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Abstracts

OR-1

Impact of hypertension on sympathetic nerve hyperactivity in the dysmetabolic syndrome

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Visceral obesity as well as abnormalities of glucose, insulin and lipoprotein metabolism are common in patients with hypertension and commonly characterise the metabolic syndrome. In people who have essential hypertension without features of the dysmetabolic syndrome it is widely accepted that an increase in sympathetic nervous system activity occurs. However, the impact of hypertension itself on the level of sympathetic nerve activity in the dysmetabolic syndrome is not known.

We therefore planned to determine the effect of hypertension on the level of central sympathetic drive to the periphery in people with the metabolic syndrome.

Using the NCEP (ATP III) definition for the metabolic syndrome, two groups of patients; one with all the metabolic syndrome criteria including hypertension (MS+EHT) and one with all criteria except hypertension (MS-EHT) were compared. These groups were matched for confounding variables, which are known to influence sympathetic nerve activity including age, body mass index (BMI), heart rate (HR), mean arterial pressure (mBP) and drug therapy. Peroneal muscle sympathetic nerve activity (MSNA) was measured by microneurography. MSNA was obtained as the resting mean frequency of bursts per 100 cardiac beats (b/100b). Waist circumference, fasting blood lipid profile and insulin were measured in each person. There were no significant differences in age, BMI, HR, mBP and waist circumference (P at least >0.05; unpaired t test) between the two groups. However in people with hypertensive metabolic syndrome both sympathetic nerve activity and the level of insulin were significantly higher than people with normotensive metabolic syndrome, ($P \leq 0.03$; unpaired t test).

In Conclusion people with hypertensive metabolic syndrome criteria have higher levels of sympathetic nerve hyperactivity than those with normotensive metabolic syndrome. The origin of this sympathetic hyperactivity may at least in part be due to higher levels of hyperinsulinaemia in hypertensive metabolic syndrome.

Keywords: Metabolic syndrome; Sympathetic nervous system; Hypertension

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OR-2

Risk and impact of incident glucose disorders in hypertensive older adults treated with an ace inhibitor, a diuretic, or a calcium channel blocker: A report from the allhat trial

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Several cardiovascular disease (CVD) trials (e.g., HOPE, SOLVD) have reported that treatment with ACE inhibitors (ACEI) is associated with a lower risk of incident diabetes mellitus (DM) as compared to placebo therapy. Several

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hypertension (HTN) trials (e.g., LIFE, ALPINE, CAPP) have shown ACEI use reduces risk of DM compared to beta blocker use. No study has compared the risk of DM and elevated fasting glucose (FG) levels associated with ACEI use against diuretic or calcium channel blocker (CCB) use. Moreover, no trial has assessed the impact of incident elevated glucose levels associated with these HTN medications on CVD risk.

We analyzed the ALLHAT data-set, a double-blind HTN trial that compared use of ACEI, diuretic, and CCB for the prevention of coronary heart disease (CHD) and other CVD. Among those with normoglycemia (FG < 110 mg/dl) at baseline, mean age was 67 years, ~30% were Black, and mean FG was 91 mg/dl. Over a mean of 4.9 years follow up, FG levels rose in all three groups. At 4 years, mean FG level for ACEI (n = 3,705), diuretic (n = 6,149) or CCB (n = 3,602) treatment groups was 98.8, 102.0, and 99.8 mg/dl, respectively ($p < 0.006$, chlorthalidone vs ACEI or CCB). The incidence of DM (any FG ≥ 126 mg/dl) was 7.6%, 11.5%, and 8.3%, respectively. For those with impaired fasting glucose (FG 110–125 mg/dl) at baseline (ACEI n = 407, diuretic n = 628, CCB n = 364), mean 4-year FG was 122.9, 138.8, and 135.0 mg/dl, respectively, (chlorthalidone vs ACEI, $p < 0.001$) and DM incidence was 36.8%, 52.5%, and 45.5%, respectively.

We conclude that DM and FG levels are lower with the use of ACEI over the 4.9 years follow up of the trial as compared to CCB and diuretic use. Nonetheless, during follow-up, these differences did not translate into more CHD events, or into higher all-cause mortality, in the chlorthalidone group, as previously reported. Indeed, risk of certain CVD outcomes was lower with chlorthalidone treatment. Data will be presented regarding the effect of hypokalemia and beta blocker use on these metabolic findings.

Keywords: Diabetes; Fasting glucose; CVD risk

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OR-3

The metabolic syndrome influences left ventricular mass and function in non-diabetic patients

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The metabolic syndrome (MS) is a cluster of closely related risk factors that together convey substantially increased cardiovascular risk. Aim of this study was to evaluate the impact of MS on left ventricular (LV) anatomy and function in non-diabetic patients (pts), without clinically detectable heart disease and never-treated with antihypertensive or lipid-lowering drugs. We enrolled 88 consecutive pts (56 men, 46 ± 12 years, BMI 27.2 ± 2.8 Kg/m^2) admitted at our out-patients' clinic because of newly discovered high clinic blood pressure (BP). Each pt underwent : 24h ambulatory BP monitoring, echocardiogram, evaluation for metabolic syndrome (following ATPIII criteria). LV diastolic function was evaluated by means of Doppler transmitral flow and pulsed tissue Doppler imaging (E/A ratio at basal septum and E/A ratio at basal lateral wall). MS was diagnosed in 40 pts. Comparing MS+ group to the 48 pts without MS (MS-), the 2 groups were similar with regard to age, gender, 24h systolic and diastolic BP (MS+ 133 ± 11/85 ± 9 vs MS-135 ± 11/84 ± 8 mmHg, ns), whereas BMI, fasting glycemia and triglycerides were significantly ($p < 0.001$) higher and HDL-cholesterol ($p < 0.001$) lower in MS+ group. The prevalence of hypertension (24hour BP > 130 and/or 80 mmHg) was similar between the 2 groups (67% vs. 75%, ns), whereas prevalence of impaired glucose tolerance, high triglycerides and low HDL-cholesterol was significantly higher ($p < 0.002$) in MS+ group.With regard to LV, end-diastolic diameter was normal (<57 mm) in all and similar between the 2 groups, whereas LV mass index was significantly higher in MS+ group (108.7 ± 23.3 vs 95.5 ± 25.8 g/m^2, $p = 0.013$), due to greater septal and posterior wall thickness; LV systolic function was normal in all and similar between the 2 groups; both TDI parameters of LV diastolic function were significantly ($p < 0.02$) lower in MS+ group. The significant difference between the groups with regard to LV mass and diastolic function held true after correction for BMI.

In conclusion, in non-diabetic never-treated patients the presence of MS is associated with greater LV mass and decreased LV diastolic function. These preclinical cardiac abnormalities are not accounted for by difference in age, gender or 24h BP and therefore could be reasonably ascribed to the interplay of the metabolic components that characterize the syndrome.

Keywords: Metabolic syndrome; Myocardial hypertrophy; Diastolic function

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OR-4

Albuminuria predicts cardiovascular outcome with losartan versus atenolol in patients with diabetes, hypertension and left ventricular hypertrophy. A life diabetes substudy

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Objectives: We have previously shown that baseline level of urinary albumin/creatinine ratio (UACR) is closely related to risk for cardiovascular (CV) events.

Aim: To investigate in patients with diabetes and hypertension a) whether baseline UACR predicts the degree of benefit of losartan on CV outcomes, b) whether changes in albuminuria across the study differ on losartan versus atenolol c) whether benefits of losartan relate to its influence on albuminuria during treatment.

Design and Methods: In 1,195 diabetic patients with hypertension and ECG-verified left ventricular hypertrophy (LVH) included in the LIFE study UACR was measured at baseline (after two weeks of placebo treatment) and at each year of treatment with either losartan or atenolol. Primary composite endpoint (CV death plus non-fatal MI and stroke) was recorded during 4.8 years of follow-up. Cox models were run including and excluding time-varying albuminuria values, and the treatment coefficients were compared.

Results: The benefits of losartan superior to atenolol were more pronounced in patients with baseline UACR above the median value (3,05 mg/mmol): a risk reduction of 30% for primary endpoint and of 50% for CVmortality, as compared to patients with UACR below the median value. Reductions in albuminuria at year one and two were app. 30% greater on losartan compared to atenolol ($p<0.001$). One-fifth of the outcome difference in favor of losartan versus atenolol could be explained by its superior effect on albuminuria.

Conclusions: In diabetic patients with hypertension and LVH baseline UACR above median value identify patients with the greatest benefit on losartan. For the same degree of BP reduction losartan reduced UACR to a greater extent than atenolol. Approximately 20% of the benefit of losartan could be attributed to a superior influence on reduction in albuminuria.

Keywords: Albuminuria; Diabetes; Left ventricular hypertrophy

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OR-5

Hunting for hypertension genes: The national millennium genome project in japan, the first report

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In 2000, national cooperative projects, under the banner of "Millennium Projects", were started in Japan. The projects are focusing on bold technological innovations in three areas which are of vital importance to Japan: informatization, the aging society and the environment. The discovery of genetic variations linked to the development of hypertension is one of the leading missions of the Millennium Project. Four other diseases, diabetes mellitus, cancer, asthma, and Alzheimer's disease were also targets for the gene hunting. This is the first interim report of the Millennium Genome Project for Hypertension.

The whole-genome case-control approaches using a hundred thousand of SNP markers and thirty thousand of microsatellite markers are being carried now. The SNPs were previously discovered from Japanese population as a national project. The microsatellite markers were assigned less than 600 kb apart. The case subjects (n=192) fulfilling the following criteria were recruited from Japanese nationwide: male, BMI $<=25$ kg/m^2, SBP=>160 mmHg and/or DBP=>100 mmHg or under untihypertensive treatment, age of onset was between 30 and 59 (y.o.), and having family history of hypertension within parents and siblings. The control subjects (n=192) were also recruited with the following criterion: male, BMI $<=25$ kg/m^2, SBP $<=120$ mmHg and DBP $<=80$ mmHg and not under untihypertensive treatment, and no family history for hypertension.

In the SNP markers approach, we identified 2 hypertension-associate locus at 7p ($p=7.5\times10^{-11}$, odds=0.457 (0.361–0.578)), and 19p ($p=1.5\times10^{-5}$, odds=1.657 (1.318–2.082)) from the 5600 SNPs analyzed so far. There were 9 SNPs with $p<0.001$. 78 SNPs showed $p<0.01$. On the other hand, we also identified several quantitative trait loci with the microsatellite markers analysis. For example, on the chromosome 17, 2 locus were strongly associated with hypertension (17p, 17q, $p<1.0\times10^{-5}$). Positive rate was 9.2% in 4202 microsatellite markers we have analyzed to date.

To eliminate the false positive markers and obtain high quality mapping of the hypertension genes, we plan to perform 2nd screening using different population. The projects are expected to be completed at the end of 2004.

Keywords: Genome-wide search; Case-control approaches; Millennium projects

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OR-6

Modifications in the proteome of hearts from spontaneously hypertensive rats (shr) treated with antihypertensive drugs

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Left ventricular hypertrophy is a common finding in hypertensive patients. Although distinct cellular and gene transcription patterns have been associated with heart hypertrophy, their molecular mechanisms remain mostly unknown. Proteomic analysis could afford novel information on potencial diagnostic and therapeutic targets.

The objectives of this study are: a) the identification of proteins differentially expressed in the hearts of SHR rats compared with Wistar-Kyoto (WKY) rats. b) to investigate the effects of antihypertensive drugs in the differential expression pattern and to find new proteins involved in cardiac hypertrophy.

Studies were performed in male SHR randomized to nontreated animals, that received 360 mg/L of the a $_1$-adrenoreceptor antagonist doxazosin, and animals that received 180 mg/L of doxazosin plus 20 mg/L of the angiotensin converting enzyme (ACE) inhibitor quinapril. As normotensive control, WKY rats of the same age were studied. Animals were followed during 36 weeks until they were sacrificed. In order to detect changes in heart proteins associated to severe hypertension, we performed the analysis of protein expression patterns by two-dimensional polyacrylamide gel electrophoresis (2-DE). From the more than 1000 spots resolved in the pH 4–7 range by 2-DE of myocardial tissue from WKY and SHR, we focused on 459 spots well resolved. In comparison with those obtained in normotensive rats, 383 spots remained invariable and 76 spots were altered in the heart of SHR. Out of 76 altered proteins in the heart of SHR, 26 were normalized by doxazosin, 37 by doxazosin plus quinapril and 33 by quinapril low doses. By mass spectrometry (MALDI-TOF, TOF-TOF and ESI), we have identified different spots such as alpha-tropomyosin, cytochrome c oxidase polypeptide Va, myosin light chain-2, haptoglobin and transthyretin, among others.

Through a proteomic approach, we have been capable of analyzing the difference heart's proteome between hypertensive and normotensive rats, showing a number of altered proteins in the damaged heart, some of them normalized or improved by antihypertensive drugs. These data offer the potential to find new disease markers and drug-target validation.

Keywords: Hypertension; Hypertrophy; Proteomic

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OR-7

Arterial elasticity and structural changes of the cardiovascular system in asymptomatic young adults: The bogalusa heart study

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The cardiovascular (CV) system is affected by the intrinsic aging process and the long term burden of clinical CV risk factors. Autopsy studies clearly show the "Silent" phase of arteriosclerosis (atherosclerosis and hypertension) occurs in early life. Earlier studies with M-mode sonography showed increasing numbers of risk factors are associated with greater arteriosclerosis in carotid arteries. Arterial elasticity, an indicator of impaired structure-function, was examined in a sample of 516 healthy young, asymptomatic subjects, aged 26–37 years (71% white, 39% male) who participated in the Bogalusa Heart Study. Arterial elasticity was measured from ultrasonography of the common carotid artery as Peterson's Elastic Modulus (Ep) and Young's Elastic Modulus (YEM). Risk factor variables include age, race, gender, systolic and diastolic blood pressures, cholesterol total/HDL ratio, LDL, and HDL triglycerides, BMI, waist, insulin, glucose, heart rate, and the double product. After controlling for age, blacks and males had higher Ep and males higher YEM. In univariate analysis, generally all risk factor variables relate to parameters of elasticity. Importantly, risk factor variables explain 38% and 21% of the variance in EP and YEM, respectively. Although these results show adverse changes in the vascular structure-function related to CV risk factors, genetic studies involving functional candidate genes provide additional clues to understanding complex traits of CV diseases. Decreased elasticity of large and medium sized arteries

has been associated with hypertension, while the endothelial nitric oxide (ENOS) gene is known to play a role in the regulation of blood pressure. The effect of the ENOS gene polymorphism (G894T) on carotid artery stiffness was examined. Blacks displayed a lower frequency of the T allele than whites (0.127 versus 0.327, $p<0.001$). After controlling for gender, age, BMI and blood pressure, the genotype effect on arterial stiffness was significant for Ep ($p=0.013$) and YEM ($p=0.033$) in blacks, although a similar trend was seen in whites. These results indicate that both structure and function changes occur in young asymptomatic individuals, consistent with the concept that genetic-environmental interactions play a role in the CV aging process. Understanding genetic and environmental interactions help provide more rational programs for preventive cardiology.

Keywords: Carotid arterial stiffness; Endothelial nitric oxide synthase; Racial (Black-White)

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OR-8

Ovarian hormones modulate neointima formation in an animal vascular injury model through effects on neutrophil chemokine production

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BACKGROUND: Neointima formation after balloon injury of the rat carotid artery has been shown to be related to neutrophil movement from the adventitia to the injured artery. Administration of estrogen (17 and beta; estradiol, E2) to ovarectomized rats greatly relieves both the neutrophil burden in the artery and the formation of neointima. We investigated whether neutrophil attractant chemokines related to Interleukin 8 (IL-8) are mediators of this inflammation, and if E2 treatment can change the levels of chemokine present. We also did in vitro neutrophil chemotaxis experiments to determine the relative biological activity for each case.
METHODS: Protein levels of the rat IL-8 homolog, cytokine induced neutrophil chemoattractant (CINC) 2α were determined by performing a multiplexed sandwich ELISA on samples derived from homogenized whole arteries (injured and uninjured) isolated from ovarectomized rats treated with either E2 or vehicle.To assess the biological activity of these arterial homogenates, in vitro chemotaxis assays were performed using isolated human neutrophils in a 96 well modified Boyden chamber appropriate for the evaluation of leukocyte chemotaxis.
RESULTS: The CINC-2α content in the injured artery from vehicle treated animals is much greater than in uninjured control arteries, while in the injured artery of E2 treated rats CINC2α levels are significantly different than the other two groups. Likewise, neutrophil chemotactic activity of injured arterial homogenates is suppressed in the E2 treated animals compared to the vehicle treated group.
CONCLUSIONS: Neutrophilic infiltration into the balloon injured rat carotid artery is mediated by IL-8 like chemokines such as CINC, and E2 treatment suppresses chemokine release at the site of injury. We therefore hypothesize that E2 induced inhibition of neointima formation in arteries subjected to endoluminal injury may be mediated, at least in part, by this novel anti-inflammatory mechanism.

Keywords: Neutrophil; Chemokines; Vascular injury

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OR-9

History of hypertension and 5-year global mortality and causes of death after acute myocardial infarction

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Aim of this study was to ascertain whether there is an association between history of hypertension (HT) and global mortality and main causes of death in long term follow up after acute myocardial infarction (AMI).

This is a prospective study which investigated 505 consecutive, unselected patients admitted to 3 coronary care units for definite AMI. All patients completed 5 years follow up and causes of death were reported from medical records (including post mortem report where available) and family doctor reports. Documented history and duration of hypertension were recorded. HT was present in 46.7% patients (mean duration 11.9 ± 9.4 years). Mean age was

69.6 ± 11.4 years among HT and 63.7 ± 11.9 among NT, $p < 0.0001$; females were 41.1% among HT and 17.8% among NT, $p < 0.0001$; CK-MB peak was 171 ± 160 IU/L among HT and 183 ± 159 among NT, ns; Killip class >1 during hospital stay was 42.8% among HT and 34.9% among NT, ns; thrombolytic agents were used in 32.6% of HT and 46.5% of NT, $p = 0.002$.

Global mortality was 44.5% among HT and 30.5% among NT ($p = 0.001$). In the present analysis causes of death were divided into 3 main sub-groups: non sudden cardiovascular mortality (non-SCVM) (30.5% among HT, 13.7% among NT, $p < 0.0001$), sudden death (SD) (8.5% among HT, 10.8% among NT, ns), and non-CV mortality (non-CVM). (5.5% among HT, 5.9% among NT, ns). At univariable Cox survival analysis, HT was associated to global mortality (RR = 1.6 CL1.2–2.2, $p < 0.0001$) and non-SCVM (RR = 2.4 CL1.6-3.6, $p < 0.0001$) while HT was not associated to SD (RR = 0.9 CL 0.5–1.6, ns) and non-CVM (RR = 1.1 CL 0.5–2.2, ns). At multivariable analysis, (models included age, gender, diabetes mellitus, previous MI or angina, CK-MB peak, heart failure, arrhythmias, thrombolysis and HT), HT was no associated to global mortality (RR = 0.9 CL 0.6–1.2, ns), SD (RR = 0.6 CL 0.2–1.1, ns) and non-CVM (RR = 0.6 CL 0.3–1.1, ns) while HT resulted independently associated to non-SCVM (RR = 1.6 CL 1.1–2.5, $p = 0.001$). All the other variables in the Cox model but gender and arrhythmias were significantly associated to non-SCVM. In conclusion, HT in AMI patients followed up for 5 years, resulted as an independent predictor for long term non-SCVM. No association was found with SD and non-CVM.

Keywords: Myocardial infarction; History of hypertension; Causes of death

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OR-10

Exercise and cardiovascular mortality among hypertension subjects

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A favorable effect of exercise on cardiovascular longevity has been repeatedly reported in the general population. Regular exercise has also been shown to lower blood pressure (BP) in hypertensive patients (HT) and therefore has been recommended as standard lifestyle/behavior management in HT. To test the impact of exercise on the long-term cardiovascular disease (CVD) mortality among HT, we have examined the National Health and Nutritional Examination Survey (NHANES I) and 1992 follow-up study. Of 14,407 NHANES I participants, we identified 4,668 HT (BP ≥ 140/90 mm Hg or on anti-hypertensive therapy) without previous history of heart disease and/or stroke. They were 42.9% male, 76.3% white, with a mean age of 56 years, and baseline BP of 151/91 mm Hg. Exercise was assessed at baseline by response to the question "Do you get much exercise in things you do for recreation, or hardly any exercise, or in between?" Answers were a) much (most) exercise (n = 746), b) moderate exercise (n = 1525) and c) least or no exercise (n = 2396). During an average of 15.6 years follow-up, there were 2,152 deaths, of which 1,152 were CVD. Compared to those with least exercise, those with most exercise had higher education and income, lower BP (150/90 vs 153/92 mm Hg, $p < 0.001$), were less likely to have diabetes (3.6 vs 6.8%, $p = 0.003$), be overweight (33.5 vs 42.4%, $p < 0.001$), and more likely to take larger amounts of total calories (1905 vs 1575 Kcal/day, $p < 0.001$). Age-gender-adjusted CVD mortality rates by exercise (least to most) were: 17.9, 14.3 and 13.3/1000 person-years ($p = 0.03$) and total mortality rates were 32.4, 27.5 and 25.9/1000 person-years ($p < 0.001$). In Cox regression analysis, adjusting for sociodemographic and clinical characteristics, dietary caloric intake and other CVD risk factors, exercise was significantly associated with CVD mortality-compared to those with most exercise, patients with least exercise had 30% higher CVD mortality (hazard ratio (HR) 1.30, 95% confidence interval 1.03–1.64). At the same time, history of diabetes (HR 2.09 (1.63–2.68)), male gender (HR 1.90 (1.58–2.30)), smoking (HR 1.59 (1.32–1.92)), increased systolic BP for each 10 mm Hg (HR 1.12 (1.08–1.16)), less than high school education (HR 1.25 (1.04–1.49)), and age for every 10 years (HR 2.31 (2.10–2.22)) were all associated with higher risk of CVD mortality.

This study is consistent with and extends previous observational data demonstrating that increased energy expenditure is associated with decreased overall and CVD mortality among HT.

Keywords: Exercise; Epidemiologic follow-up; Cardiovascular mortality

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