P-392
ANGIOTENSIN TYPE 2 RECEPTOR EXPRESSION IN KIDNEY DURING ANGIOTENSIN TYPE 1 RECEPTOR BLOCKADE

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We previously showed that a non-depressor dose of candesartan cilexidil (CC) significantly attenuated the pathological changes in the kidney in the L-NAME (40 mg/kg/day + 0.12% NaCl diet) hypertensive rat model while having no effect on the progression of the pathology in the Dahl salt-sensitive (Dahl SS; 8% NaCl diet) model of hypertension. Since evidence suggests that the angiotensin type 1 (AT1) and type 2 (AT2) receptors have counteracting actions, we reasoned that AT2 receptor expression may have a beneficial effect in tissue injury associated with hypertension. To determine whether or not the expression of the AT2 receptor differs in these two models following AT1 receptor blockade with CC (0.5 mg/kg/day), we performed immunohistostaining analysis of renal tissue for AT2 receptor content. Intensity (%) of staining by diaminobenzidine was assessed using quantitative image analysis. AT2 receptor expression increased (**p<0.005) only in the L-NAME model with AT1 receptor blockade. However, AT2 receptor expression was greater (**p < 0.005) in the Dahl SS model as compared to the L-NAME model of hypertension in the absence of CC. Thus, the L-NAME model of hypertension is associated with increased AT2 receptor expression when the AT1 receptor is inhibited. AT1 receptor blockade does not increase AT2 receptor expression in Dahl SS. These data suggest that AT1 receptor blockade does not alter AT2 receptor expression in all settings. The modulation of AT2 receptor expression may be involved in the progression of the end-organ damage that is associated with hypertension.

Model | Control | CC | n
--- | --- | --- | ---
Dahl SS | 90 ± 6 | 73 ± 7 | 3
L-NAME | 53 ± 2* | 87 ± 9** | 3

Key Words: Renal Angiotensin Type 2 Receptor Expression, Hypertension, Nitric Oxide Inhibition

P-393
SAFETY AND EFFICACY OF AN ACE INHIBITOR/CALCIUM CHANNEL BLOCKER COMBINATION VERSUS AN ACE INHIBITOR ALONE IN HYPERTENSIVE PATIENTS WITH TYPE 2 DIABETES

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Data from multiple clinical trials demonstrate that inhibition of the renin-angiotensin system (RAS) is required in patients with hypertension and type 2 diabetes. More than one agent is needed, however to achieve blood pressure (BP) goals in the majority of patients. Calcium channel blockers are useful adjunctive therapy to achieve BP goals. The current study compares the efficacy and safety of a fixed-dose combination of an ACE inhibitor (ACEI)/calcium channel blocker (CCB) to ACEI monotherapy in subjects with hypertension and type 2 diabetes. This 12-week, double-blind study randomized 214 participants, 108 to enalapril (E) (10 mg titrated to 20 mg) and 106 to the fixed-dose combination of amlodipine/benazepril, (A+B) (5/10 mg titrated to 5/20 mg). Hydrochlorothiazide 12.5 mg was added if not at goal by 8 weeks. The primary endpoint was time from baseline to BP target (<130/85 mm Hg). Secondary endpoints included the change in urinary protein excretion, glucose, and lipid levels. Mean age was 57 ± 8 years, 63% of subjects were male, and approximately 36% were African-American.

Results showed that time from baseline to achievement of BP goal was significantly shorter with the fixed-dose combination of A+B as compared with E (5.3 vs 6.4 weeks, respectively; P=0.0001). A+B resulted in significantly greater reductions as compared with E in both systolic BP (>-20.5 mm Hg vs -14.5 mm Hg, respectively; P=0.002) and diastolic BP (-13.9 mm Hg vs -9.6 mm Hg, respectively; P=0.001). Both treatment regimens were equally well tolerated.

We conclude that fixed-dose combination of amlodipine/benazepril reduced BP earlier and to a greater degree than the ACEI alone. Moreover, it was well tolerated with no adverse effects on glyemic control or lipid levels.

Key Words: Amlodipine, Benazepril, Diabetes

P-394
RISK FACTORS ASSOCIATED WITH RENAL VASCULAR LESIONS IN PATIENTS WITH PRIMARY RENAL DISEASE

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It is still unknown whether renal vascular lesions (RVL) on renal biopsies are due to the cause of renal disease or to vascular risk factors. The histological features of 184 patients with primary renal disease (59 cases of IgA nephropathy, 17 cases of minimal change nephrophy, 33 cases of membranous nephrophy, 38 cases of focal segmental glomerulosclerosis and 37 cases of interstitial nephrophy) diagnosed by renal biopsy between 1985 and 1999 were reviewed. Each renal biopsy was reexamined using histologic classification of vascular lesions as follows: arteriolsclerosis (RVL1), arteriolar hyalination (RVL2), moderate interstitial lesions (MIL=20% of biopsy surface), severe interstitial lesions (SIL=>40%). Risk factors studied at the time of renal biopsy were as follows: age, smoking (current, former or no smokers), controlled BP (<140/90 mmHg) or uncontrolled BP, dyslipidemia, obesity (BMI >27kg/m2), proteinuria >1g/24h, diabetes (without diabetic nephropathy). In univariate analysis, age, current smoker, controlled BP, uncontrolled BP, diabetes, obesity, MIL and SIL were significantly associated to RVL (RVL1 and/or RVL2). Multivariate analysis was as follows: 1) RVL were only associated with age (.0013), 2) RVL1 were associated with age (.0013), current smoker (.050), 3) RVL2 were associated with gender (.0033), renal failure (Cockcroft clearance <60 ml/min) (.0089), 4) Independent predictors a) for RVL1 were current smoking (OR =2,8), IC95%:1,7-4,0), age (OR=1,04, IC95%: 1,01-1,06), controlled BP (at the limit of significance: OR 2,6 IC95%:0,999-7,14) for RVL2 female sex was a protector factor (OR =0,30, IC95%:0,13-0,67).

These results suggest that smoking is probably a major risk factor for developing renal vascular lesions in patients with primary renal disease.

Key Words: Renal Vascular Lesions, Primary Glomerular Disease, Risk Factors

P-395
POSITIVE CORRELATION OF ALBUMINURIA TO BLOOD PRESSURE PERSISTS IN THE NORMOALBUMINURIC RANGE

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Studies have highlighted a positive correlation between the severity of albuminuria and blood pressure control. Importantly some investigators

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have shown that hypertensive subjects with microalbuminuria are at increased cardiovascular risk. However, the criteria for the diagnosis of microalbuminuria are not clear. This study investigated hypertensive non-diabetic subjects with a normal urinary albumin:creatinine ratio (ACR <3.5 mg/mmol/L) to determine whether BP influenced the level of albuminuria within the normal range.

Demographic data including office BP and urinary ACR values (analysed by immuno-turbidimetric test) from 426 subjects (Mean age 41.2 y, Female 51%, Treated 68.8%; White 82.9%) was analysed. Subjects were stratified according to office systolic BP into 3 discreet groups (A: 130-149 mmHg, B: 150-169 mmHg and C: 170+ mmHg) for comparison. Mann-Whitney and Kruskal-Wallis ANOVA statistical analyses were used.

Female subjects have significantly raised ACR values with similar BP and treatment status (ACR (all subjects): 1.00 (Female) v. 0.835 (Male) p=0.0002; ACR (untreated): 0.86 (F) v. 0.72 (M) p=0.0342). There were no differences between ethnic groups or specific anti-hypertensive therapy. Subsequent analysis was therefore gender-specific. There was significantly greater mean ACR in both male and female subjects at higher levels of BP (Female ACR: A: 0.88; B: 0.88; C: 1.23 p=0.0016. Male ACR: A: 0.64; B: 0.76; C: 1.05 p=0.0004).

Diabetic subjects with microalbuminuria, irrespective of BP, are treated specifically with ACE inhibitors to delay the onset of nephropathy. In non-diabetic hypertensive patients, this issue is currently unresolved. Our study highlights the important observation that the positive correlation of albuminuria to blood pressure continues into the normal range. Although these subjects clearly do not have overt albuminuria, this highlights the difficulty in determining an arbitrary value for microalbuminuria and thus a guide for drug-specific therapy.

Key Words: Albuminuria, Essential Hypertension, Kidney

P-396
D5 Dopamine Regulation of Phospholipase D and Blood Pressure in Mice
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D1-like receptors inhibit the proliferation and hypertrophy of vascular smooth muscle cells by suppressing phospholipase D (PLD) activity. We hypothesize that the D5 receptor is the D1-like receptor that inhibits PLD activity and serves to regulate blood pressure via this mechanism. Thus, systolic, diastolic, and mean (MAP) blood pressures were higher in D5 receptor-deficient (MAP, mm Hg: 114±4, n=70) than in wild type mice (MAP=85±1, n=67, P<0.05). The renal tubular and vascular distribution of PLD was similar in both strains but expression (units) was 2-fold higher (D5-/+ 0.5 mm Hg: 66±2, D5+/+ 0.34±2, n=3, P<0.05) and activity (units) was 70% greater (D5-/+ 0.5 mm Hg: 3.2±0.6, n=3, P<0.05) in D5-/ than in D5+/+ mice. In CHO cells expressing D5 receptors but not in control cells, the D1/D5 agonist, fenoldopam (FEN) decreased PLD expression (10 μM, 2 hr) (vehicle=40.2±8.1, FEN=12.9±2.9, n=4, P<0.05) and activity (1 μM, 30 min) (vehicle=20.1±0.22, FEN=0.13±0.01; n=4, P<0.05). In the basal state, F5 F173L, a D5 receptor that cannot stimulate adenyl cyclase, produced more reactive oxygen species, ROS (units), (131±27, n=3) than the wild type D5 receptor (81±27, n=3, P<0.05). FEN (5 M, 30 min) transiently increased ROS production to a greater extent in D5 F173L (1041±130, n=3) than in wild type D5 receptor (585±78, n=3, P<0.05). We suggest that the hypertension in the D5-/- mice is caused, in part, by increased PLD expression and increased generation of ROS.

Key Words: Phospholipase D, Reactive Oxygen Species, Dopamine Receptor

P-397
Cystatin C Versus Creatinine in Renovascular Disease
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Objective: We investigated if cystatin C, a reliable marker of GFR, may serve as a more sensitive discriminant than creatinine in a rule-out strategy in the diagnostic work-up for renovascular disease (RVD).

Design: Cystatin C was measured in 150 hypertensive patients with an intermediate to high index of clinical suspicion of RVD and slightly impaired renal function (creatinine concentration <177 micromol/L). In order to define the normal range of cystatin C, it was also measured in 128 sex-matched normotensive subjects (age interval 19 to 78 yrs) free of any drugs.

Methods: Cystatin C was measured by particle-enhanced nephelometric immunoassay. RVD diagnosis was established by renal angiography (RVD n=65, RVD-free n=85). To define RVD diagnostic accuracy of both cystatin C and creatinine, Receiving operator curves (ROC) curves were calculated. As decision thresholds, values corresponding to 90th and 95th percentiles of the distribution in healthy normotensive population were used.

Results: Cystatin C and creatinine were higher in RVD than in RVD-free patients. ROC curves for the two assays resulted quite similar (AUC 0.73 with 95% C.I. 0.64-0.8 and 0.74 with 95% C.I. 0.66-0.82 for cystatin C and creatinine, respectively). However, considering the values corresponding to 90th or 95th percentiles of normotensive population as decision thresholds (0.90-0.93 mg/L for cystatin C and 92.9-97.2 micro-mol/L for creatinine), cystatin C showed better sensitivity (87.7-92.3%) and negative predictive value (82.2-87.2%) for RVD diagnosis than did creatinine (sensitivity 70.8-72.3%; negative predictive value 74.3-76.5). Odds ratio against the occurrence of true RVD in case of cystatin C <0.90 mg/L was 4.26.

Conclusion: Cystatin C is a more sensitive discriminant than creatinine in a rule-out strategy in the diagnostic work-up for renovascular disease. Accordingly, hypertensive patients presenting cystatin C <0.90 mg/L have a low probability of RVD and may reasonably be excluded from any other complex diagnostic investigations.

Key Words: Cystatin C, Renovascular Disease, Renal Function

P-398
Loss of Renal Reserve in Obese Hypertensive Patients

To demonstrate the effects of obesity on renal hemodynamics and the role of renal kallikrein (kKal) and nitric oxide (NO) on renal response to oral protein load (renal reserve, RR), we studied 14 obese (BMI: 32.9 ± 1.1, age: 50.5 ± 0.9 yrs, SBP: 152.8 ± 2.4mmHg, DBP: 96.2 ± 2.2mmHg, 5 males and 9 females) and 9 non obese hypertensive patients (BMI=22.9±1.1, age: 50.6±2.7yrs, SBP=151.2±2.8mmHg, DBP: 97.9±2.1mmHg, 4 males and 5 females). Hemodynamic and metabolic evaluations were conducted at basal conditions and after protein challenge moment (1g/kg of weight). Glomerular filtration rate (GFR) was estimated by clearance of inulin, and renal plasma flow (RPF) was