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The rheology of severe falciparum malaria

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Submitted for publication
Chapter 5

The Theology of Severe Caliphrism

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Supporting Vocational Education Act (SV-E)

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The rheology of severe falciparum malaria

Introduction

Falciparum malaria is a potentially fatal infection. If left untreated in a non-immune subject the infection can develop quickly into severe disease, with multiple vital organ dysfunction, and a mortality of approximately 15-20% despite effective antimalarial drugs and optimal clinical care. In high transmission areas anaemia in young children is the principle manifestation of severe malaria. In mesoendemic areas cerebral malaria and metabolic acidosis in a wider age range of children are the main complications seen. In hypo-endemic (low transmission) areas, severe malaria occurs in all age groups. In this context acute renal failure, jaundice, and pulmonary oedema are more common in adult patients whereas anaemia, hypoglycaemia, and convulsions are more common in children, and cerebral malaria and metabolic acidosis occur at all ages. Many pathophysiological aspects of severe malaria are still incompletely understood. Possible contributing mechanisms can be divided into those affecting microcirculatory flow and those involving the release of parasite derived products following erythrocyte rupture and the host reaction to these events. These mechanisms are not mutually exclusive, since impaired blood flow may focus the release of host or parasite derived toxins.

In this review, a detailed description of the various contributors to the impaired rheology in falciparum malaria is given and the role of impaired microcirculatory flow in the pathogenesis of severe malaria will be discussed.

Rheological changes in severe malaria

According to the Poisseille-Hagen law, flow ($Q$) of a Newtonian fluid through a rigid tube depends on the pressure gradient ($\Delta p$) and the total resistance over the tube ($R$): $Q = \Delta p / R$. This resistance is in turn dependent on the diameter ($r$) and length ($l$) of the tube and the viscosity ($\eta$) of the blood flowing through it: $R = 8 \cdot \eta / \pi \cdot l / r$. Because of the existence in the circulatory system of complex geometries, flow pulsatility, vessel distensibility and non-Newtonian blood viscosity, the Poiseille-Hagen equation cannot be applied quantitatively to blood flow in vivo, but vascular resistance is still governed by the same parameters as in tube flow. Some of these parameters can be seriously affected in severe malaria (table 1).

Blood pressure.

Most patients with severe malaria are febrile with a high cardiac output, a low systemic vascular resistance, and a low to normal blood pressure that in itself should not limit normal tissue perfusion. In rare cases, patients may develop hypotension and shock in the absence of concomitant septicaemia, a condition called algid malaria.
Chapter 2

Reduction in flow

Arterioles
- reduced red cell deformability (both infected and uninfected cells)
- increased plasma viscosity
- anaemia

Capillaries
- cytoadherence (sequestration)
- reduced red cell deformability (both infected and uninfected cells)
- anaemia

Postcapillary venules
- cytoadherence (sequestration)
- rosette formation
- red cell aggregation
- increased plasma viscosity
- anaemia

Increase in flow

<table>
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<tr>
<th>Vessel diameter</th>
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| Although there is some evidence of autonomic nervous system dysfunction in malaria, there is no evidence that abnormal neural control of vascular tone leads to impaired tissue perfusion. In cerebral malaria (coma in severe malaria) there seems to be a normal response of the cerebral resistance vessels (small arteries and arterioles) to changes in arterial $pCO_2$. The main pathological process appears to be mechanical obstruction to flow in the small blood vessels. The lumenal diameter of the capillaries and postcapillary venules, is reduced significantly by the sequestration of erythrocytes containing the more mature stages of the parasite, a phenomenon that has been recognized since the 19th century.

<table>
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<th>Blood viscosity</th>
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| Whole blood viscosity, or resistance to flow, depends on the local shear stress, and thus the section of the circulation that is considered, as blood behaves as a non-Newtonian fluid with decreasing viscosity at higher shear rates. Whole blood viscosity in the larger vessels decreases exponentially with falling haematocrit, as in severe malaria, where anaemia is a common finding. This decrease in whole blood viscosity is counteracted by an increase in plasma viscosity through increased plasma fibrinogen levels, so that whole blood viscosity either does not change significantly or slightly increases.

Whole blood viscosity can also be increased by a reduction in red cell deformability. This is a determinant of viscosity mainly under high shear conditions. Despite lower flow rates, high shear stresses are encountered at the arteriolar end of the microcirculation (in vessels with a diameter below 250 µm), in which the red cells are elongated and migrate towards the axial centre of the vessel. This results in a lubricating plasma boundary layer along the vessel wall, which reduces viscosity considerably: the Fåhreus-Lindqvist phenomenon.

Table 1. Rheological factors affecting microcirculatory flow in falciparum malaria

<table>
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<tr>
<th>Vessel Diameter</th>
<th>Reduction in Flow</th>
<th>Increase in Flow</th>
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<tbody>
<tr>
<td>Arterioles</td>
<td></td>
<td>- anaemia</td>
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<tr>
<td>Capillaries</td>
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<td>- anaemia</td>
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<tr>
<td>Postcapillary venules</td>
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<td>- anaemia</td>
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Erythrocytes, with a normal average cell diameter of 7.5 μm, must deform considerably in their normal passage through capillaries with a midpoint diameter of 3 to 7 μm. The Fähreus-Lindqvist phenomenon still occurs in capillaries with lumenal diameters down to 5 μm. Below a vessel diameter of 5 μm, there is a sudden sharp increase in the resistance to flow, known as inversion of the Fähreus-Lindqvist phenomenon. The sequestration of parasitised red cells in the microcirculation is important in reducing the lumenal diameter of capillaries and small venules below this critical threshold. In this context red cell deformability becomes extremely important as a slight decrease in deformability may result in a hundred to thousand fold decrease in capillary flow rate. In severe malaria red cell deformability is reduced not only in the parasitised erythrocytes, but also in the uninfected erythrocytes. Indeed it is the reduction in uninfected red cell deformability that has a strong association with outcome.

Finally, on the venular side of the microcirculation, where low shear stresses are encountered, blood viscosity can be increased by red cell aggregation. The role of red cell aggregation in the pathogenesis of severe malaria remains uncertain. Aggregability is likely to be increased because of the increased plasma fibrinogen levels. In all the human malarialis, red cell aggregates can also be formed as a result of the adherence of uninfected erythrocytes to parasitised erythrocytes (rosetting) and also by agglutination of parasitised red cells. However, unlike cytoadherence, which occurs with all P. falciparum isolates in vivo, rosetting only occurs with some isolates.

Sequestration

Erythrocytes containing P. falciparum in the second half of its intraerythrocytic development (trophozoites and schizonts) adhere to vascular endothelium (cytoadherence). This leads to sequestration of parasitised red cells in the microcirculation (fig. 1). Sequestration occurs only in capillaries and post-capillary-venules. Sequestered red cells are not distributed uniformly throughout the body: in fatal cerebral malaria sequestration is greatest in the brain, particularly the white matter, but it is also prominent in the liver, kidneys, intestines and adipose tissue. In other cases of fatal falciparum malaria without cerebral involvement, there is less cerebral sequestration. Cytoadherence involves the binding of ligands protruding on the membrane of the infected erythrocyte ('adhesins') to a corresponding receptor ligand or ligands on the vascular endothelial surface.

On the red cell surface the high molecular mass variants of the strain specific P. falciparum erythrocyte membrane protein 1 or PfEMP1 has a central role as adhesion molecule. This parasite-derived variant antigen is expressed on the exterior of the parasitised red cell
in the second half of the asexual life cycle and is anchored through the membrane to accretions of another parasite-derived protein: histidine rich protein (PfHRP1). These focal points of potential vascular attachment can be seen on electron-microscopy as electron-dense knobs and are the points of adhesion to the vessel. Other putative candidates for cytoadherence on the red cell membrane, of uncertain in vivo importance, are the PfEMP₁ related protein sequestrin, expression of normally cryptic regions of the cytoskeleton protein band 3, called pfalhesin, a LFA-1-like epitope and fibrillar strands containing immunoglobulins.

The putative vascular endothelial host receptors involved in the process of cytoadherence have been defined mainly by the binding of parasitised erythrocytes to epitopes on different in vitro cell lines, such as the amelanotic melanoma cell line C32, or by binding to purified proteins. At least eight potential vascular receptors have been identified: thrombospondin, the leukocyte differentiation antigen CD36 (which binds thrombospondin), the intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin (formerly known as ECAM-1), αβ₃, PECAM-1 (CD31) and chondroitin sulphate which may be particularly important in the placenta. Of these ICAM-1 may be the most important in the brain and CD36 in other organs. Nearly all parasites isolated from patients bind well to CD36 (>90%), but adhere less well or not at all to the other potential ligands. Interestingly ICAM-1 and VCAM-1 expression on different cell lines can be upregulated by a number of factors including tumour necrosis factor (TNF), ischaemia and increased expression of ICAM-1 on vascular endothelium has been shown in autopsy studies. This suggests that the inflammatory response can influence the organ distribution of sequestration but also raises the possibility that some ICAM-1 expression may follow, rather than precede, the adherence of parasitised red cells. The increased expression of ICAM-1 is accompanied by increased plasma levels of soluble ICAM-1 in falciparum malaria.

Adhesion studies under flow conditions show that the different receptors may have complimentary roles in modulating cytoadherence in microvessels. Initial interaction at high wall shear stress may be of a rolling type, mediated by ICAM-1, P-selectin or other receptors (of which PECAM1 has been identified recently) with immobilisation and stabilisation occurring via CD36. ICAM-1 may act synergistically with CD36 in increasing the stability of cytoadherence. Under laminar flow conditions erythrocytes containing the mature forms of the parasite adhere to monolayers of cultured cell lines at wall shear stresses up to 0.1 to 0.2 Pa. These low shear stresses, are encountered in vivo only at the venular site of the microcirculation (postcapillary venules). That adherence of these parasitised red cells can have haemodynamic consequences in vivo is also suggested in studies in rat mesoappendix vasculature, where peripheral vascular resistance is increased in flow experiments using cytoadhering strains of P. falciparum.
Figure 1. Histology of a post-mortem brain biopsy in a case of cerebral malaria, showing a capillary clogged up with sequestered erythrocytes, containing the mature stages of the parasite. The remaining capillary lumen is considerably reduced.
Clinical correlates

In man, generally only *P. falciparum* causes lethal disease, and this parasite is also the only one of four species pathogenic to man that shows the phenomenon of sequestration. Autopsy studies of fatal falciparum malaria clearly show the sequestration of erythrocytes in the small blood vessels (fig. 1) and some studies show an association between the percentage of cerebral vessels containing infected erythrocytes, the density of packing, and cerebral malaria. It has proved more difficult to show a correlation between the degree of cytoadherence *in vitro* and the severity or organ distribution of disease. A correlation with the severity of disease, but not with the cerebral symptoms has been reported by some, not by others. A recent study in 150 Kenyan children with falciparum malaria showed that strains binding to ICAM-1 were more frequent in cerebral malaria patients.

Red cell deformability

**Parasitised erythrocytes**

Red blood cells infected with *P. falciparum* parasites become progressively less deformable as the intra-erythrocytic parasites mature. All parameters determining red cell deformability are affected in the parasitised red cell. Slight geometrical changes leading to a reduction in the cell surface/volume ratio (increased sphericity) already occur in infected cells while parasites are in the ring stage. As the parasite matures to the trophozoite and schizont stage the presence of the large relatively non deformable parasite itself results in a large increase in the internal viscosity of the red cell leading to marked loss in deformability. The erythrocytes containing more mature parasites also show a marked increase in membrane rigidity. There are several factors that could contribute to this increase in membrane rigidity. The structure of the cell membrane of infected erythrocytes is altered by neoantigens produced by the parasite. Some of these neoantigens are bound to the cytoskeleton, like MESA to band 4.1 and RESA to spectrin, which could influence red cell deformability. Moreover, the parasite exerts oxidative stress on the host erythrocyte. Oxidative stress can lead to loss of membrane flexibility. Finally, alteration of the membrane phospholipid organisation occurs with an associated decrease in the fluidity of the lipid bilayer. However, reduced fluidity of the membrane does not directly relate to reduced membrane deformability. Phospholipid flip-flop is accelerated and phosphatidylserine appears on the exterior, although this has been contested.

**Non-parasitised erythrocytes**

Early studies showed that the “filterability” of red cells in uncomplicated malaria was reduced, suggesting that uninfected red cells might also be less deformable. We
recently showed that in severe falciparum malaria the non-parasitised erythrocytes become considerably more rigid. Since the changes in deformability could not be restored by manipulation of the internal viscosity or cell geometry by suspending the cells in hypo- or hyperosmolar media, and there were no changes in the morphology of the uninfected red cells under light microscopy, changes in the red cell membrane are the most likely cause of the loss of deformability of these erythrocytes. The mechanism underlying these membrane changes remain to be elucidated, but could involve both rigidifying substances released by the parasite, uptake of membrane particles derived from parasitised erythrocytes at schizont rupture by the membranes of uninfected erythrocytes, systemic host factors or endothelial cell malfunction. Nauman has identified a heat labile exoantigen produced by in-vitro cultures of *P. falciparum* which binds reversibly to normal red cells and reduces their deformability. This was not confirmed by Paulitschke and Nash. Uninfected red cells containing the RESA-antigen on their membrane surface indicating previous infection and subsequent removal of the parasite could also be a source of rigid red cells, although they are insufficient in number to contribute more than a small part of the effect.

Figure 2. Mean red cell deformability (RCD) in relation to severity of disease in adult patients with falciparum malaria on the Thai-Burmese border. EL= elongation index, which is proportional with the ellipticity of the deformed erythrocytes. SS= shear stress applied on the red cells (reprinted with permission from Am J Trop Med Hyg 1997; 57: 507-511).
Clinical correlates

Cerebral malaria

Decreased red cell deformability under shear stresses encountered in arterioles and capillaries with low flow velocity, proved a strong predictor of mortality in adult Thai patients with severe falciparum malaria (fig. 2)\textsuperscript{18}. Recently this was confirmed in a separate study in Kenyan children with severe falciparum malaria (fig. 3)\textsuperscript{19}. In the Thai study, logistic regression analysis showed that red cell deformability was the most important prognostic factor for mortality, more important than other well established parameters like plasma lactate concentrations and other measures of acid base status\textsuperscript{18,67,68,69,70,71}. Blood lactate concentrations are increased in severe malaria mainly due to increased anaerobic glycolysis, and not hypermetabolism as evidenced by consistently elevated lactate-pyruvate ratios\textsuperscript{6,68,72}. Decreased red cell deformability leads to reduced microcirculatory flow and oxygen delivery in the tissues, and thus to anaerobic glycolysis. Red cell deformability correlates significantly with plasma base excess and lactate levels with an adjusted $r^2$ of 0.19 and 0.12 in children and adults with severe malaria respectively\textsuperscript{18,19}. This may be compounded by decreased lactate clearance by the liver resulting from reduced liver blood flow, where altered haemorheological factors may also play a role\textsuperscript{6,73,73}. 

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure3.png}
\caption{Probability of a fatal outcome in severe falciparum malaria in relation to admission red cell deformability (RCD) measured at a shear stress (SS) of 1.7 Pa. The measure of RCD is the elongation index (EI), which is proportional to the ellipticity of the red cells at a certain shear stress. Data derive from pooled data on adults ($n=23$) and children ($n=99$) with severe falciparum malaria\textsuperscript{18,19}.}
\end{figure}
The reduction in RCD of the infected red cells can lead to margination of the normally axial flow of the erythrocytes in the smallest blood vessels. This in turn can effect plasma skimming and red cell screening at branching points in the microcirculation. Normally the vessel branch with the lower volume flow will also receive reduced quantities of erythrocytes. Rigid parasitised red cells might escape from this, resulting in routing through capillaries with low flow favouring their cytoadherence. This could also be a factor in the observed inhomogeneity of sequestered red cells in autopsy studies.

There is a generalised small increase in systemic capillary permeability in severe malaria, but studies of computerised tomography or magnetic resonance imaging have generally shown only slight brain swelling in cerebral malaria, which was attributed to increased intracerebral blood, but no evidence of cerebral deem. In adult patients with cerebral malaria intracerebral lactate production and CSF lactate concentrations are increased. Although cerebral blood flow was within the normal range, as measured by a modified Kety-Schmidt technique using differences in cerebral arterial-venous tracer concentrations, it was low in comparison to the arterial oxygen content. Cerebral vascular resistance was increased, whereas cerebral oxygen extraction was diminished. These findings can be explained by a mechanical obstruction of the cerebral microcirculation, resulting from a combination of reduced red cell deformability and sequestration. The surprising reversibility of coma, which may last in some cases for several days, indicates that there is incomplete ischaemia in cerebral malaria, although measurable focal infarction can occur in rare cases and there could be more extensive micro-infarction, which is not obvious clinically.

Reduced flow, increased wall tensions, and the accumulation of metabolic products would all be expected to impair cellular function in the vascular territory affected. This would also provoke the release of regulatory vasodilatory factors such as nitric oxide (from eNOS), in addition to induction of nitric oxide synthesis by iNOS induced by the high concentrations of pro-inflammatory cytokines such as TNFα and interleukin-1. Besides being a potent vasodilator, nitric oxide is also a neurotransmitter, and local overproduction leading to impaired neuronal functioning has been proposed as a possible cause of coma in cerebral malaria. However, there is no direct proof of this elusive hypothesis, and there are some studies pointing to either a protective rather than deleterious effect or no effect of increased nitric oxide production in severe malaria. Nitric oxide does not seem to influence red cell deformability directly, since no reduction was observed in patients with septicaemia and high plasma NO levels. Increased shear forces caused by rigid erythrocytes can also increase the release of other endothelial factors such as prostacyclin (epoprostenol), a potent vasodilator which inhibits platelet aggregation. Damage to the endothelium leading to decreased nitric oxide or prostacyclin production could therefore further impair microcirculatory flow.
Anaemia

In addition to the strong relationship between red cell deformability and disease outcome, decreased red cell deformability is also an important cause of anaemia in falciparum malaria. Anaemia results from a combination of parasitised erythrocyte destruction at schizont rupture, accelerated removal of both parasitised and unparasitised red cells, and ineffective erythropoiesis. In Thai adults with falciparum malaria, decreased red cell deformability at high shear stresses (similar to those encountered in the spleen) correlated strongly with the severity of anaemia. Under normal circumstances rigid red cells are removed by the spleen since they will have to squeeze through the small intercellular gaps in the sinusoids of the spleen (width of 0.5-3 μm). Cells which are not able to deform are left in the cords of Billroth and removed by the immunologic effector cells. This mechanism acts synergistically with the mechanisms for clearance of antibody coated red cells. The thresholds for splenic clearance of antibody coated cells are lowered in acute malaria.

Recently we showed the same correlation between red cell deformability and anaemia in Kenyan children as in Thai adults with falciparum malaria, but in these children the correlation was also present at lower shear stresses. This could be a consequence of the different histological structure of the spleen in children. A logical deduction from these data is that very young children with severe falciparum malaria, who usually present with profound anaemia, should be relatively protected from developing cerebral malaria as the most rigid erythrocytes have already been removed by the spleen.

Rosetting

Rosette formation is the phenomenon in which uninfected red blood cells adhere to erythrocytes containing the mature forms of the parasite. More than ten uninfected erythrocytes are sometimes found stuck to a single infected erythrocyte. However, whereas all erythrocytes containing mature P. falciparum parasites cytoadhere, not all rosette. Since the peripheral blood, in general, does not contain the more mature forms of the parasite (trophozoites and schizonts), the parasites have to be cultured in vitro to show rosetting. The frequency of rosette formation in wild strains differs greatly in the various studies: from 5%-10% in both severe and non-severe patients in a recent Kenyan study, 49% in a mixed study population from African and South-American strains, to 100% in non-severe patients in Papua New Guinea. These differences could be explained partly by differences in laboratory techniques.

Rosetting in P. falciparum has been associated with surface expression of PfEMP1 and also 22 kDa or 28 kDa parasite proteins, termed 'rosettins'. On the host red blood cell receptor side the complement receptor CR1 (also known as CD35) and possibly CD36 are involved. Rosettes can be disrupted by monoclonal antibodies to PfHRP1 or
immune serum from diseased children. Various other substances such as divalent cation depletion, heparin or sulphated glycoconjugates also influence their stability.

Investigations under flow conditions suggest that rosettes are able to resist shear stresses up to 1.6 Pa, corresponding to shear stresses encountered at the arterial side of the circulation. In contrast, studies showed that very low shear stresses of 0.045 Pa were able to disrupt rosettes in a medium free of dextrans that possibly strengthen the adherence properties. If serum was added to the suspension medium, more mimicking the in vivo situation, the adhesive forces became stronger (personal observations). It is unclear if rosetting per se does occur in vivo, but parasitised cells do become sticky, and these adhesive forces may further slow the vascular passage of uninfected erythrocytes. In a rat mesoceleum vascular bed, P. falciparum strains showing both knob formation with cytoadherence as well as rosetting increased peripheral vascular resistance more than strains that only expressed knobs, but did not form rosettes.

Clinical correlates

The pathophysiologic significance of rosette formation is not clear. Some studies show a correlation between the occurrence of rosette forming strains and cerebral malaria, with severity of disease other than cerebral symptoms, or with severe anaemia only. Other studies do not show a correlation between rosetting and severity. Moreover, rosette formation has also been shown in the benign malarias caused by P. vivax, P. ovale, and P. malariae, which questions their clinical relevance, although it has to be realised that quantitatively rosette formation will be much less in the benign malarias because of the much lower parasite burdens.

Clinical implications

Measures to improve microcirculatory flow could be important as additional treatment in severe falciparum malaria. One target could be the prevention of sequestration. The artemisinin derivatives artesunate and artemether are more potent than quinine in inhibiting cytoadherence. To date however, there is no convincing evidence of a difference in mortality between patients treated with these different antimalarial drugs. Heparin as ancillary treatment in falciparum malaria has not shown to improve clinical outcome and in fact might be harmful, although it causes disruption of rosettes in vitro.

Another target could be red cell deformability, and there are some clues that this could be beneficial. Pentoxifyllin, a drug designed to improve red cell deformability but that has also an inhibitory effect on TNF production, was suggested to have a beneficial effect on duration of coma and on survival in cerebral malaria. The better outcome in the pentoxifyllin group was associated with a decline in serum levels of tumour necrosis factor
(TNF) in a few patients. However, a recent study testing pentoxifyllin as supportive treatment in uncomplicated falciparum malaria did not show any beneficial effect of pentoxifyllin on the clinical course of the disease or on the serum TNF levels. Pentoxifyllin has not been tested in the treatment of severe malaria in relation to changes in red cell deformability. Exchange transfusion is used widely in the management of severe malaria in returned travellers, although it has never been clear how it might be of benefit. The parasitised red cells causing pathology, are sequestered and not available for exchange. However, removal of rigid unparasitised cells and their replacement by more deformable new erythrocytes would provide a plausible explanation for the apparent benefit from this treatment. Patients with severely reduced red cell deformability form a subgroup that might benefit from exchange transfusion. We have recently shown that in African children with severe falciparum malaria blood transfusion does restore mean red cell deformability in a predictable way. Although administration of blood transfusions was not randomised, the data suggest that blood transfusion not only improved disease outcome through its effect on severe anaemia, but also through improvement of red cell deformability. The amount of transfused donor red cells required to improve mean red cell deformability above a certain threshold value can be calculated. With this knowledge a randomised trial of (exchange) transfusion in patients with severe malaria and severely reduced red cell deformability would be warranted.

Conclusions

Impaired microcirculatory flow is important in the pathophysiology of severe falciparum malaria. Several factors combine to reduce microcirculatory flow (fig. 4). First, parasitised red cells adhere to vascular endothelium and these rigid adherent cells simply block the vascular lumen. Second, these sequestered cells may adhere to the erythrocytes that have to squeeze past, through the processes that cause rosetting and agglutination in vitro. Thirdly the uninfected red cells are less deformable. This lack of deformability may be particularly important in areas of intense sequestration where the lumen is reduced below a critical threshold of around 5 μm (inversion of the Fåhreus-Lindqvist phenomenon).

Healthy erythrocytes can pass through pores as small as 1 μm, due to the fact that they behave in many ways like fluid drops of very low internal viscosity. However, in severe falciparum malaria as yet undefined changes in the uninfected red cell membrane occur, reducing deformability considerably. These rigid cells may obstruct microcirculatory flow and they are prone to be filtered out by the spleen and thus contribute to malarial anaemia.

The beneficial effects of exchange transfusion in severe malaria can be interpreted as resulting from replacement of undeformable cells by deformable ones. Also the addition
of deformable erythrocytes by simple blood transfusion seems to be beneficial. Drugs aimed at improving red cell deformability in falciparum malaria are a promising subject for future research.

![Diagram showing factors combining to reduce blood flow through a capillary in falciparum malaria.](image)

Figure 4. Factors combining to reduce blood flow through a capillary in falciparum malaria. Red cells containing the mature stages of the parasite stick to the endothelial surface (cytoadherence). This partly obstructs flow. As a consequence passing erythrocytes will have to deform considerably. This ability to deform can be severely disturbed in severe falciparum malaria adding considerable to the impairment in microcirculatory flow. In addition to this, the adhesive forces between parasitised and uninfected red cells involved in rosetting can further hinder capillary flow.

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