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Divergent nitric oxide bioavailability in men and women with sickle cell disease.

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Abstract

BACKGROUND: Although reduced endothelial nitric oxide (NO) bioavailability has been demonstrated in arteriosclerotic vascular disease, the integrity of this system in sickle cell disease remains uncertain.

METHODS AND RESULTS: We measured forearm blood flow in 21 patients with sickle cell disease (hemoglobin SS genotype) and 18 black control subjects before and after intra-arterial infusions of acetylcholine, nitroprusside, and the NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA). Endothelium-dependent vasodilation, measured by the percent increase in flow induced by acetylcholine infusion, was significantly greater than in controls (252+/-37% for patients versus 134+/-24% for controls; P<0.0001). However, there was a large sex difference in blood flow responses between female and male patients (340+/-46% versus 173+/-41%; P=0.035). Similarly, basal NO bioactivity, as measured by the percent decrease in flow induced by L-NMMA, was depressed in male compared with female patients (-17+/-5% versus -34+/-4%; P=0.01), as was the response to nitroprusside (86+/-21% versus 171+/-22%; P=0.008). L-NMMA reduced the blood flow response to acetylcholine in women, but not in men. Sex differences in vascular cell adhesion molecule-1 were appreciated, with significant correlations between levels of soluble vascular cell adhesion molecule-1 and blood flow responses to L-NMMA and nitroprusside (r=0.53, P=0.004 and r=-0.66, P<0.001, respectively).

CONCLUSIONS: NO bioavailability and NO responsiveness are greater in women than in men with sickle cell disease and determines adhesion molecule expression. Endothelium-dependent blood flows are largely non-NO mediated in male patients. These results provide a possible mechanism for reported sex differences in sickle cell disease morbidity and mortality and provide a basis for novel pharmacological interventions.

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