Blood Pressures and Indices of Angiogenesis, Endothelial Dysfunction and Thrombogenesis

	Healthy Controls	Hypertensive Patients	p Value
Systolic BP (mmHg)	134 ± 11	161 ± 21	<0.001
Diastolic BP (mmHg)	81 ± 7	95 ± 18	0.002
FMD (%)	11.9 ± 11.6	3.9 ± 5.8	0.002
vWf (IU/dl)	111.6 ± 32.9	103.7 ± 27.1	0.330
VEGF (pg/ml)	96 [60-130]	105 [53-1280]	0.358
sFlt-1 (ng/ml)	1.3 [0.5–2.6]	1.5 [0.5-111]	0.217
Tie-2 (ng/ml)	4.4 [2.7-6.3]	7.25 [3.5-37.5]	0.043
TF (pg/ml)	15 [11-18]	19 [13-32]	0.023

Values expressed as mean±standard deviation or median [interquartile range] and analysed by Unpaired T Test or Mann Whitney as appropriate

5:15 p.m.

832-6   Long-Term Follow-Up of Hypertensive Patients With Angiographically Normal Coronary Arteries: Prognostic Value of Epicardial Coronary Endothelial Dysfunction

Alain Nitenberg, Denis Chemla, Isabelle Antony, CHU Jean Verdier, Bondy, France, CHU Bicêtre, Le Kremlin-Bicêtre, France

Background: epicardial coronary endothelial dysfunction independently predicts cardiovascular events in patients with coronary risk factors and without coronary atherosclerosis. This study was designed to evaluate outcome of hypertensive patients (HP) on the basis of their epicardial coronary endothelial function.
Methods: 68 control subjects (CS), 53 males, 15 females (48.8±7.6 years) and 83 HP, 54 males, 29 females (51.3±7.9 years) with angiographically normal coronary arteries and without any other coronary risk factor underwent epicardial coronary reactivity assessment to cold pressor test (CPT) using quantitative coronary angiography. Unpredictable cardiovascular events (CVE) (sudden cardiac death, stable and unstable angina, myocardial infarction, stroke, angioplasty, coronary artery surgery) were recorded with a mean follow-up of 115 months (range 84-132).
Results: in CS, dilation occurred in 88.2%, no change in 11.8% (mean diameter change: +14.6±9.3%) and there was no constriction. In HP, coronary artery dilation occurred in 13.3%, no change in 25.3% (mean diameter change: +10.9±11.2%), and constriction in 61.4% (mean diameter change: -12.7±3.4%). Endothelium-independent dilation to nitrates was normal in the 2 groups (28.7±12.8% and 25.8±11.9%, respectively, NS). In CS, there was 3 CVE in 2 subjects (2.9%). In HP, there was 17 CVE in 12 patients (14,5%, p<0.01 vs CS), and in this group there was 15 CVE in the 10/51 patients (19.6%) with coronary artery constriction, and 2 CVE in the 2/33 patients (6.3%) with no change or dilation (p<0.05).
Conclusion: in hypertensive patients with angiographically normal coronary arteries and without other coronary risk factors, epicardial coronary endothelial dysfunction assessed by a simple cold pressor test is predictive of long-term cardiovascular events.

ORAL CONTRIBUTIONS

840   Novel Risk Factors and Coronary Artery Disease I

Tuesday, April 01, 2003, 8:30 a.m.-10:00 a.m.
McCormick Place, Room S405

8:30 a.m.

840-1   Relation Between Fasting Glucose and C-Reactive Protein in Middle-Aged Subjects

Doron Aronson, Peter Bartha, Oren Zinder, Arthur Kerner, Ella Shitman, Gerald J. Brook, Yishai Levi, Rambam, Haifa, Israel

Introduction: Elevation of C-reactive protein (CRP) is associated with components of the metabolic syndrome, and especially with measures of obesity. Hyperglycemia can stimulate release of cytokines from various cell types including adipocytes. However, the relation between glycemic status and CRP is not known. Methods: We studied the relation of high-sensitivity CRP to fasting glucose (FG) and components of the metabolic syndrome in a population-based cross sectional study (n = 1000; age, 50 ± 9 years).
Results: CRP increased continuously from the lowest quartile of normal FG to impaired FG and to diabetes (Figure). Increasing CRP with higher FG levels was apparent even among subjects with FG in the normal range ($P = 0.039$ for trend). Subjects with FG in the upper quartile of normal FG had higher CRP compared to subjects in the lower quartile ($P = 0.035$). There was a positive crude correlation between CRP and smoking, postmenopausal hormone use, body mass index, FG, triglycerides, hypertension, and uric acid ($P = 0.002$ to 0.0001), and a negative correlation with HDL ($P < 0.0001$) and physical activity ($P = 0.002$). After adjustment for potential confounders in a stepwise multivariate linear regression, FG remained independently related to CRP ($P = 0.019$).
Conclusion: CRP increases continuously across the spectrum of FG, beginning in the lowest quintile of normal FG. This finding suggests that improving glycemic control may mitigate the proinflammatory state in subjects with diabetes and insulin resistance.
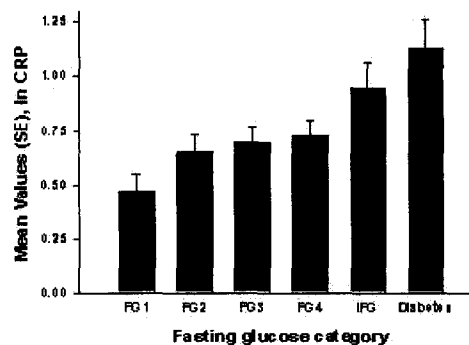
8:45 a.m.

840-2   Age Dependent Association Between High Sensitivity C-Reactive Protein and Tumor Necrosis Factor Functional Variants

Fernando Araújo, Alexandre C. Pereira, Gloria F. Motta, Daniela L. Jardim, José E. Krieger, Alfredo J. Mansur, Heart Institute - InCor, São Paulo, Brazil

High sensitivity C-Reactive protein (hs-CRP) is a promising biochemical marker for prediction of coronary events. Genetic factors may influence hs-CRP concentration. We hypothesized that a genetic variant at position-308 in the promoter region of the TNF alpha gene (TNFA2 allele), which is related to increased circulating levels of TNF, may be associated with higher hs-CRP in a Brazilian population. This study enrolled 684 healthy adults volunteers, 295 men (43. 1%) and 389 women (57. 1%), designed to quantify environmental and genetic variables associated with serum hs-CRP. Ethnic distribution was concordant with the ethnic distribution in the country. TNF -308 genotype was obtained through PCR amplification and restriction enzyme digestion in DNA from peripheral leucocytes. TNFA alleles were in Hardy-Weinberg equilibrium in this sample. Ethnicity was the single demographic variable with different distribution regarding harboring or not the TNFA2 allele (p=0.03). There was no statistically significant difference between the individuals with or without the TNFA2 allele and hs-CRP serum concentration. However, there was a tendency for higher hs-CRP serum levels in the TNFA2 group and a higher frequency of individuals with the TNFA2 allele in hs-CRP quartile 4. Through ANOVA factorial modeling using log transformed hs-CRP serum level as the dependent variable a significant association between hs-CRP and the presence of TNFA2 allele was disclosed after stratifying our analysis for age quartiles (p= 0.01). TNFA genotype was significantly associated with hs-CRP serum levels in the fourth quartile of age (geometric mean serum level in this quartile 0.096 (0.02) for TNFA1/TNFA1 individuals and 0.196 (0.051) for individuals harboring the TNFA2 allele). This association remained statistically significant after adjustmet for ethnicity (p = 0.03). Finally, the presence of TNFA2 allele in this age group increased the odds of being in the fourth quartile of hs-CRP concentration (p value = 0.04, OR = 5.1, 95% CI = 1.1 24.9).These data are consistent with an association between a functional genetic variant of the TNF alpha gene and hs-CRP levels at particular age groups

9:00 a.m.

840-3   Matrix Metalloproteinases and Their Inhibitors in Premature Coronary Atherosclerosis: Relation With Inflammation and Metabolic Markers

Samuele Nanni, Giovanni Melandri, Roeland Hanemaaijer, Vittorio Cervi, Luciana Tomasi, Chiara Melloni, Pierluigi Tricoci, Angelo Branzi, Institute of Cardiology, Bologna, Italy, T.N.O.-PG, Leiden, The Netherlands

Background: little is known on determinants of matrix metalloproteinases (MMPs) plasma concentration and activity in coronary artery disease (CAD).
Methods: we studied 80 male patients (pts) with premature (≤ 55 years) CAD (either myocardial infarction or angina with angiographic evidence of CAD) and 40 healthy male controls of similar age. The pts were subdivided into three groups as follows: 1) 20 consecutive pts with ST elevation acute myocardial infarction (STEMI), 2) 29 consecutive pts with unstable angina (UA) or non-STEMI (UA/NSTEMI), 3) 31 consecutive pts with stable CAD.
MMP-2 (i.e gelatinase A) and MMP-9 (i.e. gelatinase B) plasma total activities were measured along with concentrations of MMP-2, MMP-3 (i.e. stromelysin-1), MMP-9 and specific tissue inhibitors of MMPs, such as TIMP-1 and TIMP-2. Inflammation and metabolic markers were also evaluated.
Results: MMPs and TIMPs data are depicted in table 1. MMP-2 total activity was lower both in the whole pts population and in ACS pts compared to controls (both p ≤ 0.002). MMP-9 total activity inversely correlated with haptoglobin and blood glucose (ps 0.032). TIMP-1 strongly correlated with blood glucose and both C-reactive protein and haptoglobin (all p ≤ 0.005).
Conclusion:
in patients with premature CAD MMP-9 and TIMP-1 concentrations are increased, while TIMP-2 concentration and MMP-2 total activity are decreased. TIMP-1 and MMP-2 total activity strongly correlated with inflammation markers and with blood glucose levels.