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.