8:45 a.m.

842-2 Accumulation of a Novel Macrophage-Targeting Photodynamic Compound Within Lipid-Rich Atherosclerotic Plaques

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Vulnerable atherosclerotic plaques contain an abundance of inflammatory cells. We recently developed a photodynamic therapeutic (PDT) agent, (chlorin e6 conjugated with maleylated albumin), that is recognized by scavenger receptors and can target macrophages with high selectivity. We therefore sought to test the hypothesis that the novel macrophage-targeting photodynamic compound accumulates in experimental atherosclerotic lesions in quantities that are sufficient for photodynamic therapy.

Four New Zealand rabbits were studied, in which atherosclerotic lesions were induced in 2 by de-endothelialization of the infradiaphragmatic aorta followed by a 6% peanut oil-2% cholesterol diet for 10 weeks. Thereafter chlorin$_{e6}$ conjugated with maleylated albumin was administered intravenously to the animals. At 24 hours after injection of the PDT compound, the animals were sacrificed, and the aortas examined for uptake of the fluorescent PDT agent.

PDT uptake was significantly higher within the atherosclerotic aortas (5.2 +/- 3.2 vs. 1.9 +/- 1.2, ce6 fluorescence units/gm tissue x 10^{6}, atherosclerotic aorta vs control aorta, p<0.03, n=8 segments).

These data indicate that this macrophage-targeted photodynamic compound accumulates in atherosclerotic plaques, and support future efforts to employ PDT compounds to ablate inflammatory foci within atherosclerotic plaques.

9:00 a.m.

842-3 Statin Administration in Patients With Acute Coronary Syndromes: Results in Decreased Heat Release of Culprit Atherosclerotic Lesions

Christodoulos Stefanadis, Konstantinos Toutouzas, Eleftherios Tsiamis, Ioannis Kallikazaros, Manolis Vavouranakis, Sophia Vaina, Athanasios Trikas, Christina Chrysochoou, Dimos Panagiotakos, Pavlos Toutouzas, *Hippokration Hospital, Athens, Greece.*

Background: It has been shown, that there is thermal heterogeneity within human atherosclerotic plaques. Recent studies have suggested, that statins may induce mechanical plaque stability by reduction of inflammatory cells within the plaque. This study was designed to examine the effect of statins on atherosclerotic plaque stabilization by measuring the temperature of atherosclerotic plaques. **Methods:** We studied 60 patients (pts), 36 pts with unstable angina (UA) and 24 pts with acute myocardial infarction (AMI). All pts underwent diagnostic catheterization. Thirty-two pts (18 pts with UA and 14 pts with AMI) were under statin treatment for over a month and 28 pts were not receiving statins (18 pts with UA and 10 pts with AMI). Fifty-five pts were under aspirin treatment. Total cholesterol and low-density cholesterol were measured in all pts. A thermography catheter previously validated (Medispes S.W.A.G.zug-Switzerland) was used during the diagnostic catheterization, in order to measure the temperature difference (TD) between the atherosclerotic plaque and the healthy vessel wall. **Results:** TD was progressively increased in pts with UA compared to pts with AMI (0.41 ± 0.28 vs 0.68 ± 0.41°C, p < 0.02). When we categorized the study population into pts receiving statins and pts not treated with statins, TD was lower in the treated group (0.41 ± 0.4 vs 0.65 ± 0.3°C, p < 0.01). Moreover, untreated pts with UA or AMI had greater TD compared to treated pts (UA: 0.45 ± 0.26 vs 0.29 ± 0.25°C, p < 0.02; AMI: 0.82 ± 0.51 vs 0.56 ± 0.34° C, p < 0.01). Multivariate analysis showed that treatment with statins was an independent factor in the assessment of temperature variation, adjusted for age, hypercholesterolemia, hypertension, smoking, aspirin intake, and clinical syndrome.**Conclusions:** Pts with unstable plaques, under statin tretment have decreased heat production from the culprit lesion Thus, statins may exert a direct antinflammatory effect in the atherosclerotic plaque beyond their effects on plasma lipids.

9:15 a.m.

842-4 Association Between Ischemic Electrocardiographic Abnormalities and C-Reactive Protein in a General Population

Folkert W. Asselbergs, Ad J. van Boven, Gilles F. Diercks, Hans H. Hillege, Erik M. Stuveling, Jan A. Kors, Wiek H. van Gilst, *University of Groningen, Groningen, The Netherlands, Academic Hospital Groningen, Groningen, The Netherlands.*

Background: The inflammatory marker C-Reactive protein (CRP) and ischemic electrocardiographic (ECG) abnormalities reflects both vascular instability and are easy to obtain risk factors for fatal and nonfatal cardiac events. Their association however, has never been studied in a general population. Our objective was to test the hypothesis that there is an association between the level of CRP and the presence of electrocardiographic abnormalities.

Methods: Minnesota coded electrocardiograms were used to determine ischemic electrocardiographic abnormalities in 8501 subjects (aged 28 to 75, 49.8% male) from the PREVEND study, a population-based screenings programme in which subjects were stratified for the presence of an increased level of urinary albumin excretion. High sensitive CRP was measured by nephelometry (BN II, Dade Behring, Marburg, Germany). Abnormal T-axis was defined as -180 to -15 and 105 to 180 degrees. CRP levels were divided below and above the upper quartile (CRP>2.60 mg/dl).

Results:

Prevalence of ECG abnormalities, Odds Ratio (95% CI)

	Ischemic abnormalities	Infarct patterns	Abnormal T-axis
Elevated CRP [1]	1.56 (1.30-1.87)*	1.71 (1.32-2.22)*	3.18 (2.12-4.77)*
Elevated CRP [2]	1.39 (1.15-1.67)*	1.58 (1.21-2.01)*	2.64 (1.75-3.99)*
Elevated CRP [3]	1.24 (0.99-1.55)	1.34 (0.97-1.85)	2.18 (1.27-3.76)**

*p<0.001,**p<0.01

[1]unadjusted

[2]adjusted for age and gender

[3]adjusted for age,gender,hypercholesterolemia,diabetes, smoking,family history for atherosclerose and body mass index>27kg/m2

Conclusion: These results suggest that in a large general population, elevated CRP is associated with ECG abnormalities, suggestive for cardiac ischemia. Therefore, CRP may be useful in early risk profiling to improve cardiovascular risk assessment and treatment.

9:30 a.m.

842-5 Does Extent of Pretreatment Atherosclerosis Influence the Effects of Conjugated Equine Estrogens on Atherosclerosis Progression?

Mary S. Anthony, Thomas B. Clarkson, *Wake Forest University School of Medicine, Winston-Salem, North Carolina.*

Background: Recent clinical trial data suggest no beneficial effects of hormone replacement therapy (HRT) on coronary artery atherosclerosis progression in women with angiographically verified lumen stenosis. However, considerable observational and nonhuman primate data indicate that HRT inhibits progression of atherosclerosis in its early stages. Consequently, whether HRT has a differential effect on atherosclerosis progression depending on extent of preexisting atherosclerosis becomes important.

Methods: Cynomolgus monkeys were fed a moderately atherogenic diet for two years to induce atherosclerosis, after which a biopsy of the iliac artery was taken to quantify pretreatment atherosclerosis (measured as intimal area [IA] averaged across three sections) and all animals were ovariectomized to induce surgical menopause. For the 3-year postmenopausal period, they were randomized to no treatment (Control, *n*=56) or conjugated equine estrogens (CEE, n=62) at a dose comparable to a dose for women of 0.625 mg/day and the atherogenic diet was continued. At the end of the study atherosclerosis was quantified in the contralateral iliac artery. For this analysis, individuals were divided into tertiles based on baseline IA.

Results: Overall the CEE group had less atherosclerosis than the control group (p=0.002). As expected, IA at the end of the study was higher in the tertiles with more atherosclerosis at baseline (p for trend=0.0001). There were different effects of CEE depending on the amount of preexisting atherosclerosis (significant treatment by tertile interaction [p=0.01]). The nature of this interaction was that with increasing baseline atherosclerosis, there was less of a difference between the CEE and Control groups in outcome atherosclerosis. In the lowest tertile, IA at outcome was 0.30 mm^2 smaller in the CEE group compared to Controls (p=0.0001); in the middle tertile the CEE group IA was 0.15 mm^2 smaller (p=0.33) and in the highest tertile IA was only 0.09 mm^2 smaller (p=0.71) in the CEE group.

Conclusions: These data suggest that CEE might be less effective at inhibiting atherosclerosis progression when pretreatment atherosclerosis is more advanced.

9:45 a.m.

842-6 PPAR γ-Agonist Induces Regression of Atherosclerotic Plaques: In Vivo Study by High Resolution Magnetic Resonance Imaging

Roberto Corti, Julio I. Osende, Valentin Fuster, Samuel D. Wright*, Zahi A. Fayad, Elisha Dickstein, John T. Fallon, Juan J. Badimon, *Cardiovascular Institute Mount Sinai School of Medicine, New York, New York, *Merck Research Laboratories, New Jersey.*

Introduction Nuclear receptor PPAR-γ regulates adipogenesis and lipid metabolism. It is expressed in macrophages and may have antiatherogenic effects. We reported the ability of MRI to monitor in vivo changes in atherosclerotic (AT) lesions. Our objective was to compare the effects of simvastatin, a PPARγ-agonist (2-(2-(4-phenoxy-2-propylphoxy)ethyl)indole-5-acetic acid) and their combination on pre-established lesions in a rabbit model using MRI and histology.

Methods Aortic AT lesions were induced in rabbits by double balloon-injury and atherogenic diet. Following lesion induction,animals were MRimaged and, based on severity of the established AT lesion, assigned to the different groups: Progression (no therapy, n=5), simvastatin (5mg/kg/day, n=6), PPARγ-agonist (5mg/Kg/day, n=5) and their combination (n=7). The atherogenic diet was maintained during the study. After 6 months of treatment all rabbits were MR imaged, sacrificed and processed for histology. The effect of the treatments on AT lesions was assessed by measuring vessel wall area (VWA), a surrogate of AT burden. VWA measurements by MRI were normalized to the randomization value (each rabbit served as its own control).

Results Good agreement between MRI and histopatology measurements of VWA was found(p<0.001, R=0.88). The mean VWA at the time of randomization was 8.4±0.6 mm2 and did not differ between groups. The progression group showed a significant increase (21%; p<0.01) in VWA. All treatments significantly regressed the established AT lesions. The major therapeutic effect was observed in the simvastatin+PPAR γ group with a 14% reduction, while the simvastatin and the PPAR γ groups had a 9.5% and 5% inhibition respectively.The composition and characteristics of the plaques are being analysed.

Conclusion MRI documents serial changes in AT lesions in response to therapeutic interventions. We report striking effects on AT lesion regression by combining two mech-