Blood Reviews 30 (2016) 111–118

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

The role of blood rheology in sickle cell disease

Philippe Connes [a,b,c,d,*], Tamas Alexy [e,f], Jon Detterich [g], Marc Romana [a,b], Marie-Dominique Hardy-Dessources [a,b], Samir K. Ballas [h]

[a] Inserm UMR 1134, Hôpital Ricou, CHU de Pointe-à-Pitre, 97157 Pointe-à-Pitre, Guadeloupe
[b] Laboratory of Excellence GR-Ex «The red cell: from genesis to death», PRES Sorbonne Paris Cité, 75015 Paris, France
[c] Institut Universitaire de France, Paris, France
[d] Laboratoire CRIS EA647, Section "Vascular Biology and Red Blood Cell", Université Claude Bernard Lyon 1, 69100 Villeurbanne, France
[e] Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA
[f] Section of Cardiology, Atlanta VA Medical Center, Decatur, GA, USA
[g] Children's Hospital Los Angeles, Division of Cardiology, USA
[h] Department of Medicine, Cardeza Foundation for Hematologic Research, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA

ARTICLE INFO

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

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.

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.

* Corresponding author at: Laboratoire CRIS EA647, Section "Vascular Biology and Red Blood Cell", Université Claude Bernard Lyon 1, 69100 Villeurbanne, France.
E-mail address: pconnes@yahoo.fr (P. Connes).

http://dx.doi.org/10.1016/j.blre.2015.08.005
0268-960X/

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].

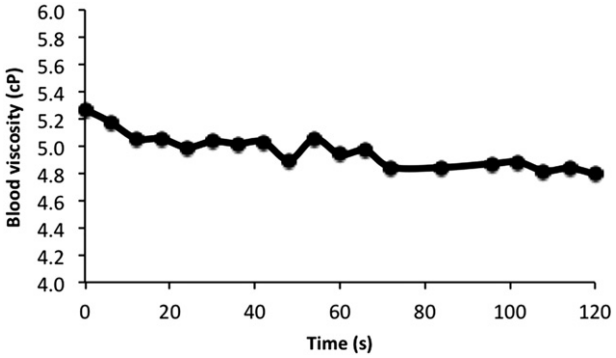

Fig. 2. Effects of time exposure at a fixed shear rate on blood viscosity. This figure shows the decrease over time (2 min) of blood viscosity when the fluid is sheared at 10 s^{-1}, which reflects the thixotropic property of blood. The progressive rupture of red blood cell aggregates over time makes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

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

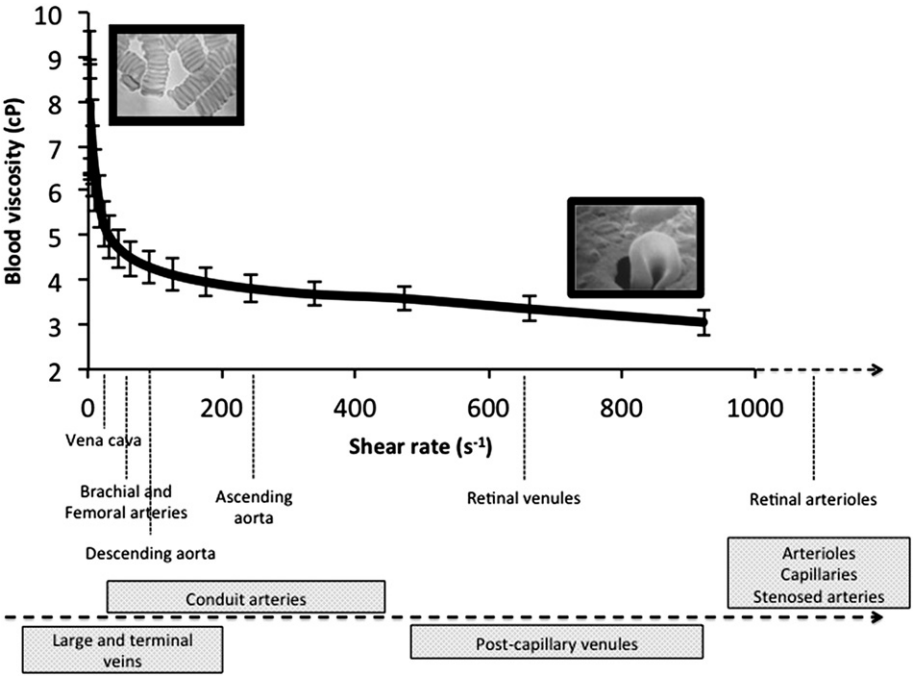

Fig. 1. Effects of shear rate and red blood cell rheological properties on blood viscosity. This figure shows the shear-thinning properties of blood, with blood viscosity decreasing when shear rate increases. At low shear rates, blood viscosity mainly depends on red blood cell aggregation. As the shear 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.