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Impaired nitric oxide bioavailability and L-arginine reversible endothelial dysfunction in adults with falciparum malaria.

Yeo TW[1], Lampah DA, Gitawati R, Tjitra E, Kenangalem E, McNeil YR, Darcy CJ, Granger DL, Weinberg JB, Lopansri BK, Price RN, Duffull SB, Celermajer DS, Anstey NM.

Author information

1 International Health Division, Menzies School of Health Research and Charles Darwin University, Darwin NT 0810, Australia.

Abstract

Severe falciparum malaria (SM) is associated with tissue ischemia related to cytoadherence of parasitized erythrocytes to microvascular endothelium and reduced levels of NO and its precursor, l-arginine. Endothelial function has not been characterized in SM but can be improved by l-arginine in cardiovascular disease. In an observational study in Indonesia, we measured endothelial function using reactive hyperemia-peripheral arterial tonometry (RH-PAT) in 51 adults with SM, 48 patients with moderately severe falciparum malaria (MSM), and 48 controls. The mean RH-PAT index was lower in SM (1.41; 95% confidence interval [CI] = 1.33-1.47) than in MSM (1.82; 95% CI = 1.7-2.02) and controls (1.93; 95% CI = 1.8-2.06; P < 0.0001). Endothelial dysfunction was associated with elevated blood lactate and measures of hemolysis. Exhaled NO was also lower in SM relative to MSM and controls. In an ascending dose study of intravenous l-arginine in 30 more patients with MSM, l-arginine increased the RH-PAT index by 19% (95% CI = 6-34; P = 0.006) and exhaled NO by 55% (95% CI = 32-73; P < 0.0001) without important side effects. Hypoargininemia and hemolysis likely reduce NO bioavailability. Endothelial dysfunction in malaria is nearly universal in severe disease, is reversible with l-arginine, and likely contributes to its pathogenesis. Clinical trials in SM of adjunctive agents to improve endothelial NO bioavailability, including l-arginine, are warranted.

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