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**BOTH BLOOD PRESSURE AND DIRECT MINERALOCORTICOID EFFECTS MEDIATE GLOMERULAR INFLAMMATION AND INJURY IN DOCA-SALT HYPERTENSION**

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We examined the contribution of high blood pressure per se versus direct effects of the mineralocorticoid to kidney injury and inflammation in experimental DOCA-salt hypertension.

Male uninephrectomized Sprague-Dawley rats received 1% NaCl for drinking and DOCA pellets (100 mg over 6 weeks) subcutaneously, or were sham operated. After 4 weeks, rats were treated with a non-hypotensive dose of spironolactone (SPL, 100 mg/kg, daily gavage, n=7), or triple therapy (TRP, hydrochlorothiazide, reserpine and hydralazine, n=8) dosed to normalize blood pressure, or with vehicle (n=14) for the final two weeks. Mean blood pressure was measured intraarterially in conscious rats. In kidney sections, macrophage infiltration, glomerulosclerosis and interstitial fibrosis were evaluated.

Mean blood pressure was elevated in vehicle-treated DOCA rats (174±9 versus 115±4 mmHg in normotensive rats, p<0.01), not affected by SPL (168±5 mmHg), and almost normalized by TRP (125±7 mmHg, p<0.05 vs. DOCA). Parallel changes of relative left ventricular weight were observed. Urinary protein excretion was grossly elevated in vehicle-treated DOCA rats, tended to be somewhat lower in SPL treated rats, and was markedly decreased by TRP. In contrast, glomerular infiltration of macrophages in DOCA rats (4.2±0.5 versus 0.9±0.1 macrophages per glomerular cross-section in normotensive controls, p<0.01) was more reduced by SPL (1.5±0.2, p<0.05) than by TRP (2.1±0.3).

DOCA rats developed marked glomerulosclerosis and interstitial fibrosis which was alleviated by SPL and TRP to a similar extent.

We conclude that in the DOCA-salt model of nephrosclerosis, direct mineralocorticoid effects contribute importantly to the infiltration of macrophages. Both high blood pressure and mineralocorticoid effects contribute independently, and to a similar extent, to the development of glomerulosclerosis and interstitial fibrosis.

Key Words: Aldosterone, Macrophages, Nephrosclerosis

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**INFLUENCE OF THE CYP11B2 -344C/T POLYMORPHISM ON PLASMA ALDOSTERONE, SODIUM EXCRETION AND BLOOD PRESSURE RESPONSES TO AEROBIC EXERCISE TRAINING IN MIDDLE-AGED TO OLDER PREHYPERTENSIVES**

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Aldosterone influences renal Na+ handling and normal blood pressure (BP) regulation but if consistently elevated, aldosterone may contribute to the development of hypertension. A few studies have found that as with BP, plasma aldosterone (PA) levels can change with aerobic exercise training (AEX) in hypertensives, but the response of these phenotypes to AEX vary by individual. The CYP11B2 (-344C/T) gene polymorphism has been associated with variability in both blood pressure and urinary and PA levels among hypertensives and may help explain the response of these phenotypes to AEX. The purpose of this study was to determine if the -344C/T polymorphism was associated with changes in PA levels, 24-hour Na+ excretion and BP after 6 months of AEX in middle-aged to older White prehypertensives. 23 Caucasian disease free, sedentary prehypertensives completed a standardized AEX program. All participants followed the AHA Step 1 diet. Blood samples were collected under fasting and supine conditions and PA was measured by RIA. The T and C allele frequencies were 0.61 and 0.39, respectively. There were 9 participants in the TT genotype group and 13 in the TC + CC genotype group. The TC+CC genotype group tended to decrease PA levels (-39±21 pg/ml, p=0.09) and had a greater reduction in PA levels with AEX than the TT genotype group after accounting for baseline plasma aldosterone levels (T:C -47±8 pg/ml; TT: -23±10 pg/ml, p<0.001). The TC+CC genotype group significantly decreased systolic BP (-4±2 pg/ml, p=0.03) and had a greater reduction in systolic BP with AEX than the TT genotype group after accounting for baseline systolic BP (TC+CC -4±2 pg/ml; TT: -2±2 mm Hg, p=0.02). Neither genotype group changed diastolic BP or 24 hour Na+ excretion and there was no difference in the change in diastolic BP and 24-hour Na+ excretion between the two genotype groups. Based on this preliminary evidence, the presence of the C allele among prehypertensives is associated with a greater reduction in plasma aldosterone and systolic BP with AEX.

Key Words: Aldosterone, CYP11B2, Prehypertensives

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**RENIN ANGIOTENSIN SYSTEM INHIBITION PREVENTS NORMALLY ADVANCED LEFT VENTRICULAR HYPERTROPHY VIA OXIDIZED STRESS SUPPRESSION**

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We designed in vivo study using high aged spontaneously hypertensive rats (SHR) treated with angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) or their combined therapy to clarify the role of reactive oxygen species (ROS) for preventing left ventricular hypertrophy (LVH) and heart failure.

We used 30 male SHR aged 50 weeks (6 rats in each group). Each group was treated for 4 weeks using osmotically mini-pump with ACEI (temocaprilat 1mg/kg/day), ARB (olmesartan 0.2mg/kg/day), combined therapy (CT; temocaprilat 0.5mg/kg/day and olmesartan 0.1mg/kg/day) or hydralazine (H; 15mg/kg/day) to reduce equivalently blood pressure (BP) and with saline as control (C). We measured Heart/body weight (Heart Weight Index), BP by tail cuff method and plasma BNP. We measured histologically myocytosize by hematoxylin eosin stain and myocardial fibrotic area by Azan stain using computerized morphometry system (MacSCOPE ver2.2). We also measured p22phox, p47phox, gp91phox, TGFβ1 and FGF2 mRNA levels by real-time PCR and serum NOx by ELISA.

Heart/body weight (Heart Weight Index) treated with ARB (p<0.05) or CT (p<0.1) was reduced. Histological myocyte size in ACEI (p<0.05), ARB (p<0.01) or CT (p<0.001) and myocardial fibrosis in ACEI (p<0.05) or CT (p<0.01) was significantly reduced. Plasma BNP and NOx level in ACEI, ARB or CT was reduced (P<0.05). By real-time PCR, TGFβ1 mRNA in ACEI (p<0.05), ARB (p<0.05) or CT (p<0.01) or FGF2 mRNA in ACEI, ARB or CT (p<0.01) were significantly suppressed. The p22phox in ACEI (p<0.05), ARB (p<0.05) or CT (p<0.01), p47phox in ACEI (p<0.01 vs. C, p<0.05 vs. H), ARB (p<0.05 vs. C) or CT (p<0.01 vs. C, p<0.05 vs. H) or gp91phox in ACEI (p<0.01), ARB (p<0.01) or CT (p<0.005) were also significantly suppressed compared those in H or C.

We conclude that the dual inhibition of RAS showed additional beneficial effects on improvement of cardiac hypertrophy via ROS suppression even in naturally advanced LVH.

Key Words: Cardiac Hypertrophy, High-Age, Oxidative Stress