significant predictor of CV death (hazard ratio [HR] 2.26, 95% CI 1.78-2.86), fatal/non-fatal MI (HR 2.16, 95% CI 1.67-2.80), fatal/non-fatal stroke (HR 1.76, 95% CI 1.39-2.21) and the composite CV endpoint (HR 1.99, 95% CI 1.70-2.33). In Cox multivariate analyses controlling for age, gender, race, diabetes, history of ischemic heart disease, congestive heart failure, stroke, or peripheral vascular disease, baseline albumin/creatinine ratio, systolic and diastolic blood pressure, baseline Cornell product and Sokolow-Lyon voltage, and for the impact of treatment with losartan vs atenolol on CV outcomes, ECG strain remained a significant predictor of CV mortality (HR 1.53, 95% CI 1.18-2.00), MI (HR 1.55, 95% CI 1.16-2.06) and of the composite CV endpoint (HR 1.33, 95% CI 1.11-1.59).

Conclusions: ECG strain is a marker of increased CV risk in hypertensive patients in the setting of aggressive blood pressure lowering. Serial assessment of lateral ST segment and T-wave findings may prove to be useful in further stratifying risk and identifying patients who may require additional antihypertensive therapy.

POSTER SESSION

1079 Genetics of Vascular Disease

Monday, March 31, 2003, 9:00 a.m.-11:00 a.m.
McCormick Place, Hall A
Presentation Hour: 10:00 a.m.-11:00 a.m.

1079-126 Increased CD40 Ligand, C-Reactive Protein, and Platelet-Monocyte Binding in Patients With Type 1 Diabetes Mellitus

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Background: Patients with type I diabetes mellitus have a markedly increased risk of developing cardiovascular disease. The CD40-CD40 ligand (L) dyad and platelet-monocyte binding (PMB) may play an important role in atherogenesis, plaque rupture and thrombosis. We hypothesized that patients with uncomplicated type I diabetes mellitus would demonstrate altered CD40L expression and PMB in keeping with a pro-inflammatory state.

Methods: Twenty-two patients with type I diabetes without clinical evidence of vascular disease, hypertension or nephropathy were compared to 22 age- and sex-matched healthy control subjects. All subjects were non-smokers and maintained on no medications except insulin. Serum concentrations of soluble (s) CD40L and C-reactive protein (CRP) were determined by ELISA and an ultra-sensitive latex enhanced immunoturbidimetric assay respectively. PMB and surface expression of CD40L on platelets were assessed by flow cytometry. Isotype control monoclonal antibodies were used to establish baseline fluorescence above which all events were deemed positive.

Results: Baseline characteristics including age, sex, body mass index, total cholesterol and HDL cholesterol were similar between the groups. Patients with type I diabetes compared with non-diabetic controls, have higher serum concentrations of CRP (0.33 ± 0.09 mg/dl vs. 0.1 ± 0.02 mg/dl, p=0.01) and soluble CD40L (10.0 ± 1.4 ng/ml vs. 4.6 ± 0.6 ng/ml, p=0.006). Patients with type I diabetes mellitus also had higher platelet expression of CD40L (13.8 ± 0.9% vs. 8.5 ± 1.1%, p<0.001) and PMB (35.9 ± 3.3% vs. 26.4 ± 2.9%, p=0.005). Both sCD40L (r=0.34, p=0.03) and platelet surface expression of CD40L (r=0.56, p<0.001) were positively correlated with HbA1c but not CRP. In contrast, PMB was positively correlated with CRP (r=0.46, p=0.02) but not HbA1c.

Conclusions: Despite the absence of clinical vascular disease, patients with uncomplicated type I diabetes mellitus have evidence of systemic inflammation that is associated with platelet activation. These findings provide novel insights that may help explain the susceptibility of patients with type I diabetes mellitus to the development of cardiovascular disease.

1079-127 The 4G/5G Promotor Polymorphism of the PAI-1 Gene Is Associated With Coronary Artery Disease and Linked to the HINDIII Polymorphism

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Background: Increased activity of plasminogen activator inhibitor type-1 (PAI-1) is an independent risk factor for coronary artery disease (CAD). The 4G/5G polymorphism in the promotor of the PAI-1 gene influences PAI-1 expression with carriers of the 4G allele exhibiting higher plasma levels of PAI-1. For the HindIII polymorphism located at the 3' end of the PAI-1 gene an association with CAD has been described for both homozygous genotypes (1/1 and 2/2). The study was designed to compare the predictive power of both polymorphisms with respect to CAD.

Methods: 112 patients with CAD who underwent percutaneous coronary intervention and 44 healthy controls were genotyped by restrictic ı fragment length polymorphism analysis for the 4G/5G and the HindIII genotypes.

Results: 41 (37%) patients were genotyped 4G/4G, 56 (50%) were 4G/5G, and 15 (13%) 5G/5G (allele frequency 4G: 0.62; 5G: 0.38). Results in controls were 9 (20%) 4G/4G, 25 (57%) 4G/5G, and 10 (23%) 5G/5G, respectively (allele frequency 4G: 0.49; 5G: 0.51), with a statistically significant higher frequency of the 4G allele in patients (p=0.027). In contrast, there was no significant difference in the distribution of the HindIII genotypes between patients and controls: 26 (23%) were genotyped 1/1, 52 (47%) 1/2, and 34 (30%) 2/2 (allele frequency 1: 0.46; 2: 0.54). 9 (20%) controls were genotyped 1/1, 20 (46%) 1/2, and 15 (34%) 2/2 (allele frequency 1: 0.43; 2: 0.57). Considering possible linkage between both polymorphisms, in patients the occurrence of the 5G/5G genotype was restricted to the 2/2 genotype (n=15) while the 1/1 genotype cumulated among carriers of the 4G/4G genotype (n=26) with similar findings in the control group. Statistical analysis revealed a strong linkage of the 2 allele with the 5G allele and of the 1 allele with the 4G allele both in patients (p<0,01) and in controls (p= 0,033).

Conclusions: The 4G/5G and the HindIII polymorphism in the PAI-1 gene exhibit strong linkage. The 4G/5G polymorphism has a higher predictive power for CAD, making it more suitable for estimation of the risk for CAD.

1079-128 Influence of CYP2C9 Polymorphism on Fluindione Dose Requirement and Anticoagulation

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Background:Fluindione, an anticoagulant of the Indanedione family, requires careful management because of individual variability and genetic susceptibility. The hepatic cytochrome CYP2C9 is the principal enzyme involved in the coumarinic family metabolism and its 2 variants, CYP2C9*2 and CYP2C9*3, are associated with lower dose requirement.However, the metabolic pathway of Fluindione degradation is not known.

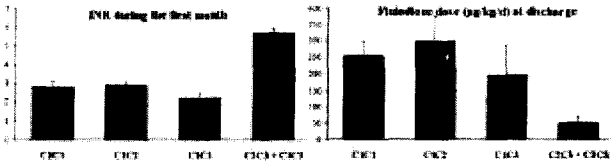
Objective:To determine the influence of CYP2C9*2 and CYP2C9*3 variants on dose requirement and anticoagulation status in a population of Fluindione-treated patients.

Methods: From May to August 2002, genotyping for the CYP2C9*2 and CYP2C9*3 alleles was done by Polymerase Chain Reaction (PCR). INR and Fluindione dose were noted at discharge and for one month.

Results:Of 40 patients with analysable data, 24(60%) had the wild-type (*1/*1) genotype, 11(27.5%) the heterozygote C2(*1/*2), 3(7.5%) the heterozygote C3(*1/*3), 1(2.5%) the heterozygote C2C3(*2/*3)and 1(2.5%) the homozygote C3(*3/*3) genotype.

Carriers of C2C3 or C3C3 variants required a significantly lower dose of Fluindione and had a significantly higher INR compared to carriers of other variants.

Conclusion:Our results suggest that the CYP2C9 polymorphism is associated with a lower dose requirement and with over-anticoagulation. Thus, the CYP2C9 could be implicated in the Fluindione metabolism.



1079-129 Genotype-Dependent Inhibition of PAI-1 Expression in Human Vascular Smooth Muscle Cells by PPAR-Gamma Agonists

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Background: The PPAR-γ agonist troglitazone has recently been shown to reduce the expression of PAI-1 in human vascular smooth muscle cells (HVSMC). In the present study we sought to determine whether this effect is a class or a agent specific one and whether it is dependant on the 4G/5G polymorphism in the promoter of the PAI-1 gene.

Methods and results: HVSMC under basal and stimulated (40 pM TGF-β) conditions were incubated with selected concentrations (0, 1, 3.3, 10 nM) of glitazones for 24 h. PAI-1 protein concentration in conditioned media (ELISA) was not significantly affected by glitazones under basal conditions. In contrast, under stimulated conditions, PAI-1 expression decreased by 56±4% (mean±SEM) with troglitazone (p=0.002) and by 63±22% with ciglitazone (p=0.027). Rosiglitazone tended to decrease PAI-1 expression by 25±18% (p=ns), pioglitazone was without effect (n=3, each in triplicate). The inhibitory effect of tro- and ciglitazone persisted for up to 72 h. Total protein synthesis was not affected by glitazones suggesting their specific action. The concomitant expose of cells to insulin did not affect the inhibition of PAI-1 expression by glitazones (also known as insulin sensitizers, n=6). PAI-1 gene expression (RT-PCR) was affected accordingly (n=4). HVSMC were genotyped with respect to the 4G/5G polymorphism and CHO cells were transfected with plasmids containing either the 4G or the 5G genotype of the PAI-1 promoter as well as luciferase as reporter gene. In HVSMC (n=29 donors) with genotype 4G/4G troglitazone reduced PAI-1 expression by 29±16%, in those with 5G/5G by 58±17% (p=0.028). In CHO (n=13 transfections) a corresponding reduction was obtained (p=ns).

Conclusions: Different glitazones at pharmacological concentrations inhibit PAI-1 expression in HVSMC to substantially different extents. The 5G allele of the 4G/5G polymorphism is more susceptible to inhibition by troglitazone than the 4G allele. Thus, the selection of glitazone and the PAI-1 genotype seem to be of pharmacodynamic and of pharmacogenetic relevance with respect to normalizing pathologically increased PAI-1 expression.