A hemodynamic analysis for determining critical hematocrit in transfusions for sickle cell patients

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Abstract. Because of complicated rheological issues related with sickle cell blood, there exists a practical need to rationally determine critical hematocrit in transfusions for sickle cell patients. In this research, two major effects, i.e. oxygen concentration and hematocrit, are considered in a theoretical hydrodynamic model incorporating oxygen transport and lubrication theory. The pressure drop depends on the compliance of red blood cells, which changes with oxygen concentration in sickle red cells. Under the assumption that after transfusion, the upper limit of the local resistance of a capillary should not surpass that in the same capillary of normal blood flow, critical hematocrit values with different exchange percentage rates are determined. The current clinical ceiling value of 35 percent for total hematocrit after the transfusion, for the first time, finds its analytical reasoning through mathematical modeling. Plots of critical hematocrit values versus the transfusion exchange percentage are provided in the paper.

Keywords: Hemodynamics, sickle cell, transfusion

1. Introduction and literature review

Sickle cell disease is the most common inherited hemoglobinopathy which mainly affects African Americans in the United States. Vasoocclusive complications account for major morbidity and often contribute to mortality among patients with sickle cell disease. It has been suggested that the formation of polymerized deoxy-hemoglobin S decreases sickle cell deformability and alters the hemodynamic properties of sickle cells. These abnormal cells interact with other blood cells and adhere to activated vascular endothelium which further compromise the rheologic process and lead to vasoocclusion.

The location of vasoocclusion may vary temporally and spatially, depending on a variety of factors including endothelial activation state and vascular bed characteristics. In the perfused rat mesooccum, most red cell adherence occurred at the level of postcapillary venules [9], suggesting that vasoocclusion is initiated at this site and mediated by endothelial cell adherence. This new data challenges previous views that vascular obstruction should occur at the precapillary arteriole level as a result of direct plugging by polymer-containing, less deformable sickle cells [14]. Lipowsky et al. [13] showed that the FITC-labeled sickle cells caused obstruction of the capillary entrance within the terminal feeding arterioles of the microvascular network. Cell trapping at locations such as arteriolar-capillary bifurcation and venular junctions has been observed in microvascular flow models [10,11]. Others have argued that vasoocclusion may involve large vessels [8].
The importance of red cell rheology to hemodynamics in sickle cell disease is evident from a variety of experiments and from clinical experiences. Two major effects are discussed in the literature that are believed to influence sickle cell rheology: oxygen tension and hematocrit. The significance of increased blood viscosity in sickle cell anemia under conditions associated with deoxygenation of sickle cells has long been recognized [2]. The rheological behavior of sickle hemoglobin (Hb S) solution following controlled deoxygenation reflected the molecular events of polymer formation. Lipowsky et al. [13] introduced human sickle cells into the microcirculation of cremaster muscle in rats and mice, and found that the apparent viscosity in single unbranched arterioles had a four-fold rise in viscosity following the reduction in intravascular oxygen tension from 40 mmHg to 7 mmHg. Increasing the hematocrit of sickle cell blood in vitro, even with nonsickled red cells, increases its viscosity and impairs its flow properties [17].

Obviously, oxygen tension and hematocrit must influence the decision for blood transfusions for sickle cell patients, which have been used routinely as an effective method of therapeutic treatment (e.g. [17]). Sickle cell patients frequently receive transfusions to reverse or prevent some of the more severe complications of the disease, such as stroke or priapism. Due to complicated rheological issues related with sickle cell blood, a critical value of total hematocrit after transfusion needs to be checked. The reason is because on one hand, the higher the hematocrit, the more efficient the transfusion would be since the number of healthy red cells included is larger. On the other hand, the higher hematocrit would lead to higher viscosity since there is a relation between hematocrit and viscosity. Higher viscosity would reduce the blood velocity and increase the flow drag, and therefore increase the possibility of having vasoocclusion. In this sense, high hematocrit may not give good results. Because of these two conflict effects of hematocrit, there has been a need to determine critical values of hematocrit in transfusions, especially for simple and partial exchange transfusions. A ceiling of 35% for total hematocrit level after the transfusion is generally accepted, but higher values are occasionally achieved, whether deliberately or inadvertently. There has not been a rational means to predict and determine critical hematocrit values in transfusions.

In this paper, in order to quantitatively calculate critical values of hematocrit, a hydrodynamic model, developed by Berger and King [1] and modified later by Cima et al. [4], has been used to describe the flow of sickle cell blood in capillary that incorporates the dependency of sickle cell rheology on local oxygen concentration. Oxygen tension levels and pressure drop in a capillary for the flow of sickle cell and normal blood are determined by using the Krogh model for oxygen transport and lubrication theory for the cell motion. The coupling and interaction between these parameters depend on the red cell compliance, which is assumed to vary with the oxygen concentration. The pressure drop, under the condition of the same level of blood flow rate, is an indicative of the local resistance. Using the criterion that such resistance should not be more than that in the normal blood after the transfusion, the maximum allowable hematocrit for transfusion at different exchange rates, and thus the total hematocrit level after the transfusion, can both be evaluated.

2. Oxygen transport

The study of [1] indicated that, under normal pressure gradients, the oxygen tensions and cell velocities for sickle cell blood are considerably higher than for normal blood, thus acting against the tendency for cells to sickle or significantly change their rheological properties in the capillaries. The reason is that the hematocrit of sickle cell blood is lower (0.25) than of normal blood (0.45). The reduced hematocrit
causes the total pressure drop across red blood cells to drop, even the pressure drop of each sickled red blood cell is higher than that of normal blood red cell.

It should be noticed that from the incompressible flow point of view, the blood velocity remains the same, while the blood pressure gradient would change to mitigate the physiologic change to maintain the same blood velocity. In this sense, the pressure gradient across capillaries should decrease in sickle cell blood flow. Hence, we investigate the oxygen tension transport under the constant blood velocity condition. Following [1], the oxygen tension transport equation for a section of conduit capillary, as shown in Fig. 1, is

\[
\frac{\partial c}{\partial \xi} = D_b \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial c}{\partial r} \right),
\]

where \(c(x, r)\) is oxygen concentration, \(x\) is the blood flow distance in the capillary, \(r\) is the radius of the capillary, \(u\) is blood velocity, \(n\) is the Hill component, \(N\) is blood oxygen binding capacity, \(K'\) is the Hill coefficient, and \(D_b\) is the radial oxygen diffusivity in blood. As explained in [1], the red cell velocity and the mass flow velocity are assumed to be the same. In Eq. (1), the effects of convection (axial), diffusion (radial), and production of oxygen due to the dissociation of oxyhemoglobin are included. Both Henry’s law and Hill equation are employed to lead to Eq. (1). Using the modified Oseen approximation [1], we have

\[
\frac{\partial c}{\partial \xi} = D_b \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial c}{\partial r} \right),
\]

where

\[
\frac{dx}{d\xi} = u \left[ 1 + \frac{nNK'c_{av}^{n-1}}{(1 + K'c_{av}^n)^2} \right],
\]

where \(c_{av}(x)\) is the averaged oxygen concentration defined as

\[
c_{av} = \frac{1}{\pi r_c^2} \int_0^{r_c} c(x, r) 2\pi r dr.
\]

The boundary condition at \(r = 0\) is the mathematical symmetry:

\[
\frac{\partial c}{\partial r}(x, 0) = 0.
\]

The inlet boundary condition is chosen for specified inlet oxygen concentration

\[
c(0, r) = c_0(r).
\]

For the purpose of the discussion in this study, we are only interested in how the averaged oxygen concentration changes at each \(x\) section. Therefore, a simple boundary condition of constant oxygen flux, as in [6], can be specified at the capillary wall \((r = r_c)\), since the issue of negative oxygen concentration on the capillary wall does not arise [16]. This boundary condition can be expressed as:

\[
\frac{\partial c}{\partial r}(x, r_c) = -\frac{A r_c}{2D_b},
\]

where \(A\) is a constant flux coefficient.
Integrating Eq. (2) following the definition of Eq. (4), and invoking the boundary conditions at \( r = 0 \) and \( r = r_c \), we can obtain

\[
\frac{dc_{av}}{d\xi} = -A.
\]

Hence, the solution for \( c_{av} \) is

\[
c_{av} = c_{av0} - A\xi,
\]

where

\[
c_{av0} = \frac{1}{\pi r_c^2} \int_0^{r_c} c_0(r) 2\pi r dr.
\]

Based on Eqs. (3) and (8), we can have

\[
\frac{dx}{dc_{av}} = -\frac{u}{A} \left[ 1 + \frac{mK'c_{av}^{n-1}}{(1 + K'c_{av})^2} \right].
\]

Solving for \( x \) from Eq. (11) using Eq. (9), we have

\[
x = u \left[ \xi + \frac{N}{A} \left( \frac{1}{1 + K'c_{av}^{n-1}} - \frac{1}{1 + K'c_{av0}^{n-1}} \right) \right].
\]

For a transfusion with \( \alpha \) percentage of normal blood, Eq. (12) becomes

\[
x = u \left\{ \xi + \frac{N}{A} \left[ \alpha \left( \frac{1}{1 + K'c_{av}^{n-1}} - \frac{1}{1 + K'c_{av0}^{n-1}} \right) \right.ight.
\]

\[
+ \left( 1 - \alpha \right) \left( \frac{1}{1 + K's c_{av}^{n-1}} - \frac{1}{1 + K's c_{av0}^{n-1}} \right) \right\},
\]

where \( K'_n \) is the Hill coefficient for normal blood, and \( K'_s \) is the Hill coefficient for sickle cell blood.
Figure 2 indicates oxygen concentration change versus the capillary length under different values of $\alpha$, by employing Eqs. (9) and (13). The parameters used in the computation are listed in Table 1. When $\alpha = 1$, the case is for the normal blood and $\alpha = 0$ is for the sickle cell blood. It shows that the deoxygenation rate is higher for the normal blood than for the sickle cell blood, until oxygen concentration becomes very small. Then the deoxygenation rate of sickle cell blood becomes faster. The $\alpha = 0.5$ case is located in between the two cases. This trend can be explained by taking partial
derivatives with respect to $K'$ on Eq. (11)

\[
\frac{\partial}{\partial K'} \left( \frac{dc_{av}}{dx} \right) = -\frac{1}{(dx/dc_{av})^2} \frac{\partial}{\partial K'} \left( \frac{dx}{dc_{av}} \right) = \frac{nNc_{av}^{n-1}}{(dx/dc_{av})^2} \frac{1 - K'c_{av}^n}{(1 + K'c_{av}^n)^3}.
\]

(14)

Therefore, when $K'c_{av}^n > 1$, which is the case at higher levels of $c_{av}$, $dc_{av}/dx$ decreases with increase of $K'$. Since $K'_n > K'_s$, thus the deoxygenation rate is higher in the normal blood than in the sickle blood when $c_{av}$ is not very low. It can also be deduced that an equivalent Hill coefficient, $K'_m$, for the mixed sickle and normal blood should satisfy $K'_n < K'_m < K'_s$, since the curves of $0 < \alpha < 1$ would all locate in between the two cases.

The oxygen concentration property is obviously related with the rightward shift of the oxyhemoglobin disassociation curve (Fig. 3) for sickle cell blood. Since the fractional saturation, $s$, is expressed using Hill equation,

\[
s = \frac{K'c_{av}^n}{1 + K'c_{av}^n},
\]

(15)

then

\[
\frac{\partial s}{\partial K'} = \frac{c_{av}^n}{(1 + K'c_{av}^n)^2} > 0.
\]

(16)

Hence, the rightward shift of the saturation curve of sickle cell blood is caused by $K'_n > K'_s$, which is the same reason for the slower decrease of oxygen concentration of sickle blood at higher levels of oxygen tension.
Figure 3 is plotted based on the same mixture of normal and sickle blood as expressed in Eq. (13), which gives

\[ s = \alpha \frac{K'_{n}c_{an}}{1 + K'_{n}c_{an}^{\alpha}} + (1 - \alpha) \frac{K'_{s}c_{av}^{\alpha}}{1 + K'_{s}c_{av}^{\alpha}} \]  

(17)

It is difficult to conduct in vivo experiments on oxygen transport in capillaries because of the many uncontrollable factors. An experimental in vitro 25-μm-diameter capillary model was used by Page et al. [15], to provide oxygen flux measurements for hemoglobin solutions, erythrocyte suspensions, and erythrocyte/hemoglobin solution mixtures. The results showed that by plotting the fractional saturation versus apparent residence time (defined as capillary axial distance divided by the flow velocity), the experimental data at different flow velocities collapsed to a single curve. In Fig. 4, the data from the theoretical model in this paper are compared with a set of experimental data from [15]. The theoretical data are calculated from Eqs. (13) and (17) for the normal blood (\( \alpha = 1 \)), and the experimental data are for erythrocyte suspension with 30% hematocrit. The lower boundary flux constant, \( A \), is the value listed in Table 1, and the upper boundary flux value is \( A = 10 \times 10^{-2} mlO_2/ml - s \). It shows that the boundary flux constant influences the slope of the curve significantly. Although part of the influence can attribute to hematocrit difference between the normal blood used in the theoretical model and the erythrocyte suspension used in the experiment, which causes the difference in the Hill coefficient, the effects are not significant based on several test cases. The experimental system in [15] could in fact have a larger boundary oxygen flux constant, with a large lumen diameter (25 μm), the silicon rubber film used as capillary wall material, and the external suffusing gas, than the boundary oxygen flux constant of the capillary considered in this paper. Including these effects, Fig. 4 shows that the theoretical model data can be considered reasonably matching the experimental data.
3. Pressure drop in the capillary

It should be noted that the significant difference of hemodynamic parameters between normal and sickle cell blood is in two key parameters: the hematocrit and the Hill coefficient. In sickle cell blood, the hematocrit is about half of the normal blood, while the Hill coefficient is about one third of the normal blood.

The low hematocrit of sickle cell blood is also in the benefit of delaying vasoocclusion since it reduces the pressure difference within a certain length of capillary if the blood velocity remains the same, as assumed in this study. If the pressure difference is the same, then the blood velocity is faster, thus reduces the time for the cell being deoxygenated. The pressure drop through each blood cell follows Lighthill’s lubrication theory [7,12,18]:

$$\Delta p = \gamma \beta^{\frac{1-k}{k}}$$  \hspace{1cm}(18)

where $\gamma$ is a coefficient related with plasma viscosity, blood velocity, capillary radius and all the constants listed in [1], $\beta$ is the compliance of the red cell, and the $k$ value depends on the capillary radius.

When using Eq. (18) to calculate the pressure drop, the key parameter distinguishing differences between normal blood and sickle cell blood is the compliance of the red cell, $\beta$. In normal blood, the red cell compliance is independent of oxygen concentration. However, in sickle cell blood, one of the key issues is the influence of oxygen concentration on sickle red cell compliance. Chien et al. [3] performed experiments to measure both viscous and elastic components of complex viscosity. That study illustrated that the viscous and elastic components increased when the oxygen saturation was reduced. Dong et al. [5] used the experimental data in [3] to model the cell deformation and hydrodynamic resistance indices. In this paper, a simple power law relationship between oxygen concentration and the red cell
compliance, as assumed in [1], is adopted:

\[ \beta = \left( \frac{c_{av}}{c_{av0}} \right)^j, \]

where \( 0 \leq j \leq 2 \), \( \beta_0 \) is the compliance of a normal cell. Eq. (18) then becomes

\[ \Delta p = \gamma \beta_0 \left( \frac{j^{1-k}}{c_{av0}} \right)^{j^{1-k}}. \]

For normal blood, \( j = 0 \), i.e., the compliance of the red cell and the oxygen concentration are not coupled.

The total pressure drop through the capillary can be calculated as \( \hat{N} \Delta p \), if the pressure drop through plasma is neglected, and the total number of the red cells, \( \hat{N} \), is expressed as

\[ \hat{N} = \left( \frac{\pi r^2 L}{V_{RBC}} \right) H = MH \]

where \( L \) is the capillary length, \( V_{RBC} \) is the volume of a red cell, and \( H \) is the volumetric hematocrit.

If a simple transfusion or partial exchange brings in healthy blood with a hematocrit of \( H_i \) and a volumetric percentage of \( \alpha \), then the resultant total pressure drop becomes

\[ \hat{N}_i \Delta p + \sum_{i=1}^{N_v} (\Delta p)_s_i \]
where
\[ \dot{N}_t = \alpha H_t M, \]
\[ (\Delta p)_n = \gamma \beta_0^{\frac{1-k}{k}} , \]
\[ \dot{N}_s = (1 - \alpha) H_s M, \]
\[ (\Delta p)_{si} = \gamma \beta_0^{\frac{1-k}{k}} \left( \frac{c_{av}(x_i)}{c_{av0}} \right) \frac{k}{k(1-k)}, \]
and
\[ x_i = \frac{L}{N_s - 1} (i - 1). \]

Here \( H_t \) and \( H_s \) are the transfusion and sickle cell blood hematocrit, respectively. We assume that \( V_{RBC} \) are the same for the normal and sickle red cells, that sickle red cells are uniformly distributed in the capillary, and that the size of the length of the red cell is neglected in comparison with the length of the capillary.

4. Determination of critical hematocrit

The local resistance of the capillary is
\[ R = \frac{\sum \Delta p}{Q}, \]
where \( R \) is the resistance, \( \sum \Delta p \) is the total pressure drop, and \( Q \) is the flow rate. When the blood velocity of the capillary remains the same as discussed previously, so does \( Q \). Therefore, the resistance is proportional to the total pressure drop in the capillary. The criterion for the critical hematocrit of transfusion blood used here is that the transfusion should not increase the total pressure drop. That is, the transfusion should not increase the total resistance through the capillary to more than that in the normal blood flow. Using this criterion, we can have
\[ H_t \leq \frac{H_n}{\alpha} - \frac{1}{\alpha M} \sum_{i=1}^{N_s} \frac{\Delta p_{si}}{\Delta p_n} = \frac{H_n}{\alpha} - \frac{1}{\alpha M} \sum_{i=1}^{N_s} \left[ \frac{c_{av}(x_i)}{c_{av0}} \right] \frac{k}{k(1-k)}, \]
where \( H_n \) and \( H_s \) have the values of 0.45 and 0.25, respectively.

Figure 5 is the plots of the maximum allowable \( H_t \) versus \( \alpha \) under two different values of \( j \). The computation is carried out with the following procedure: the oxygen concentration versus the distance in the capillary is first calculated using Eqs. (9) and (13). The data is imported into a cubic spline subroutine which can output the oxygen concentration values at uniformly distributed locations specified in Eq. (27). Then, the critical hematocrit is calculated using Eq. (29). The parameters used in the computation are those listed in Table 1.

The plots are generated for two values of \( j \). The \( j = 1 \) curve provides higher critical hematocrit values. At \( \alpha = 20\% \), the critical hematocrit value reaches almost 1, which is not physiologically
plausible. Therefore, while \( j = 2 \) is the upper bound of the \( j \) value, \( j = 1 \) is probably the lower bound of \( j \). It can be seen that the critical hematocrit value decreases with the increase of percentage of exchange, \( \alpha \). The range of \( \alpha \) is between 20\% and 80\% in this calculation, since it is the range of possible transfusions or exchange percentage. The lowest critical hematocrit asymptotes to 0.45, which is the normal blood hematocrit. Such an asymptotic behavior is reasonable since at high exchange percentages most of the blood is normal blood. For the \( j = 2 \) case, the critical hematocrit value reduces from 0.76 at \( \alpha = 20\% \) to 0.46 at \( \alpha = 80\% \). This means the higher the exchange percentage, the lower the transfusion hematocrit should be. At \( \alpha \) more than 80\%, the transfusion blood should not be concentrated to increase the number of the normal red blood cells. Instead, the blood with normal hematocrit, about 0.45, should be used. The concentration can only be used in lower exchange percentage case, in order to increase the number of normal red blood cells in transfusions.

The total hematocrit, \( H_e \), after the transfusion can be calculated as

\[
H_e = \alpha H_t + (1 - \alpha) H_s .
\]

Figure 6 shows the maximum total hematocrit, based on the maximum \( H_t \), versus different exchange percentages with the two \( j \) values. It can be seen that the total hematocrit levels are between 0.35 to 0.44, within the exchange percentage of 20\% to 80\%. The higher the exchange percentage, the higher the allowable total hematocrit. As the same case as with \( H_t \); the lower \( j \) value allows higher \( H_e \), since the lower value of \( j \) means less strong relation between the sickle cell compliance and the oxygen concentration. As shown in Fig. 5, the \( j \) value of 2 is more reasonable. In current clinic practice, the transfusion hematocrit, \( H_t \), is approximately 0.60. Then according to the \( j = 2 \) curves in Figs. 5 and 6, the exchange percentage can be as much as 30\% for the total hematocrit, \( H_e \), to reach 0.36. Therefore, the ceiling total hematocrit of 0.35 is not too far away based on the analysis in this paper, and it is the first time that such a ceiling value finds its analytical reasoning through mathematical modeling. In addition, this value can be higher if the exchange percentage is higher, since the percentage of normal blood is higher. Although the higher hematocrit normal blood still increases the viscosity, the local resistance does not increase, due to the higher compliance of normal blood red cells.

5. Conclusion

It has been shown that oxygen concentration and hematocrit influence the rheological property of sickle cell blood. Due to a lower value of the Hill coefficient in sickle cell blood, it causes the rightward shift of the saturation curve of sickle cell blood, resulting in lower deoxygenation rate than that in normal blood. However, the compliance of the sickle red cell is influenced by the oxygen concentration, so is the pressure drop of sickle cell blood flow in the capillary. Because the blood velocity remains the same for incompressible flow, the resistance of a capillary is proportional to the total pressure drop in the capillary. The pressure drop depends on the compliance of red blood cells, which changes with oxygen concentration in sickle red cells. Under the assumption that the resistance after transfusion should not be more than that in normal blood, the critical values of hematocrit in transfusion have been determined with different exchange percentages, based on the change of sickle red cell compliance due to the change of oxygen concentration. The maximum allowable transfusion hematocrit value decreases with increase of exchange percentage, while the maximum allowable total hematocrit after transfusion increases. Plots of critical hematocrit versus the exchange percentage have been generated. The rational reasons of the current clinical ceiling value of 35 percent of total hematocrit after the transfusion are for the first time presented.
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