FEATURED ORAL PRESENTATION
843FO Featured Oral Session...Novel Approaches to Antihypertensive 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 Ultrasound Study by Acoustic Densitometry

Michael Konstam, Simonetta Bussel, Carlo Priolo, Angela Moretti, Giampiero Barletta, Elisabetta Scanzano, Stefano Tartale, Antonino Savarino, 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 relation 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 (mean age 50±11; BP 150±9/10±7 mmHg), including 15 with essential hypertension (EH), 7 with unilateral renovascular disease (RVD), 10 with primary aldosteronism (PA), were studied. Plasma Aldosterone (Aldo), Endothelin (Endo), Renin activity, and Hydroxyprolineuria were measured and related to LV mass and function (M-mode echo), as well as to the average myocardial integrated backscatter (SSB, dB), obtained by AD as an estimate of myocardial fibrosis.

Results: All subjects had preserved LV systolic function. In PA and RVD patients, IBS and Aldo were higher (p<0.01) than in EH (IBS: 2.5±0.4 vs 1.7±0.7; Aldo: 15±5 vs 5±5). In EH, Endo was increased only in PA (4.4±2.7 ng/ml vs 3.7±0.7 and 3.1±0.7 in RVD and EH, respectively). In the overall population, SSB correlated directly to Aldo (r=0.41, p=0.02), Endo (r=0.57, p=0.01), Hydroxyprolineuria (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, Hydroxyprolineuria, LV mass and disease duration were independently related to IBS (adjusted R2=0.57, p=0.01), with no effect of LV mass directly related to hydroxyprolineuria (r=0.51, p=0.01), but not to hormonal factors. Endo was directly related to LV and diastolic diameter (r=0.37, p=0.05). Endo showed a trend to increase with increasing Aldo (P=0.02, p=0.07).

Conclusions: in human hypertension, myocardial fibrosis partakes of the hypertrophic process, is related to disease duration and dependent on a synergistic interaction of Endo and Aldo. The clinical modalities of primary and secondary hypertension/aldosteronism 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 S. 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 and rofecoxib 25 mg on BP control were assessed in a randomized, double-blind study in elderly patients with osteoarthritis on stable 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 in a mixed model with repeated measures. 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: All subjects had preserved LV systolic function. In PA and RVH patients, IBS and Aldo were higher (p<0.01) than in EH (IBS: 2.5±0.4 vs 1.7±0.7; Aldo: 15±5 vs 5±5). In EH, Endo was increased only in PA (4.4±2.7 ng/ml vs 3.7±0.7 and 3.1±0.7 in RVD and EH, respectively). In the overall population, SSB correlated directly to Aldo (r=0.41, p=0.02), Endo (r=0.57, p=0.01), Hydroxyprolineuria (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, Hydroxyprolineuria, LV mass and disease duration were independently related to IBS (adjusted R2=0.57, p=0.01), with no effect of LV mass directly related to hydroxyprolineuria (r=0.51, p=0.01), but not to hormonal factors. Endo was directly related to LV and diastolic diameter (r=0.37, p=0.05). Endo showed a trend to increase with increasing Aldo (P=0.02, p=0.07).

Conclusions: in human hypertension, myocardial fibrosis partakes of the hypertrophic process, is related to disease duration and dependent on a synergistic interaction of Endo and Aldo. The clinical modalities of primary and secondary hypertension/aldosteronism seem more prone to such a development than essential hypertension.

9:00 a.m.

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

Murray Estes, Yvardan Burakel, Jorge Altmannawa, Barbara Roniker, Scott Krause, Joy 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 2 diabetes mellitus and albuminuria.

Methods: After 2-4 wk on placebo, patients were randomized to fixed-dosage doses of eplerenone (Epl), losartan (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 45% with Enl (p=0.015), and Comb was more effective (74%, p=0.015 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 (6). 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: 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 dose reduces proteinuria with lower K+ changes in diabetic patients.

9:30 a.m.

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

J. N. Hopewell, Lionel Opiou, Nancy Fortian, Janet Bodner, on behalf of the VaI-HF Investigators, St. Elizabeth Zema, Thilburg, 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<0.01). 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 mmHg or antihypertensive medication or antihypertensive treatment >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 HTN patients with (HTN+) and without (HTN-) a history of hypertension (HTN) was investigated.

Methods: In 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<0.01). 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.

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