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 e8 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 by balloon injury of the infrapopliteal aorta followed by low-dose cholesterol diet for 16 weeks. The rabbits were then treated with maleylated albumin and were examined at the time. At 72 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 (20 ± 2.3 vs. 1.0 ± 1.2 gE fluence units/cm² tissue x 10⁶, atherosclerotic vs control aorta, p<0.001, n=6 segments).

These data indicate that this macrophage-targeted photodynamic compound accumulates in atherosclerotic plaques, and suggest further efforts to employ PDT compounds to ablate inflammatory foamy macrophages within atherosclerotic plaques.

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

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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 stabilisation by measuring the temperature difference (TD) between the atherosclerotic plaque and the healthy vessel wall.

Methods: We studied 60 patients (patients with unstable angina (UA) and 24 pts with acute myocardial infarction (AMI)). All pts underwent diagnostic catheterization. Thirty-two (pts) with UA and 14 pts with AMI were under statin treatment for over a month and 28 pts were not receiving statins (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 camera previously validated (Medipics S.W.A.G.-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 its pts with UA compared to pts with AMI (0.41 ± 0.29 vs 0.63 ± 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 0.85 ± 0.3°C, p < 0.02). When we categorized the study population into pts receiving statins and pts not receiving statins, TD was lower in the treated group (0.45 ± 0.26 vs 0.29 ± 0.25°C, p<0.02). Similarly, total cholesterol and low-density cholesterol were also lower in the treated group (p<0.02).

Conclusions: These data suggest that statins may exert a direct antinflammatory effect in the atherosclerotic plaque and the healthy vessel wall.

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


Background: The inflammatory marker C-reactive protein (CRP) and ischemic electrocardiographic (ECG) abnormalities reflect both vascular instability and are easy to stratify for the presence of an increased level of urinary albumin excretion. High sensitivity CRP was measured by nephelometry (BN II, Duale Behring, Marburg, Germany).

Methods: Ninety-four healthy young (aged 18 to 25, 49.6% male) and 65 (aged 26 to 55, 47.7% male) from the Groningen General Population Study were studied. All participants were examined for the presence of an increased level of urinary albumin excretion. High sensitivity CRP was measured by nephelometry (BN II, Duale Behring, Marburg, Germany).

Results: A positive correlation between levels of CRP and the presence of electrocardiographic abnormalities was found. The correlation coefficient was 0.30, p<0.01. The positive association between CRP and ECG abnormalities remained significant after adjustment for age and gender.

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.

The Major Therapeutic Effects of Combination of PPAR-γ Agonist and Simvastatin in Progression of Atherosclerosis in Cynomolgus Monkeys

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Background: Recent clinical trial data suggest no beneficial effects of hormone replacement therapy (HRT) on coronary artery atherosclerosis progression in women with angiographically verified coronary artery disease. However, observational and nonrandomized prospective 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 atherosclerotic plaques, after which a biopsy of the iliac artery was taken to quantify pretreatment atherosclerotic tissue (measured as internal area [IA] averaged across three sections) and all animals were randomized to receive no medication for the 3-year postmenopausal period, they were randomized to no treatment (control, n=66) or conventional estrogen treatment (CEE, n=64) 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 the 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<0.05]). The nature of this interaction was that with increasing baseline atherosclerosis, there was a less of a difference between the CEE and Control groups in outcome atherosclerosis.

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

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


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 PPAR-γ agonist (2-2 mg/kg/day), and their combination on pre-established lesions in a rabbit model using MRI and histology.

Methods: Arterial AT lesions were induced in rabbits by double balloon injury and atherogenic diet. Following lesion induction, animals were imaged, and, based on severity of pre-existing AT burden, they were randomized to no treatment (control), simvastatin (10 mg/kg/day, n=5), and all animals were sacrificed and processed for histology. The effect of MRI documents serial changes in AT lesions in response to therapeutic interventions. We report striking effects on AT lesion regression by combining two mechanisms.
FEATURED ORAL PRESENTATION
843FO-2 Relation of Myocardial Fibrosis to Circulating Aldosterone and Endothelin in Primary and Secondary Human Hypertension: An Ultrasound Study by Acoustic Denstometry

Michael Konradsen, Simona Bussoli, Carlo Palombo, Angelica Morrelli, Giampaolo Barletti, Isabella Susazzo, Stefano Tartarli, Antonino Santini, 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 synergistically in promoting myocardial fibrosis.

The aim of the study was to investigate the possible relation between myocardial fibrosis as assessed by an advanced ultrasound technique (Acoustic Denstometry, AD, Agilent Technologies), and circulating levels of Aldosterone and Endothelin in primary and secondary hypertension.

Methods: 32 patients (male: mean age 50±11; BP: 159±9/10±7 mmHg), including 15 with essential hypertension (EH), 7 with unilateral renovascular disease (RVH), 10 with pheochromocytoma, were studied. Plasma Aldosterone (Aldo), Endothelin (Endo), Heart 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, with essential hypertension (EH), 0.4±1.2; 4.9±1.3, with renovascular hypertension (RVH), 0.8±1.3, with pheochromocytoma, 1.19±0.7, with pheochromocytoma). In multivariate analysis, Endo, Hydroxyprolinuria, LV mass and disease duration were independently related to IBS (adjusted R²=0.7, p<0.001 for all), LV mass was directly related to hydroxyprolinuria (r=0.51, p<0.001), but not to hormonal factors. Endo was directly related to LV and diastolic diameter (r=0.35, p<0.05). In multivariate analysis, Endo, Hydroxyprolinuria, LV mass and disease duration were independently related to IBS (adjusted R²=0.7, p<0.001 for all), LV mass was directly related to hydroxyprolinuria (r=0.51, p<0.001), but not to hormonal factors. Endo was directly related to LV and diastolic diameter (r=0.35, p<0.05) and showed a trend to increase with increasing Aldo (R²=0.3, p=0.07).

Conclusions: In human hypertension, myocardial fibrosis parallels the pathogenic process, is related to disease duration and dependent on a synergic interaction of Endo and Aldo. The clinical modalities 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 R. White, Andrew Whitlock, 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 blood pressure were assessed in a randomized, double-blind study in elderly patients with essential hyper- tension (n=373) and hypertension (n=360) treated with at least one antihypertensive drug.

Methods: 1038 patients received celecoxib (n=549) or rofecoxib (n=543) with their antihypertensive therapy. Mean age was 73.2 yrs: 62% were women. There were no significant changes from baseline in mean SBP in the celecoxib or rofecoxib groups. Primary end points were changes in diastolic and systolic SBP. 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 or DBP in the celecoxib or rofecoxib groups treated with ACEI, blockers or blockers 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 other COX-2 specific inhibitors. Mean changes in SBP (mmHg) are shown in the table.

Conclusions: Data demonstrate that rofecoxib attenuates SBP control in patients on ACEI, 8-blocker alone and in combination with a diuretic but not on the calcium antagonist. 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 E. Stein, Vardaman Burkard, Jorge Altamirano, Barbara Roniker, Scott Krause, Jay Kleinman, 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-furtrated 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 amiodipine was added to control BP. The primary endpoint was the mean % change in albumin to creatinine ratio (UACR) at 24 wk. Secondary endpoints were blood pressure (BP) changes and tolerability.

Results: Epl reduced UACR by 62% vs 46% with Enl (p=0.015) and Comb was more effective (74%, p=0.018 vs Epl and p=0.012 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 (6), 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.

Conclusions: Difference 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.

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. H. Howard, Lionel Opiyo, Nancy Forciante, Janet Bodner, on behalf of the VA-HEFT Investigators, St Andrew's Zealandiahus, Tbilis, The Netherlands.

Background: Patients with hypertension commonly progress to heart failure (HF) despite treatment with currently recommended drugs. In the Valsartan Heart Failure Trial (VA-HEFT), morbidity risk was significantly reduced by 13.2% with valsartan (40-150 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=0.011). In the post-hoc analysis of VA-HEFT patients, the effect of valsartan compared to placebo on outcomes in patients with a history of hypertension (HTN) was investigated.

Methods: VA-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 (SBP) >140 mmHg or diastolic BP >90 mmHg, 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 morbidity event (death, sudden death with resuscitation, hospitalization for HF, intravascular inotropic or vasodialator 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 mortality and morbidity were generally consistent with the overall study population. The risk ratio for the primary outcome in patients with HTN was 1.04 (95% CI 0.88, 1.23) in HTN+ and 1.05 (95% CI 0.88, 1.23) in HTN- patients. Risk of morbidity was lower for valsartan than placebo in HTN+ patients (RR = 0.89, 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 HTN in HTN+ (RR = 0.78, 95% CI 0.63-0.93) and HTN- patients (RR = 0.69, 95% CI 0.57, 0.84).

Conclusions: 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.