Background: The multifactorial pathogenesis of ischaemic heart disease (IHD) includes a combination of environmental and genetic factors. Activation of inflammatory pathways is common in IHD, but mechanisms are still unknown. We and others have recently proposed that a polymorphism in the CD14 receptor gene of monocytes may be involved in IHD. In this study, we assessed whether other polymorphisms of genes coding for pro-inflammatory mediators are involved in the inflammatory response observed in IHD.

Methods: We studied 87 pts with Braunwald class III/IV unstable angina (Group 1) and 32 pts with stable angina (Group 2). The following polymorphisms were detected by polymerase chain reaction and restriction analysis: -174 C/G of IL-6, Thr/Asn of TNF-α and four polymorphisms of TNF-α (-375 G/A, -308 G/A, -244 G/A, -238 G/A). Genotype and allele frequencies were correlated with C-reactive protein (CRP) levels and IL-6 production by circulating monocytes in response to LPS-stimulation (1ng/ml for 4 hours).

Results: Genotype and allele frequencies of the investigated polymorphisms were not different among groups. However, elevated levels of CRP (>3mg/l) were observed in 61% of the overall carriers of Thr/Thr genotype of TNF-α gene and 21% of thrs carriers (p<0.05). Moreover, IL-6 production in response to LPS was higher in GG homozygotes of IL-6 gene than in GT heterozygotes (4.4 ng/ml vs 2.0 ng/ml; p<0.05). No correlation was found between CRP levels, IL-6 production and polymorphisms of TNF-α gene.

Conclusion: Our study suggests that in a polygenic and multifactorial syndrome such as IHD, polymorphisms of TNF-α and IL-6 gene, but not of TNF-α, are related with an enhanced pro-inflammatory response.

The 894G T Polymorphism In The Endothelial Nitric Oxide Synthase Gene Influences Risk For Acute Myocardial Infarction Only In Subjects With Low Risk For Coronary Events

George K. Andrikopoulos, Dimitri Richter, Dimitri Grammatopoulos, Sevasti Zervou, Michalis Zaris, Elias Karabinos, Antonios Pantazis, Dimitris Manolatos, Nikolettos Exadaktylos, Christodoulos Stefanadis, Stefanos Fouass, John Gialafos, Edward Hillhouse, Pavlos Toutouzas, Hippokration Hospital, Athens, Greece, Department of Biostatistics, University of Warwick, Warwick, United Kingdom.

Background: Homozygosity for the 894 G-T polymorphism in the endothelial Nitric Oxide Synthase (eNOS) gene, which encodes a Glu298-Asp substitution in eNOS, has been related to increased risk of acute myocardial infarction (AMI). We examined the role of this genetic variant in the pathogenesis of AMI in a relatively homogeneous, low coronary risk Caucasian population.

Methods: 1629 consecutive AMI patients (mean age 62 ± 13 years), enrolled into the GEMIG study were recruited on admission from 9 Cardiac Departments located in three cities. The GEMIG study was a multicentre prospective study, specifically designed to investigate the genetic background of ischemic heart disease in the Greek population. The control group (n=605, mean age 58 ± 15 years) was derived from an epidemiological study that investigated the frequency of the same genetic variants in a representative sample of the general adult population. Results: The frequency of the Asp298 variant was not significantly higher in AMI patients compared to controls (11.2 vs 10.4%, P=0.342). Adjustment for age and gender did not alter these results, but subgroup analysis showed an excess of homozygotes for the Asp298 allele among cases (12.9 vs 7.8%, p<0.05). The corresponding figures in pts with STE were: 10, 18, 27%, respectively; in pts with no STE were: 20, 24, 35%, respectively; and in pts with STD gradually increased (14, 24, 28%, respectively, p for trend <0.0001). The frequency of no chest pain/atypical symptoms on presentation increased with age for all ACS pts (14, 21, 32%, respectively, p for trend <0.0001). The corresponding figures in pts with STE were: 10, 18, 27%, respectively; in pts with no STE were: 20, 24, 35%, respectively; and in pts with ST-depression (STD) were: 17, 25, 32%, respectively (p for trend <0.0001, for all). In ACS pts, STE on admission ECG decreased with advancing age (P=0.48; 95% CI 0.37-0.63). The use of acute reperfusion therapy (thrombolysis or primary PCI) declined with advancing age (35% in 1986-2000, p<0.0001) and increased in ACS pts with increasing age, no chest pain/atypical symptoms are increasing in frequency. In the older age groups, STE is becoming gradually less frequent.