recovery. The phenomenon is likely related to the lysis of the most rigid and fragile sickled cells and probably, to a lesser extent, to the blockade of the most rigid RBCs into the microcirculation. Unfortunately, however, no data is available at steady state in these patients. Kenny et al. [26] showed that RBC deformability was significantly reduced on day 1 of crisis in nine SCA patients and 24 h before the onset of pain in one additional patient. RBC deformability gradually returned to pre-crisis values by day 8 to 9. Ballas and Smith [24] expanded these observations by conducting prospective studies on 36 SCA patients over five years and found that RBC deformability was reduced early in the crisis and increased to values higher than the steady state as the crisis resolved. Given that RBC deformability varies inversely with the number of irreversible sickle cells and dense cells [27,28], the uniform description of changes in RBC deformability during the evolution of the vaso-occlusive crisis by these different

groups supports the reciprocal changes in the percentage of dense cells as the vaso-occlusive event evolves. Available data to date suggests the following RBC changes during the evolution of a VOC: [1] extensive hemolysis in some, but not all, patients; [2] the overall percentage of sickled cells (including reversibly and irreversibly sickled cells) increases one to three days prior to the clinical crisis followed by a decrease as patients recover; [3] consequently, bulk RBC deformability decreases early in the crisis and increases later as the percentage of rigid cells decreases [24,26–28].

No study to date measured the changes in RBC aggregation during a vaso-occlusive event in SCA and only limited data is available on erythrocyte sedimentation rate (ESR), a parameter that is affected by both Hct and RBC aggregation [29,30]. The increase of fibrinogen during VOC could promote RBC aggregation [30] but further studies are needed to directly investigate this parameter during crisis.

Several studies reported an increase in apparent plasma viscosity during VOC with peak values on or after day 6 [29,31,32]. The observation also suggests that the increase, at least in part, is secondary to the increase in plasma fibrinogen.

Each of the hemorheological abnormality previously described may increase blood viscosity at low and/or high shear rates, further altering blood flow.

5. Hemorheological predictors of SCD complications

One of the most challenging tasks in the field of SCD is the prediction and prevention of acute and chronic disease complications with the aim to improve the clinical management of affected patients. Several bio-markers and physiological parameters have been evaluated in this regard and the work is still underway. Recently, a new model of SCA pathophysiology has been proposed [33,34] with the presence of two clinical/biological phenotypes: 1) the hemolytic-endothelial dysfunction phenotype and 2) the viscosity–vaso-occlusion phenotype. These two sub-phenotypes overlap and are not completely distinct [34].

5.1. Hemolytic-endothelial dysfunction phenotype

The hemolytic-endothelial dysfunction phenotype in SCA is characterized by a high rate of hemolysis that not only impacts vascular physiology at the pre-capillary arteriole level, but also in large arteries [34, 35]. As a result of hemolysis, free hemoglobin is released into plasma. Part of the free hemoglobin quickly reacts with haptoglobin and the complex is cleared from plasma. However, this system is insufficient to eliminate the excess of free circulating hemoglobin in SCA and a large amount reacts with nitric oxide (NO) to produce methemoglobin and nitrate ultimately leading to reduced NO bioavailability [34]. The release of RBC arginase into the plasma catabolizes plasma arginine reducing its bioavailability. In addition, heme and heme-iron dissociate from Hb catalyzing the production of reactive oxygen species (ROS) that serve as potent NO scavengers [34]. The increased oxidative stress stimulates RBC senescence, RBC phagocytosis by macrophages and extravascular hemolysis. Oxidization of the flippase enzyme and/or activation of the phospholipid transporter scramblase lead to the disruption of membrane phospholipid asymmetry followed by phosphatylserine exposure on the outer membrane leaflet and

membrane vesiculation resulting in a release of RBC microparticles. RBC microparticles have been recently demonstrated to cause vaso-occlusion at the kidney level in a murine model of SCD [36] and to scavenge NO, hence reducing its bioavailability [37]. The decline in blood NO content leads to endothelial dysfunction, over-expression of vascular adhesion molecules and impaired vasomotor tone [38,39]. In support of these mechanisms, plasma from patients with SCA contains cell-free ferrous oxyhemoglobin, which stoichiometrically consumes micromolar quantities of NO and abrogates forearm blood flow response to NO donor infusion [40]. Although not shared by all the scientific community [41], these biological alterations seem to be involved in the development of pulmonary hypertension [42], glomerulopathy [43], leg ulcers [44], priapism [34], cerebral vasculopathy [35], ischemic stroke [45] and clinically silent cerebral infarction [46]. In SCA patients with glomerulopathy, Lamarre et al. [47] reported lower Hb level and RBC deformability as well as higher RBC aggregates strength when compared to subjects with normal kidney function. Decreased RBC deformability and elevated RBC aggregates strength may disturb blood flow at the pre-capillary level, thereby promoting impaired oxygen delivery, tissue damage and end organ dysfunction. Connes et al. [48] also reported decreased RBC deformability and lower Hct/blood viscosity ratio in SCA patients with recurrent leg ulcers compared to those who never had this complication. Decreased RBC deformability seems to be the hallmark of the hemolytic phenotype with the more rigid RBCs being more fragile [21]. The findings of Bartollucci et al. [49] are in agreement with this hypothesis as they reported higher number of dense RBCs in patients with leg ulcers, renal dysfunction and priapism. It is unknown whether patients with pulmonary hypertension and cerebral vasculopathy are also characterized by the presence of increased number of rigid RBCs but it has been recently [35] suggested that this might indeed be the case. Further studies are needed to explore this hypothesis.

5.2. Viscosity–vaso-occlusion phenotype

Painful vaso-occlusion, acute chest syndrome and osteonecrosis have been considered in the viscosity–vaso-occlusion phenotype with vascular occlusion beginning primarily in the post-capillary venules [34]. A large epidemiological study in the United States (the Cooperative Study of Sickle Cell Disease) demonstrated that high Hct and Hb increased the risks for VOC [50] and acute chest syndrome [51], respectively, in SCA. This is in agreement with previous findings showing that Hb value is an independent predictor for the development of acute pain crisis in SCA [52]. As discussed before, Hct is a key determinant of blood viscosity, particularly at low shear where the rise in viscosity is exponential. Two recent works further strengthened this observation: one performed in SCA adults [53] and the other one in children [54]. These studies found that SCA patients with more frequent hospital admissions for VOC had higher blood viscosity at steady state than patients with less frequent hospitalizations. Moreover, blood viscosity was shown to rise further during a vaso-occlusive episode [30].

SC patients generally have higher blood viscosity than SCA subjects at native Hct [15]. Despite this observation, SC patients are at lower risk for developing VOC. One possible explanation is that overall vascular function and vasoreactivity would be better preserved in SC than in SCA patients [55,56], owing to the reduced amount of circulating toxic plasma

free Hb and heme-derived products. Nevertheless, elevated blood viscosity in SC patients seems to predispose this population to proliferative retinopathy [57] and certain otologic disorders [58].

The pathogenesis of osteonecrosis in SCA subjects is not yet entirely clear [59]. The proximal epiphyseal segments of the humerus and the femur are in tightly enclosed spaces with a single feeding artery and draining vein. One possible scenario is that increased blood viscosity limits venous outflow leading to an increase in tissue pressure within the enclosed space [59]. This pressure then could reduce arterial input with resultant hypoxia of the marrow and bone. While abnormal blood viscosity is definitely involved in the pathophysiology of acute painful VOC in SCA, its role is less clear in the development of osteonecrosis [60,61]. This paradox is due to the fact that patients with osteonecrosis have increased RBC deformability, which compensates for the increased Hct and leads to a relative “normalization” of blood viscosity in SCA patients [60]. This hemorheological picture seems to be specific of SCA patients with osteonecrosis since SC patients with and without this complication are not different regarding blood rheology or hematology [58].

Although an increase of RBC deformability is beneficial for blood flow and tissue perfusion in the healthy population, increased RBC deformability in SCA patients seems to increase the risks for osteonecrosis [60] and acute painful vaso-occlusion [52,54]. While RBC deformability is decreased during vaso-occlusive events, Ballas et al. [24] demonstrated that high level of RBC deformability during the recovery phase of a painful vaso-occlusive event was a predictor of a new painful crisis. Lande et al. [52] also reported a significant and positive correlation between the incidence of painful crisis in SCA and RBC deformability, a result initially reported by Ballas et al. [62,63] This surprising finding may be explained by the fact that sickle RBCs with the highest deformability are also the most adherent RBCs to the vascular wall, thus decreasing the lumen of microvessels, slowing blood flow and initiating vascular occlusion [63–65]. While increased or decreased RBC deformability is not a predictor of the occurrence of VOC or osteonecrosis in SC patients, reduced RBC deformability seems to increase the risks for retinopathy in this population [58].

6. Modulators of blood rheology in SCD

Evidence accumulates that two overlapping phenotypes of SCD exists: 1) patients prone to hemolytic complications as indicated by decreased Hct, low blood viscosity, decreased RBC deformability and RBC aggregation abnormalities; 2) patients prone to vaso-occlusive events as marked by increased Hct, increased RBC deformability (but with values below the normal controls) and increased blood viscosity. A few molecular and cellular modulators have been identified to possibly explain these phenotypic differences.

6.1. α-Gene deletions/α-thalassemia

About 30–40% of SCD patients have coincidental α-gene deletions [66]. The presence of α-thalassemia has been shown to modulate the clinical presentation of SCA [34]. Several studies reported a protective effect of α-thalassemia in SCA for the following complications: glomerulopathy [43,47,67], cerebral vasculopathy/ischemic stroke [35,45,68], leg ulcers [69,70], and priapism [71]. The reduced proportion of HbS, lower mean corpuscular

hemoglobin concentration and decreased hemolysis are likely to provide the protection against the above complications [72,73]. The reduced rate of hemolysis in SCA patients with at least one α-gene deleted could lead to improved NO bio-availability and bio-activity, hence better conserved vascular function although this hypothesis has never been tested [34]. Complementary to the above papers, the recent study of Lamarre et al. [47] found that α-thalassemia may protect from vascular complications, specifically from glomerulopathy, through its effect on RBC rheology. The authors demonstrated that the presence of α-thalassemia in SCA patients improved RBC deformability, a finding also reported previously by others [63,72], and decreased the strength of RBC aggregates. These RBC rheological effects may mechanically improve blood flow and tissue perfusion while limiting hemolysis at the same time. On the other hand, co-existence of α-thalassemia and SCA has been shown to increase the incidence of painful VOC and the risk of osteonecrosis [50,60,61,74]. The greater RBC deformability observed in SCA patients with α-thalassemia could predispose them to develop VOC and osteonecrosis because more deformable sickle RBCs are more adherent to the vascular wall than dense rigid RBCs, hence initiating vaso-occlusion [63–65]. In contrast to SCA patients, the presence of α-thalassemia in sickle SC disease seems to protect patients from developing osteonecrosis or vaso-occlusive events [34,66]. Further studies are warranted to understand the reasons of this protection.

6.2. β-globin haplotypes

The HbS gene may be found on a genetic background of four to five major β-globin-like gene cluster haplotypes [75]. Very few studies investigated the effects of β-globin haplotypes on hematological and hemorheological parameters in SCA but Powars et al. [76] reported lower RBC deformability in patients with the CAR/BEN haplotypes, known to be one of the haplotype configuration associated with a severe expression of the disease. This was mainly due to a low HbF level. Further studies are needed to test the effects of β-globin haplotypes on the other hemorheological parameters, as well as the effects of β-globin haplotypes combined or not with α-thalassemia.

6.3. HbF level

The large Cooperative Study on Sickle Cell Disease previously demonstrated an inverse correlation between HbF levels and the frequency of painful crises and early death [50,77]. Moreover, it was shown that the majority of SCA patients from some regions of Saudi Arabia [78] and India [79] who co-inherit another genetic determinant associated with high HbF levels, have a very mild sickling disorder. These clinical and epidemiological observations are supported by laboratory studies showing that the exclusion of HbF from the HbS polymer inhibits HbS polymerization [80]. The increase of HbF and F-cells in patients under hydroxyurea treatment results in a decrease of the proportion of dense dehydrated RBCs, an improvement of the mean RBC deformability and a decrease of the robustness of RBC aggregates [81,82], hence decreasing the clinical severity of SCA patients [83]. Note that the impact of hydroxyurea on HbF and RBC rheology is not the only factor involved in the improvement of the clinical severity of SCA patients receiving this medication: the pleiotropic effects of hydroxyurea on endothelial activation and adhesion processes, nitric oxide metabolism, oxidative stress, microparticles genesis and thrombosis, also play a role [84,85]. While the associations between variable levels of HbF and disease severity in SCA

have been widely investigated, the role of HbF, as well as HbF enhancer such as hydroxyurea, is not well defined in SC disease [85].

6.4. Oxidative stress

Oxygen free radicals have been demonstrated to damage RBCs from healthy donors by decreasing their deformability and aggregability, and by increasing the strength of RBC aggregates [86]. RBCs from SCA patients have been reported to generate a 2-fold greater amounts of super-oxide anion (O2•–), hydrogen peroxide (H_2O_2) and hydroxyl radical (•OH) than healthy RBCs [87–92]. Hierso et al. [93] recently reported higher RBC reactive oxygen species (ROS) content in both SCA and SC patients compared to healthy subjects, with the highest RBC ROS content observed in SCA patients. In parallel, RBC glutathione (GSH) content was lower in sickle cell patients compared to healthy subjects, especially in SCA patients. The increased pro-oxidant generation in SCA patients results in excessive antioxidant consumption and thus decreased antioxidant capacity [94,95]. Hierso et al. [93] recently use t-butyl hydroperoxide (TBHP) as an in-vitro agent to mimic oxidative stress on RBCs from sickle cell patients. The authors showed that TBHP treatment increased RBC ROS production and decreased RBC GSH content in SCA and SC patients, as well as on RBCs from healthy subjects. Concomitantly, TBHP decreased RBC aggregation and increased the strength of RBC aggregates in these three groups but the increase in RBC aggregates strength was greater in sickle cell patients. TBHP also decreased RBC deformability in the three groups but the impairment was of higher magnitude in sickle cell patients. These data suggest that RBCs from sickle cell patients have an exaggerated response to oxidative stress, which is accompanied by a profound abnormal hemorheological profile, with greater alterations in SCA than in SC patients. Further studies are needed to test the effects of oxidative stress on RBCs from sickle cell patients with or without α-thalassemia or glucose-6-phosphate deficiency, which are well known to modulate the antioxidant capacity of patients.

6.5. Nitric oxide (NO)

Recent evidence supports a key role of the RBC nitric oxide synthase (NOS) activity and RBC NO production in the modulation of RBC deformability of healthy individuals [96–98], through S-nitrosylation process of the α- and β-spectrin chains of the RBC [99]. Grau et al. [99] demonstrated that stimulating the RBC NOS by the PI3 kinase/Akt pathway resulted in a greater amount of RBC nitrite and an improvement in RBC deformability in healthy subjects. Grau et al. [100] and Mozar et al. [101] recently focused on the RBC-NOS in SCA and SC patients, respectively: surprisingly, they found higher activity in comparison with healthy individuals, which resulted in a high amount of RBC nitrite and S-nitrosylated α- and β-spectrins. However, in contrast to what happened in healthy RBCs [99], the accumulation of NO into the RBCs of SCA patients was not associated with an improvement of RBC deformability [100]. It is suspected that the rapid conversion of RBC NO into peroxynitrite would further affect RBC deformability [100].

Several works also investigated the effects of various NO donors, such as sodium nitroprusside (SNP) or deta NONOate, on the RBC deformability of healthy individuals [98]. While some studies showed a positive effect [99,102], others did not report any effect

[103]. In fact, recent studies found that NO donors protect against the loss of deformability caused by calcium in normal RBCs but no effect of any donors is observed when calcium influx is not induced [103,104]. NO is suggested to act as an anti-eryptotic agent (eryptosis = RBC “apoptotic-like” death) [105]. Importantly, the effects of NO donors have been recently tested on sickle RBCs [103]. The authors demonstrated that the addition of SNP (or to a lesser extent, sodium nitrite) on sickle RBCs exposed to deoxygenation to promote dehydration, resulted in substantial improvements in RBC deformability and hydration [103]. SNP had no effect on calcium influx but reduced potassium efflux leading the authors to suggest that SNP and perhaps certain nitrogen oxides (like nitrite) inhibit the Gardos channel and may be able to protect sickle cells from dehydration. These findings are particularly important in the context of complications such as leg ulcers [48] and glomerulopathy [47] where RBC deformability is very reduced. Minitti et al. [106] showed that local application of sodium nitrite 2% cream on leg ulcers of SCA patients caused a decrease in ulcer size and increased peri-wound cutaneous blood flow. Improved vascular function, as well as hemorheological effects, could be at the origin of these beneficial adaptations.

7. Conclusion

Progress has been made in the last decades in the understanding of the pathophysiological mechanisms involved in SCD. Previous and recent studies identified several potential biomarkers and hemorheological predictors of various acute and chronic complications that paved the way for stimulating novel approaches to develop appropriate therapies. Due to its positive effects on various biological parameters, the incorporation of hydroxyurea in the therapeutic arsenal of SCA significantly improved the clinical severity and the quality of life of patients but, can, in some cases, produce medically significant side effects. Several drugs with potential hemorheological impact, such as the Aes-103 molecule (Baxter, USA) which prevents HbS polymerization and the formation of rigid RBCs or the poloxamer 188 (Mast Therapeutics, USA) which would decrease RBC aggregability and RBC adhesiveness, are currently tested in the context of SCD. There is no doubt that these recent developments in association with collaborative efforts between scientists from different fields should allow further improvement of the clinical condition of SCD patients.

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Practice points

- The study of blood rheology in patients with SCD might allow for the identification of biomarkers of acute VOC.
- Study of blood rheological parameters and genetic/epigenetic factors may help in identifying sickle cell subgroups at risk for specific acute and chronic complications.

Research agenda

- Development of efficient strategies and therapies to improve the hemorheological abnormalities and clinical condition of patients with Hb SC disease.
- Identification of biomarkers predicting adverse clinical events in SC disease.
- Development of efficient hemorheological therapies to prevent and improve the clinical management of vaso-occlusive complications in sickle cell disease.

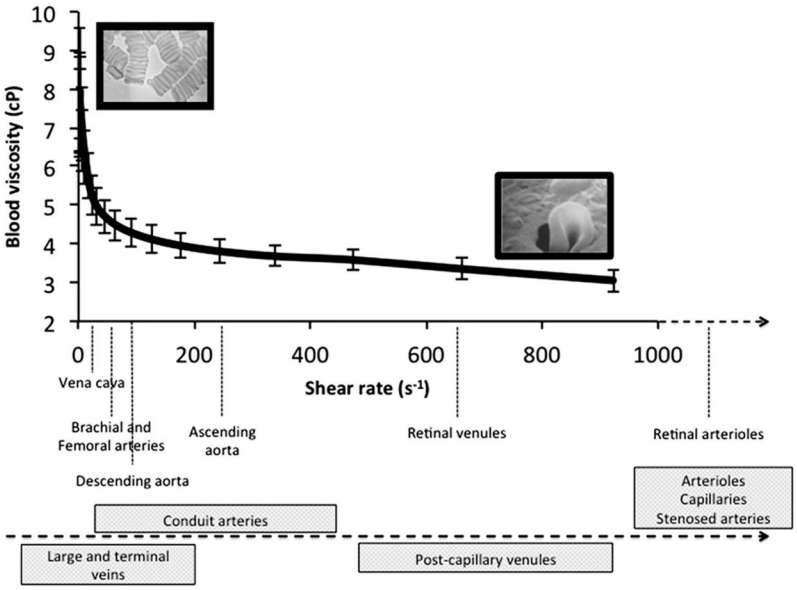

Fig. 1.

Effects of shear rate and red blood cell rheological properties on blood viscosity. This figure shows the shear-thinning properties of blood, with blood viscosity decreasing when shear rate increases. At low shear rates, blood viscosity mainly depends on red blood cell aggregation. As the shear rate increases, red blood cell aggregates progressively dissociate. At high shear rate, the ability of red blood cell to deform under shear affects blood viscosity. The figure also gives information about the shear rate values that can be found in the vascular system [107–111]. In a given vessel, shear rate can be estimated by 8 * mean centerline blood velocity / diameter of the vessel. Photography (courtesy of Dr. Max R Hardeman): on the left = red blood cell aggregates; on the right: red blood cell in the process of deforming to pass through a micropore of 5 μm.

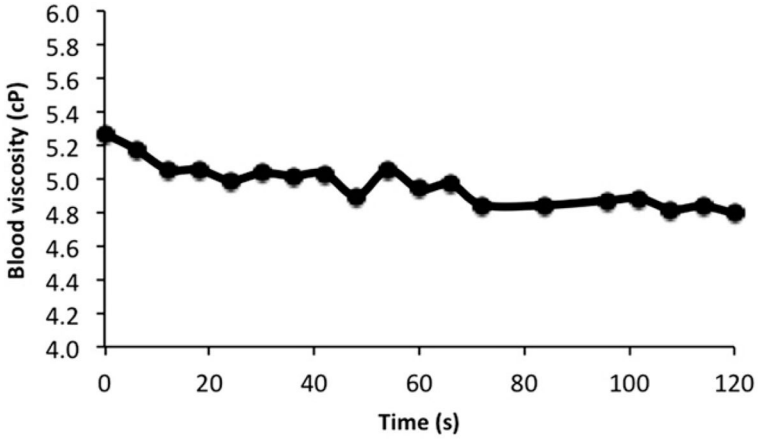

Fig. 2.

Effects of time exposure at a fixed shear rate on blood viscosity. This figure shows the decrease over time (2 min) of blood viscosity when the fluid is sheared at 10 s^{-1}, which reflects the thixotropic property of blood. The progressive rupture of red blood cell aggregates over time makes the blood less viscous.

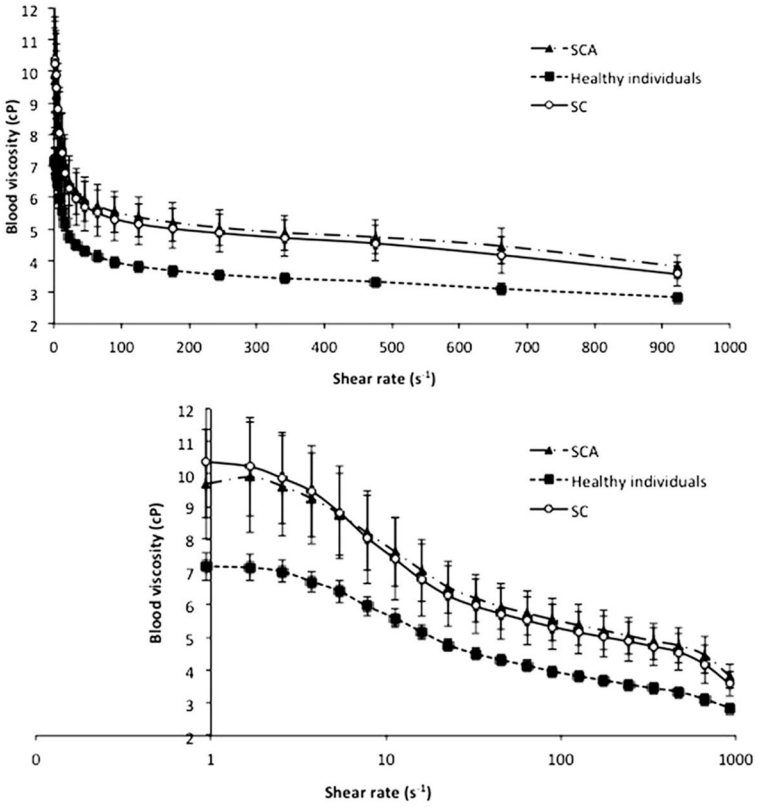

Fig. 3.

Blood viscosity vs shear rate curves in healthy individuals, SC and SCA patients at adjusted hematocrit (40%). The second graphic (at the bottom) shows the same data than the first one (at the top) but shear rate values are log transformed to better see the difference at low shear rates. The two sickle cell groups exhibit higher blood viscosity at 40% hematocrit than the healthy population because of the presence of robust red blood cell aggregates and rigid red blood cells.