8:45 a.m.

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

Ahmed Tawakol, Alan Fischman, Tayyaba Hasan, Touqir Zahra, James Muller, Michael Hamblin, *Massachusetts General Hospital, Boston, Massachusetts.*

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^{o}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^{o}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^{o}C, $p < 0.02$; AMI: 0.82 ± 0.51 vs 0.56 ± 0.34^{o} 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-

anistically distinct therapeutic agents, simvastatin and PPARγ-agonist. The effects of the hypolipidemic simvastatin, confirm the sensitivity of MRI measurements, and the effects of the PPARγ-agonist suggest a novel class of antiarteriosclerotic compounds.

FEATURED ORAL PRESENTATION

843FO Featured Oral Session...Novel Approaches to Antihypertension Therapy

Tuesday, March 19, 2002, 8:30 a.m.-10:00 a.m.
Georgia World Congress Center, Room 255W

8:45 a.m.

843FO-2 Relation of Myocardial Fibrosis to Circulating Aldosterone and Endothelin in Primary and Secondary Human Hypertension: An Ultrasonic Study by Acoustic Densitometry

Michaela Kozakova, Simona Buralli, Carlo Palombo, Angelica Moretti, Giampaolo Bernini, Isabella Sudano, Stefano Taddei, Antonio Salvetti, *Department of Internal Medicine, University Medical School, Pisa, Italy, CNR Institute of Clinical Physiology, Pisa, Italy.*

Myocardial fibrosis is found in the experimental hypertensive heart and may be a major cause of heart failure in man. In experimental models, Endothelin and Aldosterone were shown to act synergically in promoting myocardial fibrosis.
Aim of the study was to investigate the possible relations between myocardial fibrosis as assessed by an advanced ultrasound technique (Acoustic Densitometry, AD, Agilent Technologies), and circulating levels of Endothelin and Aldosterone in primary and secondary hypertension.
Methods: 32 patients (21 males; mean age 50±11; BP 159±9/101±7 mmHg), including 15 with essential hypertension (EH), 7 with unilateral reno-vascular disease (RVH), 10 with primary aldosteronism (PA), were studied. plasma Aldosterone (Aldo), Endothelin (Endo), Renin activity, and Hydroxyprolinuria were measured and related to LV mass and function (M-mode echo), as well as to the average myocardial Integrated Backscatter (IBS; dB), obtained by AD as an estimate of myocardial fibrosis.
Results: All subjects had preserved LV systolic function. In PA and RVH patients, IBS and Aldo were higher ($p<0.01$) than in EH (IBS: 25±5 and 24±7 vs 18±4 dB; Aldo: 1.19±0.7, 1.16±0.5 and 0.64±0.2 nmol/L), while Endo was increased only in PA (4.3±0.7 pg/ml vs 3.7±0.7 and 3.1±0.8 in RVH and EH, $p<0.01$). In the overall population, IBS correlated directly to Aldo ($r=0.41$, $p<0.02$), Endo ($r=0.57$, $p<0.01$), Hydroxyprolinuria ($r=0.47$, $p<0.01$), LV mass ($r=0.54$, $p<0.01$), disease duration ($r=0.35$, $p<0.05$). In multivariate analysis, Endo, Hydroxyprolinuria, LV mass and disease duration were independently related to IBS (adjusted $R2=0.67$, $p<0.01$ for all). LV mass was directly related to hydroxyprolinuria ($r=0.51$, $p<0.01$), but not to hormonal factors. Endo was directly related to LV end-diastolic diameter ($r=0.37$, $p<0.05$) and showed a trend to increase with increasing Aldo ($R=0.32$, $p=0.07$).
Conclusions: in human hypertension, myocardial fibrosis partakes of the hypertrophic process, is related to disease duration and dependent on a synergic interaction of Endo and Aldo. The clinical models of primary and secondary hyperaldosteronism seem more prone to such a development than essential hypertension.

9:00 a.m.

843FO-3 Rofecoxib but Not Celecoxib Increases Systolic Blood Pressure in Hypertensive Patients Treated With Ace Inhibitors and Beta-Blockers

William B. White, Andrew Whelton, John G. Fort, *University of Connecticut School of Medicine, Farmington, Connecticut, Johns Hopkins University, Baltimore, Maryland.*

Background: The effects of celecoxib 200 mg/d and rofecoxib 25 mg/d on BP control were assessed in a randomized, double-blind study in elderly patients with osteoarthritis on stable (>3 months) antihypertensive therapy.
Methods: 1092 patients received celecoxib (n=549) or rofecoxib (n=543) with their antihypertensive regimen for 6 weeks. Primary endpoints were changes in systolic and diastolic BP. Changes from baseline in SBP by type of antihypertensive therapy were analyzed using least-square means based on baseline score, gender, race, and treatment.
Results: Mean age was 73.2 yrs; 62% were women. There were no significant changes from baseline in mean SBP in the celecoxib arm for patients on any therapy. Significant increases in SBP were observed in the rofecoxib group when treated with ACEI, β-blockers, or these agents in combination with a diuretic ($P<0.05$). There were no changes from baseline in mean DBP in either COX-2 inhibitor arm. Calcium antagonists and diuretics had less interaction with either COX-2 specific inhibitor. Mean changes in SBP (mmHg) are shown:

Antihypertensive therapy by class	Mean change (SD), mm Hg		Adjusted LS Mean Difference [95% CI]	P value
	Celecoxib	Rofecoxib		
ACEI (n=161)	-0.4 (12.7)	4.9 (13.3)	-3.9 [-6.2 to -1.6]	<0.001
ACEI/diuretic (n=82)	-1.0 (11.1)	2.8 (15.3)	-3.1 [-6.1 to -0.1]	0.04
β-Blocker (n=106)	1.1 (12.8)	4.9 (13.0)	-2.9 [-5.7 to -0.2]	0.04
β-Blocker/diuretic (n=78)	-1.2 (11.0)	4.9(14.3)	-4.8 [-7.9 to -1.7]	0.003
Calcium antagonist (n=114)	0.4 (11.4)	0.1 (11.6)	0.2 [-2.0 to 2.4]	0.87
Calcium antagonist/ diuretic (n=65)	-1.1 (10.2)	0.1 (12.8)	-1.2 [-4.0 to 1.6]	0.4

Conclusions: Data demonstrate that rofecoxib attenuates SBP control in patients on ACEI, β-blocker alone and in combination with a diuretic but not on the calcium antagonists. Furthermore, celecoxib does not attenuate BP control in patients on any class of antihypertensive drugs.

9:15 a.m.

843FO-4 Eplerenone Reduces Proteinuria in Type II Diabetes Mellitus: Implications for Aldosterone Involvement in the Pathogenesis of Renal Dysfunction

Murray Epstein, Vardaman Buckalew, Jorge Altamirano, Barbara Roniker, Scott Krause, Jay Kleiman, *University of Miami School of Medicine, Miami, Florida, Wake Forest University School of Medicine, Winston-Salem, North Carolina.*

Background: Aldosterone may promote renal dysfunction. We investigated whether the selective aldosterone receptor antagonist (SARA) eplerenone reduces proteinuria in hypertensive patients with type II diabetes mellitus and albuminuria.
Methods: After 2-4 wk on placebo, patients were randomized to forced-titrated doses of eplerenone (Epl), enalapril (Enl), or Epl and Enl in combination (Comb) for 24 wk. If DBP was >90 mm Hg at ≥ 8 wk, hydrochlorothiazide or amlodipine was added to control BP. The primary endpoint was the mean % change in urinary albumin to creatinine ratio (UACR) at 24 wk. Secondary endpoints were blood pressure (BP) changes and tolerability.
Results: Epl reduced UACR by 62% vs 45% with Enl ($p=0.015$), and Comb was more effective (74%, $p=0.018$ vs Epl and $p<0.001$ vs Enl). BP decreases were not different between Epl and Enl (Table). Both drugs were well tolerated. No gynecomastia was reported. Incidence of K^+ ≥6.0 mEq/L was Epl (8), Enl (2), and Comb (8). More patients were withdrawn because of sustained hyperkalemia in the Comb group (14) than in Epl (6) or Enl (2) groups. Other adverse events were similar among treatment groups.
Conclusion: Differences in proteinuria reduction despite similar BP lowering indicate that renal protection is independent of blood pressure reduction, consistent with the hypothesis that selective aldosterone antagonism is renoprotective. Further investigation will determine whether lower Epl doses reduce proteinuria with fewer K^+ changes in diabetic patients.

	Epl (50 up to 200 mg) (N=74)	Enl (10 up to 40 mg) (N=74)	Comb Enl 10 mg/ Epl (50 up to 200 mg) (N=67)
UACR (mg/g) at Baseline	611.4	483.3	470.9
UACR at 24 wk	248.8	285.3	120.8
Δ BP at 24 wk (SBP/DBP)	-19.5/-13.2* (N=89)	-20.4/-15.0 (N=83)	-21.8/-16.2 (N=85)

*p=0.015 vs Comb

9:30 a.m.

843FO-5 Effect of Valsartan on Morbidity and Mortality in Heart Failure Patients With a History of Hypertension: Results From the Valsartan Heart Failure Trial

N. J. Holwerda, Lionel Opie, Nancy Feliciano, Janet Bodner, on behalf of the Val-HeFT Investigators, *Sint Elisabeth Zeikenhuis, Tilburg, The Netherlands.*

Background: Patients with hypertension commonly progress to heart failure (HF) despite treatment with currently recommended drugs. In the Valsartan Heart Failure Trial (Val-HeFT), morbidity risk was significantly reduced by 13.2% with valsartan (40-160 mg bid) compared to placebo ($p=0.009$), with similar all-cause mortality risk in the two groups. Risk for time to first HF hospitalization (with mortality censoring) was significantly reduced by 27.5% with valsartan ($p<0.001$). In the post-hoc analysis of Val-HeFT patients, the effect of valsartan compared to placebo on outcomes in patients with a history of hypertension (HTN) was investigated.
Methods: Val-HeFT was an international, multicenter, randomized, double blind trial in 5010 patients with New York Heart Association (NYHA) class II-IV HF. History of HTN was defined as: pre-randomization systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90, reported past medical history of HTN, or HTN reported as the primary etiology of HF. The primary efficacy outcomes were time to death and time to first morbid event (death, sudden death with resuscitation, hospitalization for HF, intravenous inotropic or vasodilator therapy >4 hours). A secondary efficacy outcome was time to first HF hospitalization.
Results: A subgroup of 2372 patients had a documented history of HTN at baseline, 1143 of whom were randomized to receive valsartan and 1229 to placebo. The effects of valsartan on morbidity and mortality in HF patients with (HTN+) and without (HTN-) a history of HTN were generally consistent with the overall study population. The risk ratio (RR) of all-cause mortality for valsartan vs. placebo was 0.99 (95% CI 0.83, 1.18) in HTN+ and 1.05 (95% CI 0.88, 1.25) in HTN- patients. Risk of morbidity was lower for valsartan than placebo in HTN+ (RR = 0.88, 95% CI 0.77, 1.02) and HTN- patients (RR = 0.85, 95% CI 0.74, 0.99). The results were similar for the risk of first hospitalization for HF in HTN+ (RR = 0.76, 95% CI 0.63 - 0.93) and HTN- patients (RR = 0.69, 95% CI 0.57, 0.84).
Conclusion: Valsartan treatment has beneficial effects in the treatment of HF when added to prescribed therapy in HF patients with or without a history of hypertension.