Journal of Biomechanics 50 (2017) 34–41

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Biomechanics and biorheology of red blood cells in sickle cell anemia

Xuejin Li [a,*], Ming Dao [b], George Lykotrafitis [c,d], George Em Karniadakis [a,*]

[a] Division of Applied Mathematics, Brown University, Providence, RI 02912, USA
[b] Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[c] Department of Biomedical Engineering, University of Connecticut, Storrs, CT 06269, USA
[d] Department of Mechanical Engineering, University of Connecticut, Storrs, CT 06269, USA

ARTICLE INFO

Article history:
Accepted 2 November 2016

Keywords:
Sickle cell disease
Erythrocyte
Biomechanics
Biorheology
Adhesion

ABSTRACT

Sickle cell anemia (SCA) is an inherited blood disorder that causes painful crises due to vaso-occlusion of small blood vessels. The primary cause of the clinical phenotype of SCA is the intracellular polymerization of sickle hemoglobin resulting in sickling of red blood cells (RBCs) in deoxygenated conditions. In this review, we discuss the biomechanical and biorheological characteristics of sickle RBCs and sickle blood as well as their implications toward a better understanding of the pathophysiology and pathogenesis of SCA. Additionally, we highlight the adhesive heterogeneity of RBCs in SCA and their specific contribution to vaso-occlusive crisis.

1. Introduction

Sickle cell anemia (SCA), the first identified "molecular disease" (Pauling et al., 1949; Strasser, 1999), is one of the most common genetic inherited hematological disorders, which can cause several types of chronic complications such as vaso-occlusive crisis (VOC), hemolytic anemia, and sequestration crisis (Bunn, 1997; Barabino et al., 2010). The pathogenesis of vaso-occlusion involves several processes across multiple time and length scales, from $\mathcal{O}(10^{-1}\ \mathrm{s})$ to $\mathcal{O}(10^{3}\ \mathrm{s})$ for the kinetics of HbS polymerization to the hemodynamics of sickle blood flow, and from $\mathcal{O}(10^{-9}\ \mathrm{m})$ to $\mathcal{O}(10^{-5}\ \mathrm{m})$ for the size of the protein to the dimensions of the microcirculatory vessels. During the past few decades, different aspects of this disease have been successfully investigated (Barabino et al., 2010; Steinberg, 1999; Frenette and Atweh, 2007; Yazdani et al., 2016). At the molecular scale, the HbS polymerization process has been characterized by a double nucleation mechanism. At the cellular scale, sickle RBCs are characterized by remarkable heterogeneity in density, morphology, and rigidity. The affected RBCs become more rigid and "sticky" compared to normal RBCs, causing frequent vaso-occlusive episodes and depriving tissues and organs of oxygen. At the microvascular scale, early studies postulated that the HbS polymerization resulted in the entrapment of sickle RBCs in capillaries (Fig. 1) (Kaul et al., 1986), and subsequent studies further revealed the *multi-interactional* and *multi-stage* nature of the VOC (Kaul et al., 1989, 1994, 2009; Kaul and Fabry, 2004).

Currently, hydroxyurea (HU) is the only approved medication in widespread use for the treatment of SCA (Ware, 2010). The treatment of SCA patients with HU has the following beneficial effects: (i) increased production of fetal hemoglobin (HbF) and therefore increased *delay time* of the RBC sickling process (Bridges et al., 1996; Atweh and Schechter, 2001), (ii) reduction of white blood cell (WBC) count and expression pattern of cellular adhesion molecules (Charache et al., 1996), and (iii) reduction in the frequencies of blood transfusion (Ware et al., 1999). These beneficial effects ameliorate the severity of SCA. However, clinical studies report that HU is ineffective for many patients for unclear reasons (Manwani and Frenette, 2013). Moreover, the aforementioned studies indicate that the clinical expression of SCA is heterogeneous, making it hard to predict the risk of VOC, resulting in a serious challenge for disease management. Here, we review experimental studies and predictive simulations related to biomechanical and biorheological properties as well as heterogeneity-related issues associated with SCA.

2. Biomechanical and biorheological properties of sickle RBCs

Quantification of the biomechanical and biorheological characteristics of RBCs can improve our understanding of the etiology of a number of human diseases. In SCA, partial deoxygenation of sickle RBCs in post-capillary venules causes HBS polymerization followed by possible RBC sickling. Repeated RBC sickling can result in the development of defects in the RBC membrane, reduced RBC

* Corresponding authors.
E-mail addresses: Xuejin_Li@brown.edu (X. Li), George_Karniadakis@brown.edu (G.E. Karniadakis).

http://dx.doi.org/10.1016/j.jbiomech.2016.11.022
0021-9290/

deformability, increased time of RBC adherence to venules, and eventually in vaso-occlusion.

2.1. Sickle cell biomechanics

Over the past few decades researchers investigated the biomechanics of sickle RBCs as indicators of the severity of the disease. The available experimental methods can measure the biomechanical properties of a large number of sickle RBCs at the same time (Chien et al., 1970; Messmann et al., 1990; Connes et al., 2014), or isolated sickle RBCs (Byun et al., 2012; Maciaszek and Lykotrafitis, 2011). For example, early studies using filtration (Chien et al., 1970) or ektacytometry (Messmann et al., 1990) directly examined the biomechanical properties of the sickle RBC membrane and determined that sickle RBCs are less deformable than normal RBCs. In a recent study, decreased RBC deformability and aggregation, measured using ektacytometry and laser backscatter of Percoll-separated sickle RBCs, have been shown to correlate with hemolysis (Connes et al., 2014). However, these techniques measure properties averaged over all RBCs in a blood sample, without regard to the cell heterogeneity within sickle blood sample. Single-cell experimental methods include micropipette aspiration, optical tweezers, flickering analysis, atomic force microscopy (AFM), diffraction phase microscopy, and recently, microfluidics and ultrasounds. The optical tweezers and micropipette aspiration techniques subject the RBC directly to mechanical deformation and yield shear modulus of sickle RBCs in the range of 8–20 μN m^{-1}

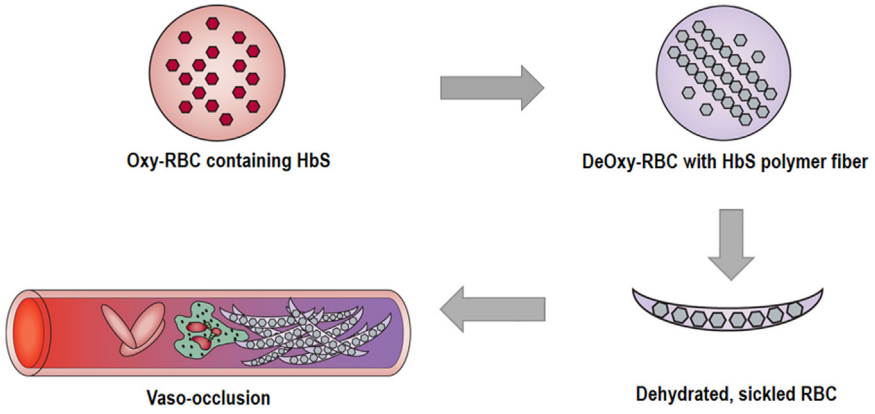

Fig. 1. *Vaso-occlusive crisis in SCA*. Entrapment of sickle RBCs in microcapillaries. The polymerization of HbS molecules under Deoxy causes cell sickling and damage to the membrane. Some sickle RBCs get trapped in the microvasculature leading to vaso-occlusion. Adapted with permission from Rees et al. (2010).

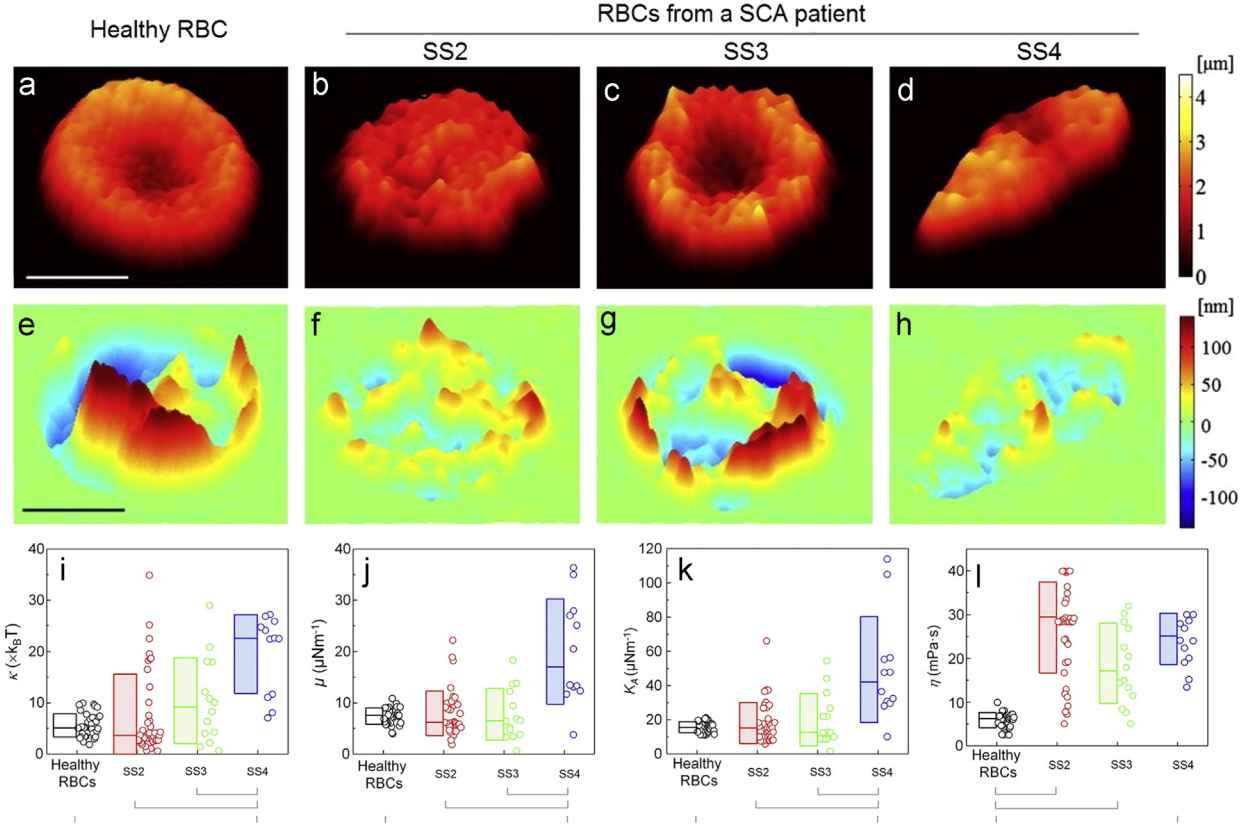

Fig. 2. *Biomechanical properties of RBCs in health and in SCA*. (a–d) Topographies of individual RBCs from healthy individuals (a), SS2 sickle RBC (b), SS3 sickle RBC (c), and SS4 sickle RBC (d). (e–h) Instantaneous membrane displacement maps of RBCs in (a–d). Measurements of (i) bending modulus κ, (j) shear modulus μ, (k) area modulus K_A, and (l) viscosity η for healthy, and SS2, SS3 and SS4 RBCs in SCA. Reprinted with permission from Byun et al. (2012).