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Title: Macrophage migration inhibitory factor (MIF) promoter polymorphisms are associated with favorable hemodynamic indices in systemic sclerosis-associated pulmonary arterial hypertension

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Body: RATIONALE: Inflammatory mediators are increasingly associated with pathogenesis in pulmonary arterial hypertension (PAH). We have previously observed a 3.7-fold increase in serum levels of the pro-inflammatory macrophage migration inhibitory factor (MIF) in PAH patients. MIF promoter polymorphisms (-173*C, -794CATT$^{5-8}$) have been associated with disease susceptibility or phenotype in several inflammatory syndromes. We hypothesized that MIF promoter polymorphisms may influence PAH development or severity. METHODS: Genomic DNA was isolated from 117 European-American PAH patients, including idiopathic (IPAH; N = 35) and systemic sclerosis-associated PAH (SSc-PAH; N = 82), healthy European-American controls (N=264), and SSc patients without PAH (N=343). Allele and genotype frequencies for the MIF -173*C single nucleotide polymorphism and the -794CATT$^{5-8}$ variable nucleotide tandem repeat were compared between PAH patients and controls, and were compared with initial hemodynamic indices and survival in PAH patients. RESULTS: We found no significant difference in the frequencies of either MIF promoter polymorphism between controls and PAH patients. SSc-PAH patients with the MIF -173*C polymorphism had higher cardiac output (P=0.04), cardiac index (P=0.003), and stroke volume index (P=0.01) at diagnosis. Neither polymorphism predicted survival in PAH patients. CONCLUSION: The MIF -173*C polymorphism may improve initial hemodynamics in SSc-PAH. However, MIF promoter polymorphisms do not predict PAH susceptibility or survival. These results suggest that MIF may function as a disease-modifying gene in SSc-PAH.