

Influence of Chronic Cardiovascular Diseases on the Severity of Imported Falciparum Malaria

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Abstract

Falciparum malaria has a unique and complex pathophysiology. While sequestration of parasitized and non-parasitized erythrocytes leads to a progressive obstruction of the microcirculation, a marked systemic inflammation with endothelial dysfunction and consecutive increase in vascular permeability develops. Furthermore, most patients with severe disease present with some degree of hypovolemia. Due to the reduction in pre-load, direct myocardial suppression and increase in after-load acute falciparum malaria exerts diverse effects on the cardiovascular system. Increasing numbers of aging tourists and immigrants with chronic co-morbidities travel to countries where falciparum malaria is endemic. Age has consistently been described as a prominent risk factor for both severe disease and death from imported falciparum malaria in several large studies. Although for long suspected age-related chronic disorders have only recently been identified as risk factors for severe disease. Herein, we review the current concepts of the impact of age-related chronic medical conditions on the severity of imported falciparum malaria.

Introduction

Malaria is a disease with a unique and complex pathophysiology. Parasitized, as well as non-parasitized red blood cells (RBC) become less deformable and adhere to the endothelium¹. A progressive obstruction of the microcirculation is the consequence. Simultaneously, a marked systemic inflammation with endothelial dysfunction and increased vascular permeability ensues². In falciparum malaria, the parasite biomass increases 6- to 20-fold with each replication cycle. The exponential growth of parasite biomass every 48 hours is a major reason for the well-described spectrum of life-threatening complications that can occur abruptly and unpredictably within hours of presentation, making *Plasmodium falciparum* the most dangerous of the five species known to affect humans. Prognostically, the two most important of these so-called criteria of severe malaria (Table 1) are metabolic acidosis and cerebral malaria³.

Currently, more than 90 countries and territories are areas at risk of malaria transmission. In countries where malaria is not endemic, it frequently represents the most important imported tropical disease. As such, malaria occurs in specific populations. International travel to countries where malaria is endemic increases steadily. Among such travelers are not only immigrants from endemic countries visiting friends and relatives (VFR), but also increasing numbers of aging tourists with chronic co-morbidities⁴. In addition, patterns of migration change rapidly. Coinciding with an influx of large numbers

Table 1: Criteria of Severe Malaria in Adults According to the 2014 World Health Organization (WHO) definition

Criterion	Specification
Impaired consciousness	Glasgow coma scale (GCS) <11
Metabolic acidosis	A base deficit >8 mmol/L, plasma bicarbonate <15 mmol/L or venous lactate ≥45 mg/dL (>5 mmol/L)
Hypoglycaemia	Blood glucose level <40 mg/dl (<2.2 μmol/L)
Severe malarial anaemia	Haemoglobin level <7 g/dL or haematocrit <20% together with a parasite count >10.000/μL and not related to other causes than malaria
Renal impairment	Plasma or serum creatinine >3 mg/dL (>265 μmol/L) or blood urea > 120 mg/dL (>20 μmol/L)
Jaundice	Bilirubin >3 mg/dL (>50 μmol/L) together with a parasite count >100.000/μL
Pulmonary oedema	Confirmed radiologically, or oxygen saturation <92% on room air with a respiratory rate ≥30 breaths/min
Significant bleeding	Including recurrent or prolonged bleeding from the nose, gums, venepuncture sites, hematemeses or melaena
Decompensated shock	Systolic blood pressure <80 mm Hg with evidence of impaired perfusion
Hyperparasitaemia	<i>P. falciparum</i> parasitemia >10%; (in non-endemic areas >5%)

of refugees, for instance, a sharp increase in malaria cases was notified in Germany in 2014⁵.

Risk factors for both, severe disease and death, have been identified for imported infections in several studies comprising several thousand cases each (⁶⁻⁸, reviewed in ⁹). Among these are inappropriate or no chemoprophylaxis, delay in seeking care and establishment of the diagnosis, the immune status concerning malaria, and co-infection with HIV. Increasing age has also consistently been described as a prominent risk factor in these studies^{6,10}. In a large British study, patients aged >65 years had 10times the risk of dying compared to those 18-35 years old⁶. The exact reasons for this association, however, remain to be elucidated.

Here, we review the current concepts of the impact of age-related chronic medical conditions in general, and cardiovascular diseases in particular, on the severity of imported falciparum malaria.

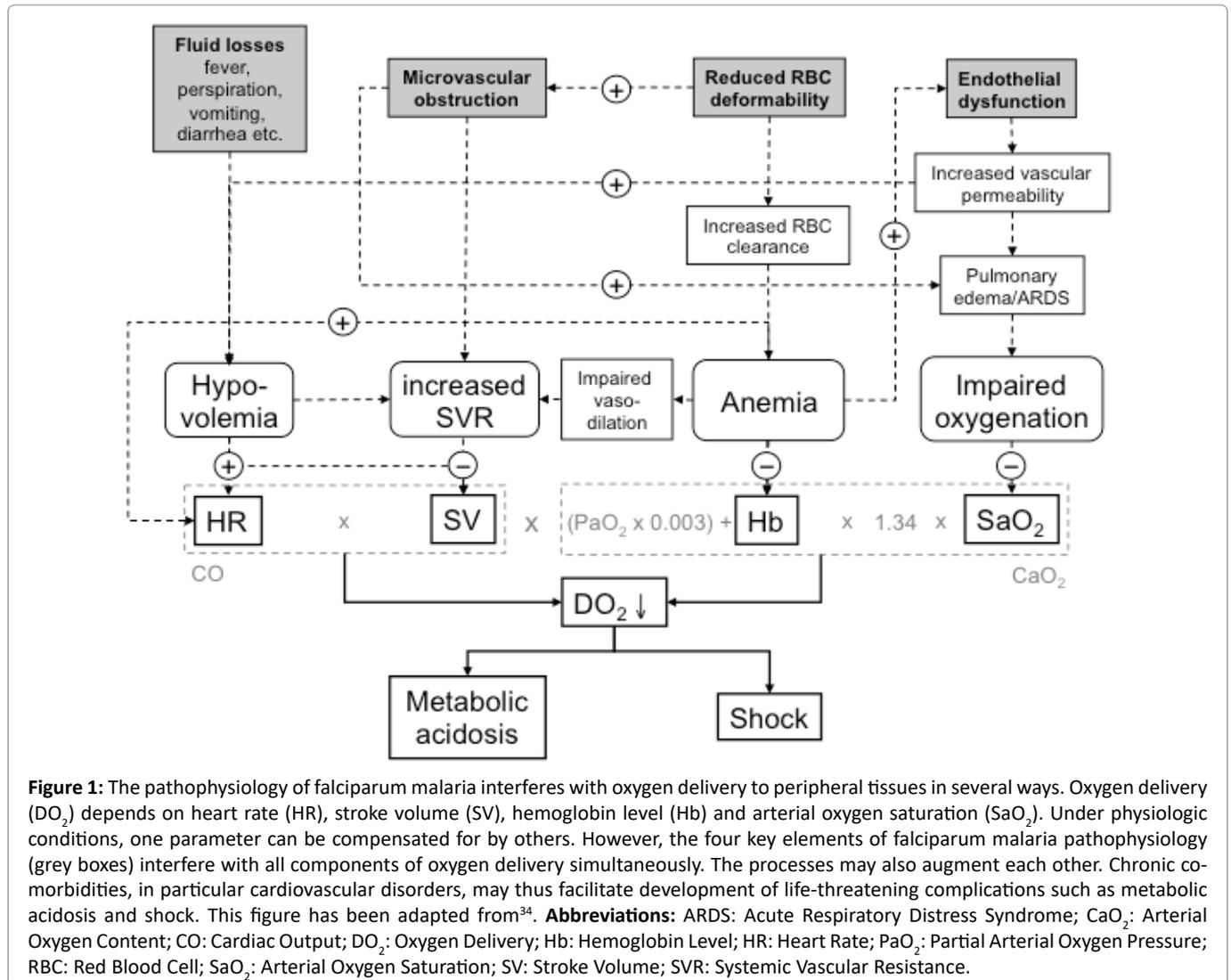
Basic Pathophysiologic Concepts of Falciparum Malaria

Although still incompletely understood recent research has revealed that four elements play a key role in the pathophysiology of falciparum malaria (Figure 1). Parasitized as well as uninfected red blood cells (RBC) become less deformable and are cleared from the circulation^{1,11}. Hemolysis reduces the hemoglobin (Hb) level and may ultimately result in anemia¹². Cell-free Hb released from ruptured erythrocytes acts as a nitric oxide (NO) scavenger¹³ and increases the plasma concentration of asymmetric dimethylarginine (ADMA), a NO synthase inhibitor¹⁴. Reduced NO bioavailability leads not only to increased myocardial wall stress and pulmonary pressures¹⁵ but also to enhanced endothelial dysfunction with subsequently impaired vasodilation¹³. Reduced RBC deformability also promotes microvascular obstruction^{1,16}, the extent of which correlates with metabolic acidosis¹⁶ and cerebral malaria¹⁷, the most important prognostic markers in severe malaria. Simultaneously, parasite toxins such as *P. falciparum* histidine-rich protein-2 (PfHRP-2) systemically

activate endothelial cells leading to the release of mediators such as Angiopoietin-2 (Ang-2) and von-Willebrand factor (vWF). Angiopoietin-2 promotes the breakdown of endothelial barrier integrity and thus increased vascular permeability, leading to cerebral, peripheral and pulmonary oedema formation with subsequently impaired oxygenation². Finally, due to fluid losses from fever, perspiration, vomiting, diarrhea, insufficient oral fluid intake, increased vascular permeability and other reasons nearly all patients with severe malaria present with some degree of hypovolemia^{18,19}.

Effects of Falciparum Malaria on the Cardiovascular System

The diverse effects of acute falciparum malaria on the cardiovascular system have been described in numerous studies in recent years (reviewed in²⁰). Hypovolemia and anemia result in reduced pre-load, which is physiologically compensated for by an increase in heart rate and vasoconstriction. More severe tachycardia, lower stroke volume (SV) index, and higher vena cava collapsibility index have been identified in acidotic malaria patients compared to less severely affected individuals²¹. An increase in the systemic vascular resistance (SVR) due to microcirculatory obstruction, vasoconstriction, and other reasons may also contribute to decreases in stroke volume. Higher baseline SVR indexes have been reported in patients who died from severe malaria compared to survivors¹⁹. Pro-inflammatory cytokines such as tumor necrosis factor (TNF), which are excessively liberated in the context of severe malaria, can directly depress myocardial function^{22,23}. Elevated levels of N-terminal brain natriuretic peptide (NT-pro-BNP) and heart-type fatty acid-binding protein (H-FABP) have been found in severe but not in uncomplicated falciparum malaria cases²³. Importantly, these processes occur simultaneously and may augment each other. With decreasing SV and increasing HR the cardiac cycle becomes less efficient and cardiac output (CO) diminishes²⁴. Together with anemia and impaired oxygenation reduced oxygen delivery (DO₂) to peripheral tissues and hence complicated malaria is the consequence.



Effects of Chronic Medical Conditions on the Outcome of Falciparum Malaria

In light of these considerations, it appears plausible that chronic disorders, in particular pre-existing cardiovascular diseases, can add to malaria pathophysiology. In endemic areas, however, the opposite seems to be the case. In fact, as a result of a longstanding host-pathogen interaction malaria has proved a powerful evolutionary driving force for the selection of polymorphisms that confer some degree of innate protection against severe forms of the disease²⁵. This selection process focused on the RBC as an essential component of the parasite's life cycle and includes polymorphisms of hemoglobin, intracellular enzymes, channels, surface markers, and morphology of the RBC, to name a few²⁶. Since the prevalence of hypertension is strikingly higher in populations constantly exposed to malaria than in those who are not²⁷, a co-evolutionary link between these two disorders has been suspected, too^{28,29}. Angiotensin II (Ang II) has in fact been shown to inhibit plasmodial growth in vitro directly³⁰. It also appears to have

a protective effect on the blood-brain barrier integrity³¹. In Indian adults polymorphisms in the angiotensin-converting enzyme (ACE) gene that lead to elevated levels of Ang II and thus hypertension, have been associated with protection against cerebral malaria³².

Host genetic factors are estimated to account for one quarter of the total variability in malaria severity³². In imported falciparum malaria, the genetic background of the affected populations is highly diverse and hence the clinical situation different from that of endemic areas. Accordingly, chronic co-morbidities may have a significant impact on the severity of imported malaria. Recently, with obesity and diabetes the first two age-related conditions have been identified as risk factors for severe imported falciparum malaria in a nation-wide study from Sweden³³. Although statistically not significant in the final multivariate model there was also a strong association between hypertension and cardiovascular diseases with an increased risk of severe malaria in this study. Together with dyslipidaemia the latter two conditions were also found to be associated

with severe disease in patients with *falciparum malaria* imported to Berlin, Germany³⁴. Diabetes, hypertension and lipid disorders play key roles in the development of microangiopathy. Hypertension induces two types of structural changes in the microcirculation: rarefaction and remodelling. Rarefaction describes an abnormal reduction in the density of arterioles, capillaries and possibly venules³⁵, while remodelling is a structural reduction in lumen diameter of resistance small arteries and arterioles³⁶. Both structural modifications appear in hypertensive individuals, but remodelling seems to play a paramount role in long-term elevation of SVR. Metabolic diseases appear to influence the pattern of structural changes in the microvasculature. While non-diabetic hypertensives develop inward eutrophic remodelling of the microvasculature consisting of a reduction in lumen diameter without changes in vessel cross sectional area^{36,37}, diabetics with and without hypertension undergo media vessel hypertrophy without a reduction of lumen diameter³⁸. In addition to such structural changes, functional changes of these vessels are also induced by hypertension and diabetes. Both disorders cause endothelial dysfunction that leads to a reduced bioavailability of local vasodilators (such as NO and prostacyclin) and increased formation of vasoconstrictors and reactive oxygen species (ROS), balancing the microvasculature towards vasoconstriction. Together, these structural and functional changes of the microvasculature result in increased SVR and reduced oxygen delivery to target organs³⁹. Pre-existing microangiopathy may thus potentiate the reduced oxygen supply to vital organs caused by imported *falciparum malaria*, thereby facilitating severe forms of the disease³⁴. Furthermore, hypertension-related cardiovascular diseases such as congestive heart failure, ischemic heart disease, and atrial fibrillation may contribute themselves to a decreased cardiac output in the setting of acute infection as outlined in Figure 1. Likewise, the risk for sepsis, a condition that shares certain features with *falciparum malaria*, has been shown to increase with older age, diabetes, atrial fibrillation, dyslipidemia, hypertension, and increasing total number of chronic medical conditions⁴⁰.

Why is That Important?

The single most important therapeutic intervention in severe malaria is the immediate institution of a causative therapy. Much depends on the timely initiation and correct choice of the antimalarial⁴¹. However, this is not the only intervention of importance. Optimal supportive care meeting the specific pathophysiologic requirements of the disease is also essential. A recent British study reported a strong, inverse correlation between mortality and the number of cases seen in a given region⁶. In the largest study on severe imported malaria carried out so far a total of 400 patients treated on 45 different intensive care units

in France were included⁴². The mortality in this study was 10.5%. When treatment takes place in specialized centers only mortality can be kept below 2%^{34,43}.

The purpose of this mini-review is therefore not only to summarize the diverse effects of acute *falciparum malaria* on the cardiovascular system. Another main objective is to outline the numerous interventions that exist to support it. Due to simultaneous microcirculatory obstruction with often markedly increased vascular permeability hypovolaemia should be corrected cautiously^{18,19}. In case of atrial fibrillation, controlling tachycardia may improve cardiac output, especially in patients with hypertensive heart disease and concomitant congestive heart failure. Adequate hemoglobin levels are important to maintain sufficient oxygenation. This is of particular importance in patients with coronary artery disease. In myocardial failure inotropes can be provided. Early application of positive end-expiratory pressures may not only be beneficial for pulmonary edema of multifactorial etiology, but may also decrease left ventricular afterload, thereby improving left ventricular ejection, cardiac output and myocardial oxygen demand⁴⁴. Significantly elevated blood pressures in hypertensive individuals may be treated with appropriate antihypertensives. Angiotensin-I antagonists are probably superior to other substances in this context²⁸. It must be emphasized, however, that unlike the choice of antimalarial none of the aforementioned interventions has been subjected to a controlled randomized clinical trial.

Conclusions

With its four key elements hypovolemia, increase in systemic vascular resistance, anemia and impaired oxygenation imported *falciparum malaria* exerts diverse effects on the cardiovascular system. Pre-existing cardiovascular diseases may add to this complex pathophysiology and thereby facilitate the development of complications. Microangiopathy seems to play a pivotal role in this context. Fortunately, the clinician can rely on numerous interventions to optimize supportive care.

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