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Characterization of Reduced Viscoelasticity in Sickle Cell Disease Mouse Red Blood Cells Using Parallel Plate Rheometry

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ABSTRACT Sickle Cell Disease (SCD) is a genetic disorder characterized by the abnormal deformation of red blood cells (RBCs) into a sickle shape, leading to a cascade of complications that severely affect the circulatory system. Under normal physiological conditions, the viscoelastic properties of RBCs allow them to deform and navigate through narrow capillaries, facilitating efficient blood flow and oxygen delivery. However, in SCD, the sickled RBCs exhibit significantly altered viscoelastic properties, impairing their ability to deform. This rigidity, combined with the increased tendency of sickled RBCs to adhere to the vascular endothelium, contributes to vaso-occlusive crises, where blood flow is obstructed, leading to tissue ischemia and severe pain. Understanding the critical role of viscoelasticity in RBCs function, and how its disruption in SCD contributes to the pathophysiology of the disease, underscores the importance of targeted therapeutic strategies aimed at restoring or compensating for these mechanical deficiencies in sickled RBCs. In this study we intend to compare the viscoelastic properties of SCD blood to regular blood to quantify RBC rigidity in terms of viscosity and yield stress as a factor when developing new treatments for sickled RBCs.

Using a TA Instruments Discovery HR-2 rheometer (New Castle, Delaware, United States), equipped with an aluminum 40 mm flat plate, we quantified the viscoelastic behavior of SCD blood from male 8- to 12-week-old homozygous Townes [B6; 129-Hbatm1(HBA)Tow Hbbtm2(HBG1, HBB) Tow/Hbbtm3(HBG1, HBB) Tow/J] transgenic SCD mice of C57BL/6J background and compared to wild-type blood from healthy male 8- to 12-week-old C57BL/6J mice, both blood samples hematocrits were equated to ensure rheological normalization and temperature was maintained at 37 degrees Celsius to simulate body conditions. The comparison was based on viscosity at varying shear rates, along with the phase angle of each sample as oscillatory strain increased. To determine how fluid viscosity varies between SCD and regular blood, a steady-state flow shear rate sweep test was performed between 1 and 1000 s−1^{-1}−1, both from the minimum shear rate to the maximum shear rate and vice versa. Afterward, an amplitude strain sweep test was conducted at a constant frequency of 0.5 Hz with varying stress between 0.002 and 2.0 Pa to measure the storage and loss modulus, and to determine the yield stress of each sample based on the strain value at which the phase angle becomes 45 degrees, signifying the transition from elastic to viscous behavior.

The flow sweep tests revealed that SCD blood maintained a higher viscosity at a low shear rate of 25 s−1^{-1}−1 compared to wild type blood (15 vs. 6.7 cP), with higher stress being applied to induce steady state flow in SCD blood, along with plastic behavior from the RBCs. The amplitude sweep tests showed that SCD blood could not reach a yield stress point, as the phase angle did not achieve 45 degrees, indicating an inability to properly transition from elastic forces dominating the fluid to viscous forces that allow flow within a system. In contrast, the wild-type blood achieved a yield stress point at a specific oscillation strain (5%), corresponding to a pressure of 0.03 Pa, indicating normal viscoelastic behavior that facilitates blood flow through a living system. These results provide a benchmark for viscoelasticity in blood to maintain normal living conditions, and preliminary values for SCD blood that new therapies can target to affect. By accounting for the viscoelastic behavior of SCD blood, we can quantify the biomechanical properties of blood that should be considered in therapeutic strategies for restoring blood flow activity.