1103-167 **Accelerated Coronary Stenosis Progression Is Associated With the ApolipoproteinC-III Content of ApoB Particles Among Those With Diabetes Mellitus**

B. Greg Brown, Josh Morse, Carmen Quiroga, Nancy Simpson, Carolyn Knight Gibson, Xue-Qiao Zhao, Alan Chait, Peter Alaupovic, University of Washington, Seattle, WA, Oklahoma Medical Research Foundation, Oklahoma City, OK

Background: Coronary events have been independently associated with plasma levels of apolipoprotein (apo) B-containing particles that also contain apoC-III (Lp-B:C+).This effect may be most pronounced among diabetics and may help to explain its increased vascular risk. **Methods:** Patients (n= 144) with coronary disease and low HDL-cholesterol were randomized in an angiographic trial to simvastatin plus niacin [SN(+);10–20 mg and 2–4 gm, qd], or to their placebos [SN(-)]. Mean severity of proximal stenosis, per pt, was measured at baseline and at 3-yrs follow-up. The correlation of the 3-yr change in mean stenosis severity (Δ%S) with Lp-B:C+ levels during treatment, and with Lp-B+(no C-III) levels, was computed. Adjustment was made for smoking, and baseline stenosis severity. **Results:** There were 32 men and women with diabetes (DM) or impaired fasting glucose (IFG) and 94 without DM or IFG, equally randomized to SN(+) or SN(-). Lp-B:C+ levels at baseline were 48.5 mg/dl among DM/IFG, and 46.6 among non-DM/IFG. During active therapy, Lp-B:C+ fell 32% among DM/IFG, and 25% among non-DM/IFG; Lp-B+ fell comparably in DM/IFG and in non-DM/IFG. SN(-) had minimal impact (<3% change) on these variables. Among those with DM/IFG the adjusted correlations (Spearman) between Δ%S and Lp-B:C+ was r = 0.45 (P = 0.01). Among non-DM/IFG, r = 0.04 (P = 0.71). The corresponding values for LpB+ were r = 0.34 (P = 0.05) and r = 0.25 (P < 0.01). For the tertiles of Lp-B:C+ among DM/IFG, mean Δ%S was 0.6, 2.4, and 5.1%S (P=0.03); corresponding values for non-DM/IFG were 0.9, 1.6, and 1.1 %S.
Conclusions: Levels of apoB particles lacking apoCIII were equally atherogenic among diabetics and normals; however, stenosis progression attributable to Lp-B:C+ is seen only among those with DM/IFG. Above-average levels of Lp-B:C+ may serve as markers, or as mediators, for the accelerated atherosclerosis of diabetes.

1103-170 **Enhanced Coronary Artery Disease Risk by Combining Pathogen Burden, C-Reactive Protein and Heat Shock Protein 60 Antibodies in the Absence of Heat Shock Protein 70**

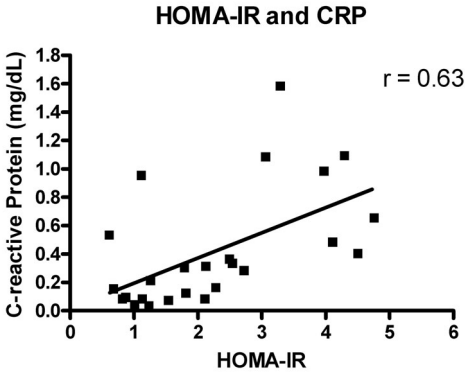
Jianhui Zhu, Arshed Quyyumi, David Rott, Daniel Canos, Stephen Epstein, Washington Hospital Center, Washington, DC

Background: We previously demonstrated that risk of coronary artery disease (CAD) was increased when pathogen burden, C-reactive protein (CRP), heat shock protein (HSP) 60 antibodies were combined, compared to considering them separately. We subsequently demonstrated that plasma levels of HSP70 (a molecule with anti-inflammatory activity) were inversely associated with CAD risk. Methods: In the present study, we analyzed the relative importance and joint effects of pathogen burden (numbers of positive serologies to cytomegalovirus, hepatitis A virus, C*hlamydia pneumoniae, Helicobacter pylori,* herpes simplex virus type 1 and type 2), CRP levels and the presence of anti-HSP60 antibodies as well as HSP70 for the risk of CAD in 421 patients (62% men, mean age 57 years). CAD was documented by angiography. Results: Traditional CAD risk factors, including age, male gender, diabetes and hypercholesterolemia, were significantly associated with CAD. High pathogen burden (>=5 antibody seropositivities), elevated CRP levels (>0.5 mg/dL) and HSP60 antibodies were also associated with, but posed a similar risk for CAD: the odds ratio (OR) with 95% CL was 1.7 (1.0-3.0) for high pathogen burden, 1.7 (1.0-3.1) for elevated CRP levels, and 1.7 (0.9-2.9) for HSP60 antibodies, respectively. However, pathogen burden combined with elevated CRP levels and HSP60 antibodies (which constituted 40% of the cohort) was more strongly associated with CAD (OR 10.6 with 95% CL 2.8-41.7). The significance persisted after adjustment for traditional risk factors. Most importantly, we found that, in the patients with high pathogen burden, elevated CRP levels and HSP60 antibodies, and who had no detectable plasma HSP70 protein (which constituted 9% of the cohort), the risk of CAD was dramatically increased. The OR of CAD reached 37.5 (4.3-330.6). Conclusion: Although confirmatory studies need to be conducted in larger cohorts, this study demonstrated that the prediction of CAD risk can be markedly increased by combining these non-traditional risk factors that reflect different processes predisposing to CAD.

1103-193 **Independent Relationship Between C-Reactive Protein and Markers of Insulin Resistance in Overweight and Obese Children**

Aaron S. Kelly, Rachel J. Wetzsteon, Daniel R. Kaiser, Julia Steinberger, Alan J. Bank, Donald R. Dengel, University of Minnesota, Minneapolis, MN, St. Paul Heart Clinic, St. Paul, MN

Background: In adults, systemic inflammation is associated with insulin resistance independent of obesity, however, data are lacking in children. The purpose of this study was to assess the relationship between plasma C-reactive protein (CRP) and markers of insulin resistance in overweight and obese children (BMI > 85th percentile for age/gender). **Methods:** Ultra-sensitive CRP, fasting insulin and glucose, and body composition (dual-energy x-ray absorptiometry) were assessed in 25 healthy overweight and obese children (M = 12, F = 13; age = 10.9 ± 2.0 years; BMI = 30.4 ± 6.7 kg/m^2; body fat = 44.1 ± 6.6%). The log of CRP was used for all analyses. **Results:** CRP was significantly correlated with percent body fat (r = 0.64; p = 0.001), the homeostasis model assessment for insulin resistance (HOMA-IR) (r = 0.63; p = 0.001), and fasting insulin (r = 0.62; p = 0.001) (Figure). After adjusting for percent body fat, the relationships remained significant for CRP and HOMA-IR (r = 0.49; p = 0.014), and for CRP and fasting insulin (r = 0.49; p = 0.014). **Conclusions:** 1) CRP is significantly correlated with body fatness and markers of insulin resistance in healthy overweight and obese children. 2) The association between CRP and insulin is independent of percent body fat in these individuals. These results provide evidence that in overweight and obese persons a relationship between sub-clinical inflammation and insulin resistance occurs early in life, long before the development of overt diabetes and cardiovascular disease.



1103-194 **Identification of Novel Genetic Markers Associated With Risk of Myocardial Infarction From a Genomic Scale Scan of Putative Functional Polmorphisms**

Dov Shiffman, May Luke, Olga Iakoubova, Bradley E. Aouizerat, Christian A. Zellner, Clive R. Pullinger, Denis W. Drew, Joseph J. Catanese, Diane U. Leong, Dongming Liu, Judy Z. Louie, David Lew, Carmen H. Tong, David A. Ross, Linda B. McAllister, Charles M. Rowland, Kit F. Lau, James J. Devlin, Mary J. Malloy, John P. Kane, University of California, San Francisco, San Francisco, CA, Celera Diagnostics, Inc., Alameda, CA

Background: Myocardial infarction (MI) is a multi-factorial disease associated with both environmental and genetic factors. Identification of genetic polymorphisms associated with increased risk of MI could lead to prediction of risk and provide a mechanistic basis for individualized therapeutic intervention. Methods: We set out to identify novel single nucleotide polymorphisms (SNPs) that are associated with risk of MI. We tested a comprehensive set of 16,000 SNPs selected for their putative functional properties. The majority of the SNPs we tested (~80%) are exonic putative functional SNPs, i.e. missense, nonsense and splice donor/acceptor polymorphisms. The rest were selected for their potential effect on transcription and mRNA stability. Results: Allele frequencies in 340 male MI cases and 503 male controls were determined for all 16,000 SNPs by a PCR based methodology. To increase the speed and capacity of the screen, allele frequencies were measured in pooled samples. Pools of DNAs from 50 individuals with similar phenotypes were generated. This small pool size enabled stratified analysis of the data. A thousand markers were selected for further study based on their effect size, significance level, and the presence of significantly associated neighboring SNPs. To date, eighty markers were retested in a second sample set. Conclusions: We have validated the association of MI with three previously reported genes (e.g. PON1, P-Selectin and ICAM-1). We also have independently replicated association of missense SNPs in three novel genes (an immune cell receptor on chromosome 20p, a zinc finger protein on 3q and a WD repeat protein on 2q) not previously reported to be associated with MI. Two additional SNPs are located in predicted but uncharacterized genes on chromosomes 1 and 3. The p values of the replicated markers range from 0.04 to 0.004, and their odds ratios range from 1.3 to 1.7. The moderate effect size of these markers and their relatively high risk allele frequencies (12 to 95 percent) are consistent with the common disease - common variant hypothesis.

1103-195 **Genetic Predictive Factors for Restenosis in Diabetic Patients After Percutaneous Transluminal Coronary Angioplasty**

Pascalle S. Monraats, Willem R.P Agema, Aeilko H. Zwinderman, Robbert J. de Winter, Rene A. Tio, Pieter A.F.M Doevendans, Harry J.G.M Crijns, Moniek P.M de Maat, Douwe E. Atsma, Arnoud van der Laarse, Ernst E. van der Wall, J.Wouter Jukema, Leiden University Medical Center, Leiden, The Netherlands

Background: Patients with diabetes mellitus have a worse clinical outcome after percutaneous transluminal coronary angioplasty (PTCA) in comparison to non-diabetic patients. Different mechanisms are thought to play a role in the pronounced neointimal formation, which is probably the main process of restenosis in diabetic patients. Genetic epidemiology might provide more insights into these mechanisms. Furthermore, stratification according to the genetic make-up will enable tailoring of interventional treatment to the individual patient. The aim of this study was to evaluate if various gene polymorphisms can predict clinically important restenosis after PTCA in patients with diabetes mellitus.
Methods: The GEnetic DEterminants of Restenosis (GENDER) project was a multicenter prospective cohort study, which included 3,146 patients after successful PTCA of which 459 (14.6%) were diabetics. Six patients were excluded from follow-up because of an event in the first 30 days. Genotyping in these patients was performed for different polymorphisms in several candidate genes.
Results: A total of 453 diabetic patients, with a mean age of 64.01±10.47 were followed. Of these patients 150 (33.1%) were insulin dependent, stenting was performed in 317 (70.0%) patients and most patients were treated for stable angina (314, 69.3%). The pri-