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Simple chronic transfusion therapy, a crucial therapeutic option for sickle cell disease, improves but does not normalize blood rheology: What should be our goals for transfusion therapy?

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Abstract

Sickle cell anemia is characterized by a mutation resulting in the formation of an abnormal beta-hemoglobin called hemoglobin S. Hemoglobin S polymerizes upon deoxygenation, causing impaired red blood cell deformability and increased blood viscosity at equivalent hematocrits. Thus, sickle cell disease is a hemorheologic disease that results in various pathologic processes involving multiple organ systems including the lungs, heart, kidneys and brain. Red blood cell mechanics and the perturbations on blood flow-endothelial interaction underlie much of the pathology found in sickle cell disease. Transfusion therapy is one of the few therapeutic options available to patients, acting as both primary and secondary prevention of stroke. Transfusion therapy, both simple and exchange, is also used for unremitting and frequent pain crises and pulmonary hypertension. Therefore, understanding basic rheologic changes following transfusion inform other therapeutic options that aim to mitigate this diffuse pathologic process. This review will aim to highlight transfusion effects on blood rheology.

1. Introduction

Sickle cell disease (SCD) stems from a single base pair mutation in the beta-globin gene, converting the sixth amino acid, glutamic acid, to valine [38]. This conversion from a hydrophilic amino acid to a hydrophobic amino acid changes the structure of the beta globin protein such that it polymerizes when it becomes deoxygenated [56]. This leads to decreased erythrocyte deformability and increased whole blood viscosity at equal hematocrit; thus making sickle cell anemia the model for hemorheologic disease [6, 29, 33].

Throughout this issue of the journal, articles will describe various sickle cell disease features, displaying the vast array of downstream molecular, cellular and clinical consequences. Despite the “simplicity” of the gene defect, there is no distinct clinical phenotype [9, 11, 14]. Patients may have any number of clinical sequelae: stroke, acute chest

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syndrome, chronic pain, acute pain crisis, pulmonary hypertension, leg ulcers and renal dysfunction. Phenotypic classification of patients is difficult due to varying symptomatology. The inability to clinically phenotype the patients and the variable timing with which they have crises makes it difficult to devise treatment strategies [10, 12].

There are two prophylactic therapies available, chronic transfusion and hydroxyurea. The former replaces sickle (SS) RBC with healthy (AA) red blood cells (RBC), and the latter creates a mosaic of hemoglobin S and fetal hemoglobin within RBC. Hydroxyurea turns on the genes that produce fetal hemoglobin, which results in varying amounts of hemoglobin S in each individual red blood cell [50, 51, 67]. Bone marrow transplant and gene therapy are being studied for their potential to replace the abnormal beta-globin gene in erythropoietic stem cells, the precursors to mature RBC. Gene therapy is still in the experimental stages and has not become a clinically viable strategy as of yet [16, 30, 72]. Bone marrow transplant therapy has been used clinically, but it is reserved for patients who have undergone significant counseling about the procedure and have a sibling match [69].

Hydroxyurea and bone marrow transplant are aimed at replacing hemoglobin S at the level of the bone marrow, decreasing the internal erythrocyte hemoglobin S concentration. Chronic transfusion therapy improves erythrocyte deformability, anemia and oxygen carrying capacity via whole cell replacement, not internal RBC hemoglobin replacement. Simple transfusion therapy adds AA RBC to the blood stream without removal of SS RBC, with the goal of slow replacement of SS red blood cells over time. This leads to significant iron burden from addition of red blood cells. Exchange transfusion is the simultaneous removal of SS RBC and replacement with AA RBC, which decreases the iron load found in simple chronic transfusions but it is a significant blood resource burden. This article is going to focus on the hemorheologic effects of chronic transfusion therapy.

2. Transfusion as therapy for sickle cell disease – a historic perspective

Transfusion therapy has been a proposed treatment for sickle cell anemia since the disease was first described. Herrick first described the characteristic “sickle shape” of red blood cells in 1910, in an African-American dental student [52]. Shortly thereafter, as transfusion medicine began to grow after World War I, blood transfusion became a therapeutic option for patients with sickle cell disease [8].

2.1. Acute transfusion therapy for sickle cell disease

Acute transfusion therapy is used as a therapy for many different acute crisis events, specifically aplastic crisis, acute chest syndrome, stroke and splenic sequestration [34, 71]. If multi-organ failure occurs, exchange or partial exchange transfusion has been used, with some success, to reverse end-organ failure [35]. An important failure in transfusion therapy was its attempted use in acute vasocclusive pain episodes where it had limited utility and potentially worsened the pain crisis [13].

2.2. Chronic transfusion therapy for sickle cell disease

Chronic transfusion therapy has become standard therapy since the STOP I and STOP II trials demonstrated that transfusion therapy acts as both primary and secondary prevention

of large vessel ischemic stroke, one of the most devastating disease processes in patients with sickle cell anemia [2, 3, 57, 60]. Screening transcranial Doppler (TCD) is an ultrasound measure of middle cerebral artery (MCA) velocity and is used in children with SCD [1, 4, 22]. Increased transcranial Doppler (TCD) velocity is able to predict those patients at high risk for stroke and is utilized to determine which patients should be started on chronic transfusion therapy. Chronic transfusion therapy has been utilized for many years to treat prolonged and unremitting pain episodes [7] and in select patients with chronic renal failure, pulmonary hypertension and recurrent acute chest syndrome [26, 27, 59].

The decision whether to use red cell exchange or simple chronic transfusion therapy is dependent on available resources and the clinical status of the patient. Red cell exchange limits iron overload to some degree but has a higher burden on the blood supply. There are numerous modifications to both simple chronic transfusions and red cell exchange but this review will not delve into this topic. Despite the widespread use of transfusion therapy and its long history in SCD, it is used sparingly; this is due to potential side effects such as hyperviscosity syndrome, hemolytic transfusion reactions, volume overload, and iron overload. With adequate pre-transfusion care that includes blood type, regular screening for alloantibodies, documenting and reviewing all prior transfusion history, and avoiding unnecessary transfusions, the patients can tolerate transfusion therapy with minimal risk.

3. Goals of transfusion therapy and rheologic changes following transfusion

Removing hemoglobin S containing cells while partially correcting the anemia, improving oxygen carrying capacity and improving erythrocyte deformability are the overarching goals of transfusion therapy. An excellent description of blood rheology was provided by Drs. Herbert Meiselman and Oguz Baskurt: “Blood is a two-phase suspension of formed elements (i.e., red blood cells (RBCs), white blood cells (WBCs), platelets) suspended in an aqueous solution of organic molecules, proteins, and salts called plasma. The apparent viscosity of blood depends on the existing shear forces (i.e., blood behaves as a non-Newtonian fluid) and is determined by hematocrit, plasma viscosity, RBC aggregation, and the mechanical properties of RBCs. RBCs are highly deformable, and this physical property significantly contributes to aiding blood flow both under bulk flow conditions and in the microcirculation. The tendency of RBCs to undergo reversible aggregation is an important determinant of apparent viscosity because the size of RBC aggregates is inversely proportional to the magnitude of shear forces; the aggregates are dispersed with increasing shear forces, then reform under low-flow or static conditions. RBC aggregation also affects the *in vivo* fluidity of blood, especially in the low-shear regions of the circulatory system [15].” Ideally, blood flows through the circulatory system with minimal resistance, transitioning smoothly from the conduit arteries, to the small muscular arteries, through the resistance arterioles and into the capillary bed. At each transition and as bulk blood flow interacts with the endothelium, erythrocyte deformability, whole blood viscosity and erythrocyte aggregation combine to play a critical role in minimizing energy loss and resistance to flow [15]. The fundamental abnormality of sickle cell anemia, the presence of

hemoglobin S, impairs deformability, aggregation and whole blood viscosity and thus impairs blood flow [45, 49, 66].

3.1. Whole blood viscosity

Blood is a non-Newtonian shear-thinning fluid (Fig. 1 panel A). In patients with SCD, decreased hematocrit will shift the entire viscosity curve down (Fig. 1 panel B), upon deoxygenation the viscosity curve shifts upward closer to healthy RBC. If hematocrits were equal in patients with sickle cell anemia and healthy subjects, the whole blood viscosity curve under oxygenated conditions would shift upward, surpassing healthy blood viscosity. Deoxygenation of the blood in a patient with sickle cell anemia would shift it even further upward. These are the conditions which predispose to hyperviscosity syndrome in patients with sickle cell anemia if the goal of transfusion were to normalize hematocrit. Figure 1 panel C demonstrates that transfusion therapy increases blood viscosity both acutely and chronically and reaches values that are similar to whole blood viscosity in healthy subjects. The acute increase in viscosity following a transfusion is similar to the increase in whole blood viscosity upon deoxygenation of whole blood from non-transfused SCD patients (Fig. 1 panels B and C). In our experience, there is no difference in whole blood viscosity between non-transfused patients with SCD and chronically transfused patients, when measured immediately pre-transfusion. However, the % SS RBC is much lower, oxygen carrying capacity is increased and the increase in viscosity upon deoxygenation is diminished with improved resistance to blood flow [23].

The goal of transfusion therapy, whether acute or chronic, is not to normalize hemoglobin/hematocrit. For transfusion during an acute crisis, raising hemoglobin slowly by 3 g/dl or slowly returning to baseline hemoglobin/hematocrit is preferred. Transfusion to hemoglobin/hematocrit levels above the patient's usual baseline, in an acute setting, may lead to hyperviscosity syndrome and worsening of the crisis event [40, 42]. The long-term goal for chronic transfusion therapy is hemoglobin of 10 g/dl and <30% HbS cells. Hydroxyurea therapy, a proposed alternative to chronic transfusion therapy for stroke, has been shown to increase hemoglobin and hematocrit without significantly increasing viscosity [43, 44]. Exchange or partial exchange transfusion also maintains or decreases whole blood viscosity as the hemoglobin S percent decreases and hematocrit remains relatively unchanged (Fig. 1 panel D).

3.2. Aggregation and aggregability

Increased viscosity at low shear rate blood flow is driven by RBC aggregation, which is a low energy attraction between RBC that is easily reversed upon increased shear force application [53, 58]. RBC aggregates form rouleaux in the low velocity/shear venous system and rouleaux that are formed in the venous system become disaggregated as they are pumped through the right heart. Hematocrit, plasma protein content, RBC deformability and RBC surface proteins determine the tendency of RBC to aggregate. While plasma fibrinogen content receives much of the attention of RBC aggregation and aggregability in the literature, the size and concentration of the protein in suspension is known to be important for determining RBC aggregation via the depletion model of RBC aggregation. This is why we use 70kDa dextran suspension to determine RBC aggregability [53, 54]. We also correct

all samples to 40% hematocrit to remove the strong effect of hematocrit on measures of aggregation. More recent evidence has pointed to von willebrand factor (500 to 20,000kDa) and thrombospondin 1 (120kDa), in addition to fibrinogen, as determinants of aggregate strength [47]. It is important to note that aggregate strength is determined experimentally by the shear force required to disaggregate RBC whereas aggregation and aggregability is determined by the time over which it takes RBC to aggregate. In order to measure the tendency of RBC to aggregate and to isolate RBC specific properties, termed RBC aggregability, plasma is replaced by 70kd dextran (or similar) as the suspending medium [54]. There is evidence for increased strength of RBC aggregates despite lower aggregation overall in SCD, suggesting that there are opposing aggregation forces at work in patients with SCD [64].

We found that aggregability is increased in SCD but there is no difference from control when aggregation is measured in plasma. Therefore, plasma effects and red cell specific effects on aggregation appear to be in opposition, with the plasma working to decrease aggregation in SCA patients while red cell specific properties work to increase aggregation. Further, aggregation is lower in patients with SCD on chronic transfusion therapy compared to non-transfused SCD patients (Fig. 2), when tested at stasis and low shear-rate. When we compare our data to the recent publication by Nader and colleagues, we see that aggregation at stasis and low shear is not different from control subjects. Further, the effect of SCA plasma on aggregation in the transfused patients is in opposition to their plasma switching experiments, whereby chronically transfused SCA patients show a significantly lower aggregation tendency at both stasis and shear. In that publication they do not state the conditions under which aggregation was measured, specifically if there was any adjustment of hematocrit so perhaps the experimental conditions were different. This highlights the complex relationship between plasma properties and RBC surface properties that promote aggregation, aggregability and aggregate strength, which are not interchangeable terms.

Aggregability is slightly but significantly decreased in banked blood after storage for 7 weeks, potentially complicating the acute effect of transfusion on aggregation in plasma, which may partially explain the lower aggregation and aggregability in the transfused subjects [65]. We found no acute effect of transfusion on aggregation or aggregability (Fig. 3), suggesting that the lower aggregation or aggregability in the chronically transfused group is more likely due to SCA plasma differences and not the infusion of stored AA red blood cells. The clinical implications of plasma acting to decrease aggregation in SCD is unknown, if changes in plasma protein content can significantly alter red blood cell aggregation and deformability, then macro- and microcirculatory blood flow may be significantly altered during periods of crisis and during periods of relative health. We cannot stress enough that the plasma protein rheo-mechanical effect on tendency toward aggregation is dependent on the size and concentration of various proteins, but it says nothing about the aggregate strength if there are adhesion proteins that make RBC more adherent to one another once they are in contact. Interestingly, Nader and colleagues showed that SCA plasma mixed with AA red blood cells caused lower deformability in the AA red blood cells, suggesting that there is an effect of the plasma on either the red cell membrane or internal structure of the red blood cell. Interpretation of mechanical changes must be taken in the context of the

biology of the entire system, including red blood cell internal properties, membrane properties and plasma protein composition.

3.3. Deformability

The average size of RBC is 8 microns, while the average diameter of a capillary is 5–6 microns; therefore, RBC must have the ability to deform as they traverse the microcirculation [15]. The increased surface area to volume ratio of a biconcave disc is why RBC are able to deform to fit through the capillary bed [62]. This allows direct RBC-endothelial membrane interaction for optimal gas exchange. In larger venous blood vessels with slower moving blood flow, aggregation is a major determinant of low shear rate viscosity and therefore resistance to flow [41]. In larger arterial blood vessels with faster and pulsatile blood flow, RBC deformability determines high shear rate viscosity and wall shear forces. Deformability of RBC determines resistance to blood flow and adequate tissue perfusion for gas exchange in the microcirculation [15, 18].

In patients with SCD there is significantly impaired RBC deformability, under both oxygenated and deoxygenated conditions [6, 20]. Impaired RBC deformability is due to constant cycling of polymerization and depolymerization of hemoglobin S. It would be expected that red cell deformability improves as SS RBC are replaced by AA RBC, despite some evidence that RBC deformability decreases as storage time increases [31, 46]. Chronic transfusion therapy increases deformability when compared to RBC from non-transfused SCD patients (Fig. 4). However, there is no acute improvement in RBC deformability at any shear stress after transfusion, (Fig. 4 solid green line to dashed green line). Therefore, we would expect improved microcirculatory blood flow and potentially tissue oxygenation in patients with SCD on chronic transfusion.

3.4. Hematocrit:Viscosity – measure of oxygen delivery potential?

Oxygen delivery is dependent on oxygen carrying capacity (hemoglobin) and cardiac output. Increasing hemoglobin improves oxygen carrying capacity, however, it occurs with an increase in hematocrit and thus viscosity. It has been shown that there is a point at which increasing hematocrit will cause hyperviscosity, slowing of low shear venous blood flow, decreasing blood flow and oxygen delivery. Hyperviscosity syndrome in patients with SCD causes adverse clinical outcomes [63]. Work performed by Chien and colleagues attempted to explain this effect by assessing blood viscosity over various shear rates and at varying hematocrits [39, 55]. They found there is an optimal hematocrit over which any further increase in hematocrit will lead to decreased hematocrit:viscosity ratio (HVR), a mechanical estimate of oxygen delivery potential in the microcirculation (Fig. 5).

In order to determine the optimum hematocrit for patients with SCD, HVR was measured in patients with SCD at various hemoglobin S %, mimicking transfusion. The first series of experiments by Schmalzer and colleagues demonstrated that there is an optimal hematocrit at all shear rates; however, these studies were performed in a non-aggregating media (Fig. 5A) [61]. The second series of experiments by Alexy and colleagues were performed in autologous plasma, an aggregating media, and demonstrated that there is an optimal hematocrit at high shear rates ($>11\text{ s}^{-1}$) but at low shear, HVR only decreases with the

addition of RBC (Fig. 5B) [5]. In order to better understand the effects of transfusion, Alexy and colleagues performed these studies over varying %hemoglobin S RBC under oxygenated and deoxygenated conditions. They found that increasing hematocrit, increasing %hemoglobin S RBC and deoxygenation of RBC decreases HVR in a predictable manner at low shear. The theoretical effect of deoxygenation on low shear HVR is demonstrated in Fig. 6 panel A. In a simple transfusion, despite an increase in hematocrit with addition of AA RBC, the theoretical HVR curve should shift slightly upward due to decreased %hemoglobin S RBC (Fig. 6B).

The disparity in results of the two studies discussed above is related to the non-Newtonian behavior of blood. In non-aggregating media, the non-linear relationship between HVR and hematocrit was similar at all shear rates; however, in autologous plasma (an aggregating media), there was no optimal hematocrit at shear rates between 3 and 11s⁻¹. Based on the work by Alexy and colleagues, we could predict that red cell exchange would lead to the largest increase in HVR due to a large decrease in %hemoglobin S RBC, diminished effect of deoxygenation and no significant change in hematocrit (Fig. 6C).

We evaluated HVR in healthy subjects and non-transfused patients with SCD (Fig. 7A), after a simple transfusion in chronically transfused SCD patients (Fig. 7B), and after an exchange transfusion (Fig. 7C) [23]. We found that HVR in the chronically transfused patients is increased at high shear but not significantly different at low shear rates <10s⁻¹ compared to healthy subjects and non-transfused patients. Acutely after a simple transfusion, HVR decreased significantly at shear rates below 50s⁻¹ but increased at higher shear rates. We had 3 patients on exchange transfusion so we looked at HVR pre- and post-exchange and there was an increase in HVR at all shear rates. While the sample size is too small to be significant, it is important to note the potential difference in the mechanics of blood flow after simple and after exchange transfusion. Red cell exchange would be expected to improve oxygen delivery across all shear rates found in the vasculature due to a relatively steep decrease in SS RBC % and relatively small change in hematocrit. Based on our data, simple transfusion would be expected to improve delivery in the portions of the vasculature where high shear predominates but potentially limit delivery if low shear venous blood flow is taken into account. This may be evident from the improvement in large ischemic infarcts after initiation of chronic transfusion therapy, whereas, silent cerebral infarction, which is thought to be microcirculatory in origin, may not be improved by simple chronic transfusion[17, 21, 32, 37]. This highlights the complex relationship between HVR, hematocrit and shear rate and their potential effects on oxygen delivery in the microcirculation. The relationship is further complicated in patients with sickle cell disease when blood viscosity is dependent on the percent of hemoglobin S RBC and oxygen saturation.

4. The metabolic function of the red blood cell – oxygen delivery, tissue oxygenation and potential differences between SS and AA RBC

While we know blood rheologic abnormalities adversely affect mechanics of blood flow, do blood rheologic abnormalities alter tissue oxygenation? There is some evidence suggesting

that decreased deformability, increased viscosity and decreased hematocrit:viscosity ratio adversely affect the interaction between RBC and the endothelium and tissue oxygenation [24, 48, 70].

As RBC traverse the capillary, efficient unloading of oxygen is necessary to supply the tissue. Adequate unloading of oxygen is controlled by the cooperative nature of O₂ binding, the tissue oxygen gradient, temperature and the allosteric binding of CO₂, H⁺, and 2,3 DPG. SS RBC have a right shifted oxygen dissociation curve (Fig. 8), meaning that hemoglobin does not bind oxygen as strongly and oxy-hemoglobin saturation will be lower in SS RBC compared to AA RBC at equivalent blood PaO₂ [19]. The curve is shifted further right in denser RBC, which is consistent with polymerized hemoglobin S having lower oxygen affinity than non-polymerized form of hemoglobin S [25].

In addition to oxygen binding, RBC can produce and bind nitric oxide when hemoglobin is deoxygenated, acting as a source of nitric oxide equivalents in the circulation. RBC nitric oxide contributes to hypoxic vasodilation and adequate matching of tissue oxygen supply and demand. There has been disagreement in the literature as to whether nitric oxide affects the oxygen dissociation curve, although more recent evidence suggests that nitric oxide does not alter oxygen dissociation [28, 36]. There is also evidence that nitrite conversion to nitric oxide by deoxygenated hemoglobin decreases platelet activation, leukocyte adhesion and RBC adhesion in human and sickle mouse models [68]. Therefore, the metabolic effects of RBC nitric oxide may improve microcirculatory flow and therefore oxygen delivery to the tissue. Converging research strategies in RBC biochemistry, rheology and blood flow in both human and animal models are beginning to illuminate the mechanisms of disease in SCD RBC with particular attention to the interaction between mechanical changes and biochemical changes in the vascular system.

If the primary function of RBC in the microcirculation is the transfer of O₂ and CO₂, the right shift in the dissociation curve of hemoglobin S should be advantageous during periods of severe anemia or ischemia, acting to preserve oxygen delivery to the tissue. Unfortunately, we have found that tissue oxygenation measured by near infrared spectroscopy (NIRS), which is a measure of oxy and deoxy-hemoglobin, is decreased in patients with SCD despite augmented cardiac output that preserves oxygen delivery in the face of chronic anemia. Chronic transfusion therapy does appear to improve NIRS measure of tissue oxygenation (Fig. 9). Whether this is due primarily to increased hemoglobin after transfusion, improved mechanics in AA RBC vs SS RBC, or a change in the metabolic behavior of RBC remains to be seen.

5. Conclusion

Transfusion therapy leads to significant improvements in blood viscosity, red cell deformability and red cell aggregation, but there may be significant rheologic and physiologic differences between simple chronic transfusion and red blood cell exchange that surpass simple replacement of SS RBC with AA RBC. Many of the rheologic abnormalities are ameliorated but not fully corrected, which may allow abnormal microcirculatory flow and decreased tissue oxygenation to persist in sickle cell disease. Hematocrit appears to be

the primary determinant of viscosity at all shear rates and any increase in hematocrit leads to an increase in viscosity. The effect of increased viscosity in the microcirculation on tissue oxygen delivery is a delicate balance between increasing oxygen carrying capacity versus potentially worsening blood flow. Despite the acute effect of increasing viscosity, chronic transfusion therapy improves hematocrit:viscosity ratio over the long term, which improves tissue oxygenation chronically. Gaining a better understanding of the effects of transfusion related rheology and studying their effect on the diffuse vascular disease found in SCD patients will allow us to better understand fundamental mechanical, metabolic and biochemical interactions. We hope this will lead to novel or improved therapeutic options for these patients.

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Fig. 1.

Blood viscosity in healthy subjects and patients with sickle cell anemia. Panel A shows the shear thinning behavior of blood viscosity in a group of healthy subjects. Panel B shows the effect of deoxygenation on whole blood viscosity at native hematocrit in patients with sickle cell anemia. The open square-dash dot line represents viscosity in an oxygenated sample and the closed square-dash line is the deoxygenated sample. Panel C shows the increase in whole blood viscosity at native hematocrit following a single transfusion in chronically transfused patients with sickle cell anemia. The open square-dash dot line is the pre-transfusion viscosity and the closed square-dash line is the post-transfusion viscosity. Panel D shows that whole blood viscosity at native hematocrit slightly decreases following red cell exchange transfusion. The open square-dash dot line is the pre-transfusion viscosity and the closed square-dash line is the post-transfusion viscosity.

Fig. 2.

The effect of simple transfusion therapy on red cell aggregation and aggregability in patients with sickle cell anemia. All measurements are made at 40% hematocrit. Panels A and B show that SS RBC cause increased aggregation and this is ameliorated in chronically transfused patients. Panels C and D demonstrate that plasma from patients with sickle cell disease decrease aggregation to normal. Therefore, in patients with sickle cell anemia, there are opposing effects on aggregation. Red cell specific effects such as surface protein content and deformability act to increase aggregation and plasma decreases it.

Fig. 3. Shows that there is no significant, acute change in aggregation or aggregability after a single transfusion in the chronically transfused patients with SCD.

Fig. 4. Shows deformability increases in chronically transfused patients with SCD (closed square solid line: pre-transfusion and open triangle dashed lines: post transfusion), as would be expected with replacement of hemoglobin S RBC with AA RBC. There is no acute change in deformability from pre to post transfusion. The open circle-dotted line (lowest deformability) is a sample of non-transfused sickle cell disease patients.

Fig. 5. Shows two different relationships between hematocrit:viscosity ratio (HVR), a marker of oxygen delivery efficiency in the microcirculation, and hematocrit. Panel A shows the relationship when a non-aggregating media is used to generate the HVR curves. Panel B shows the HVR curves for RBC in plasma.

Fig. 6. Demonstrates the theoretical effects of deoxygenation (panel A), simple transfusion (panel B) and red cell exchange (panel C) on low shear HVR, a marker of oxygen delivery efficiency in the microcirculation.

Fig. 7.

Panel A shows the HVR curves over a wide range of shear rates for healthy, non-transfused and chronically transfused patients with SCD. Panel B shows the effect of a single transfusion in chronically transfused patients with SCD. Panel C shows the effect of a single red cell exchange on HVR.

Fig. 8. Shows oxygen dissociation curves for fetal hemoglobin, hemoglobin A, hemoglobin S and denser SS RBC. Hemoglobin S shifts the dissociation curve rightward with hemoglobin S polymerization further shifting the curve rightward.

Fig. 9.

Shows tissue oxygenation, measured by NIRS, is impaired in non-transfused SCD patients but is improved by chronic transfusion therapy.