

Folate improves endothelial function in coronary artery disease: an effect mediated by reduction of intracellular superoxide?

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Abstract:

Homocysteine is a risk factor for coronary artery disease (CAD). Folic acid lowers homocysteine and may improve endothelial function in CAD, although the mechanism is unclear. We investigated the effect of folic acid on endothelial function, homocysteine, and oxidative stress in patients with CAD. We also examined the acute effect of 5-methyltetrahydrofolate (5-MTHF), the principal circulating folate, on endothelial function in vivo and on intracellular superoxide in cultured endothelial cells. A randomized crossover study of folic acid (5 mg daily) for 6 weeks was undertaken in 52 patients with CAD. Ten further patients were given intra-arterial 5-MTHF. Endothelial function was assessed by flow-mediated dilatation (FMD). Folic acid increased plasma folate ($P<0.001$), lowered homocysteine by 19% ($P<0.001$), and improved FMD ($P<0.001$). FMD improvement did not correlate with homocysteine reduction. Malondialdehyde and total plasma antioxidant capacity, markers of oxidative stress, were unchanged. 5-MTHF acutely improved FMD ($P<0.001$) without altering homocysteine ($P=0.47$). In vitro, 5-MTHF abolished homocysteine-induced intracellular superoxide increase ($P<0.001$); this effect was also observed with folic acid and tetrahydrobiopterin. Our data support the beneficial effect of folic acid on endothelial function in CAD but suggest that the mechanism is independent of homocysteine. Reduction of intracellular endothelial superoxide may have contributed to the effect.