Short Term Estrogen Replacement Therapy Improves Cardiovascular Autonomic Response in Postmenopausal Women: A Double-Blind Randomized Placebo-Controlled Trial

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BACKGROUND: Estrogen deficit may lead to cardiac autonomic function imbalance in the postmenopausal women that may potentially increase cardiovascular risk. The physiological mechanism by which estrogen replacement therapy (ERT) regulates the autonomic nervous system in postmenopausal women remains unclear.

METHODS: Thirty-nine patients aged 45-65 years with a previous total hysterectomy and amenorrhea for 1 year prior to the surgery were enrolled in this prospective, randomized double-blind, placebo-controlled trial. Women with obesity, cardiovascular, neurological or metabolic disease were excluded. Conjugated estrogens were administered at a dose of 0.625 mg daily during 12 weeks in 19 patients (P2.6±7.1 years), and matched placebo in 20 women (53.8±5.4 years). Cardiopulmonary and arterial baroreceptor response was determined after 3 months of treatment in both groups. Arterial baroreflex sensitivity (BRS) was determined after the intravenous bolus administration of noradrenaline (300 mcg). Cardiopulmonary baroreflex response (CBR) was calculated using venous occlusion plethysmography by determining forearm blood flow changes (FFB) and peripheral vascular resistance (PVR) to –10 mmHg lower-body negative pressure (LBNP). All measurements were performed between 8am-12m. All signals were analyzed with the winCPNPS software (Absolutely Aliens, Finland).

RESULTS: A significant increase in BRS was found after 3 months of ERT compared with placebo; Phenylephrine: 9.8±3.72 vs. 15.9±10.22, p=0.09 and Nitroprussiure; 6.9±2.73 vs. 10.6±2.4, p=0.01. During a P<2 higher FFB (1.1±0.39 vs. 0.8±0.15, p=0.05) was associated with lower PVR (97.7±32.5 vs. 129±43.5, p=0.05) in the group receiving ERT compared to the placebo group.

CONCLUSIONS: Short term ERT (3 months) may modulate cardiovascular autonomic responses leading to reduced sympathetic activity (PVR) and improving cardiovascular response by increasing arterial baroreflex sensitivity in postmenopausal women. (Co-\n
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Irbetasan Significantly Reduces C-Reactive Protein After One Month of Therapy in Unstable Angina

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Background: A growing body of evidence supports the pathophysiological role of renin-angiotension-in system (RAS) in the athero-trombotic process, in cardiac remodelling and in apoptosis. Angiotension II (AgII) blockade seems to be able to reduce the progression of atherosclerosis and to improve through an anti-inflammatory mechanism. A reduction in events has also been observed in trials with these classes of drugs. Therefore we evaluated whether Irbetasan (a selective AgII blocking agent) may modulate the infarctional response in unstable angina (UA). Methods: We studied 25 UA (Braunwald’s class IIIb) with UA or NSTEMI with no prior history of hypertension, diabetes, or heart failure. Patients were treated with full conventional anti-ischemic therapy (i.v. nitrates, aspirin, clopidogrel, etc). Blood samples were collected before and 1 week after the ST program. Resting Systolic and Diastolic BP were measured on six separate occasions before and after ST for each subject. AGT genotyping was performed from each subject’s genomic DNA.

Methods and Results: Significant training induced reductions were noticed in systolic BP of female subjects, which dropped from 123.4 ± 11.3 mm Hg to 120.1 ± 11.4 mm Hg (P<0.05). The male subjects dropped their diastolic BP from 77.2 ± 7.6 mm Hg to 75.0 ± 7.1 mm Hg (P<0.05). When analyzed using ANCOVA, accounting for the genotype and the differences in pre-systolic BP between the two genotypes, the change in systolic BP was significantly greater in AA genotype than AC/CC genotype. Systolic BP in AA genotype dropped from 128.2 ± 2.0 mm Hg to 123.9 ± 1.6 mm Hg (P<0.05). When controlled for the differences in pre-diastolic BP between the two genotypes, the change in diastolic BP was not significantly different between the two genotypes.

Conclusion: AGT (-20) genotype influences resting blood pressure response to strength training such that training reduces systolic BP in homozygotes to a more degree than that in heterozygotes.

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Upregulation of Akt and Endothelial Nitric Oxide Synthase Induces Vascular Smooth Muscle Cell Differentiation in Hypertension In Vivo

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Recent studies have shown that angiotensin II type 1 (AT1) receptor-mediated Akt activation induced vascular smooth muscle cell (VSMC) dedifferentiation in vitro. However, the critical signal transduction affecting the VSMC phenotype remain unclear in vivo. Thus, we aimed to examine which signal transduction acting through the AT1 receptor could regulate the VSMC phenotype in SHRSP in vivo. Methods and Results: Male stroke-prone hypertensive rats (SHRSP) were randomised and treated for 6 weeks with a vehicle (n=20), an AT1 receptor antagonist (E4177, 30 mg/kg/day, n=20), or an angiotensin-converting enzyme (ACE) inhibitor (cilazapril, 10 mg/kg/day, n=20). Protein expressions were analyzed by immunoblot, and NAD(P)H oxidase activity measured by luminescence assay. Both drugs showed equipotent effects on blood pressure, aortic morphology, collagen deposition, p38 mitogen-activated protein kinase and p42/44 extracellular signal-regulated kinase expression in the aorta (P>0.05 vs. the vehicle group, respect-
Stromelysin-1 (MMP-3) Gene 5A/6A Promoter Polymorphism Is Associated With Blood Pressure in a Community Population

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Background: Vascular remodelling of large and small arteries contributes to the development of hypertension. Stromelysin-1, a member of the matrix metalloproteinase (MMP) family may contribute to arterial remodelling. The expression of stromelysin-1 gene is partly regulated by a common polymorphism in the promoter region of either five or six consecutive adenine bases (5A/6A) that alter transcription factor binding.

Methods: A community study of 1,111 randomly selected community residents (553 males and 558 females), age 27-77 years, who were assessed for conventional cardiovascular risk factors and the stromelysin-1 5A-1171/6A genotype. Mean common carotid intima-media wall thickness (IMT) and presence of plaque was determined by carotid ultrasound.

Results: The frequency of the stromelysin-1-1171/5A allele was 0.45. Univariate analysis demonstrated an association between the stromelysin-1-5A-1171/6A genotype and blood pressure in the whole population. Multivariate analysis showed an independent association between the stromelysin-1 genotype and systolic and diastolic blood pressure (both P<0.005) in the whole sample. When the population was split by smoking status, an independent association with systolic blood pressure (P<0.0001) and diastolic blood pressure (P<0.006) was present only in smokers. Subjects who smoked and carried the 5A/5A genotype had a higher mean systolic (+6.0 mmHg) and diastolic (+2.5 mmHg) blood pressure compared to 5A/6A and 6A/6A carriers. The association between the stromelysin-1 genotypes and blood pressure was recessive with the effect only seen with the 5A/5A genotype. Multivariate analysis in the whole population showed there was no association with mean IMT (P=0.42) or the likelihood of carotid plaque formation (P=0.08).

Conclusions: In this large randomly selected, cross-sectional population, the 5A/5A variant in the stromelysin-1 gene promoter was independently associated with increased blood pressure in the whole population and in smokers but was not associated with either increased carotid IMT or plaque formation.

Pulse Pressure and Interactions Between Polymorphisms in the Angiotensin II Type 1 Receptor and Uncoating Protein 1 Genes in Hypertensive Hong Kong Chinese

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Background: Hypertension and obesity are strongly inter-related, and both have multifactorial genetic and environmental components. The angiotensin II type 1 receptor (AT1R) is involved in the regulation of blood pressure and polymorphisms in this gene have been implicated in the development of hypertension. The uncoating protein 1 (UCP1) gene is solely expressed in brown adipose tissue and genetic polymorphisms affecting this may be associated with obesity. The present study was performed to assess the contribution of polymorphisms of these two genes on blood pressure or obesity parameters in a family study.

Methods: We studied 96 families with a hypertensive proband, including 282 siblings, of which 133 were hypertensive and 144 were obese. Blood pressure, pulse pressure, body mass index (BMI) and waist:hip ratio (WHR) were recorded for each sibling. The AT1R gene 1166C polymorphism and the UCP1 gene A-3826G polymorphism were identified with polymerase chain reaction based Restriction Fragment Length Polymorphism (RFLP) protocols. A multi-level linear mixed model for quantitative trait locus (QTL) analysis was applied to identify whether these genetic polymorphism loci were related to blood pressure, pulse pressure or body weight.

Results: No significant association was found between the AT1R and UCP1 gene polymorphisms and systolic or diastolic blood pressure. Age and the BMI/WHHR ratio were strongly related to the systolic blood pressure (p=0.0001), diastolic blood pressure (p=0.0001) and pulse pressure (p=0.0001). Gender was only related to pulse pressure (p=0.0003). For the AT1R and UCP1 gene polymorphisms, the QTL analysis showed that the AT1R gene A1166C polymorphism was related to pulse pressure after adjustment for age, gender and BMI/WHHR ratio (p=0.038). A significant gene-gene interaction for pulse pressure was found between the two gene polymorphisms after adjustment for age, gender and BMI/WHHR ratio (p=0.031).

Conclusions: Genetic variation at the AT1R gene locus may modify the risk of developing abnormal pulse pressure. An interaction between the AT1R genotype and UCP1 genotype suggests these loci may be important in determining abnormal blood pressures in relation to obesity.

Platelet-Derived Vascular Endothelial Growth Factor in Patients With Hypertension: Relationship to Platelet Activation and Plasma Indices of Angiogenesis

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Aims: Platelet activation is an important part of the pathogenesis of complications in hypertension (HT). Hypertension is also associated with abnormal angiogenesis. We hypothesised a relationship of platelet derived Vascular Endothelial Growth Factor (VEGF) to plasma markers of angiogenesis (VEGF, Angiopoietin (Ang)-1 and 2, and Ang receptor Tie-2) and platelet activation (soluble P-selectin) in hypertension.

Methods: We studied 199 (151 males, mean age 67 ± 9 years) patients with HT and 59 normotensive controls (41 male; mean age 68±11 years). Plasma levels of angiogenesis such as VEGF, Ang-1, and Ang-2, and Tie-2 were determined by ELISA. Platelet derived VEGF was measured by lysis of a fixed number of platelets, and measuring the levels in the plasma obtained.

Results: Plasma indices were abnormal in HT versus controls (Table 1). Platelet derived VEGF did not vary with the use of aspirin or antihypertensive agents. Platelet derived VEGF correlated with plasma levels of VEGF, Angiopoietin (p=0.057, p<0.001) Ang-1 (p=0.005, p<0.001), and Tie-2 (p=0.057, p<0.001). Conclusions: Hypertensive patients have raised platelet derived VEGF which correlates with the plasma levels of VEGF and Ang-1. This suggests a role for platelets in the abnormal angiogenesis that is seen in hypertension.

Carvedilol Reduces Serum Concentration of DNA-Damage Biomarker 8-Hydroxydeoxyguanosine in Human Hypertension

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Background: Oxidative DNA damage due to reactive oxygen species (ROS) has been implicated in cardiovascular diseases. Deoxyguanosine is one of the constituents of DNA and can be oxidized, it is altered into 8-OHdG. The serum concentration of the DNA repair product 8-OHdG has been proposed as a noninvasive biomarker of oxidative DNA damage in human vivo. Carvedilol has shown to have antioxidant actions in patients by reduction of anti-oxidized LDL antibodies and to reduce ROS in normal human subjects. However, there has been no data that carvedilol reduce DNA damage in human hypertension.

Methods: Seventeen newly diagnosed hypertension patients (mean age ±51±11, male/female=11/6) who have not taken antihypertensive medication previously were enrolled in this prospective study. Fasting blood sample were collected at baseline in tubes with EDTA as an anticoagulant. The subjects were given carvedilol PO once a day for 2 months. Two months later, another blood sample was collected as above. Age and sex matched control subjects (n=22, mean age ±45±12, male/female=14/8), not given any drugs, also had 2 samples taken 2 months apart. None of the subjects were on any medications, including NSAIDs, Vitamin E, or other antioxidants. Serum 8-OHdG was measured with ELISA method. High sensitivity C-reactive protein (hs-CRP) was also checked two times. There were no statistical differences in smoking, diabetes, and total cholesterol level between hypertension and control group. Results: The hypertension group, DNA damage biomarker 8-OHdG at baseline was 9.0±4.43 ng/ml (mean±SD). After carvedilol administration, it fell to 5.74±3.89 ng/ml (p=0.002). In the control group, the 8-OHdG concentrations were 3.41±2.03, 3.01±2.65 ng/ml at baseline and 2 months later, respectively (p<0.05). The baseline 8-OHdG was higher in the group of hypertension than in control group(0.001). hs-CRP had no significant difference before and after and carvedilol treatment in the hypertension group (0.21±0.51, 0.19±0.37 mg/dl).

Conclusion: DNA damage due to ROS occurs more in hypertensive patients than in normal blood pressure people. Carvedilol may significantly reduce DNA damage in hypertension patients.

Modulatory Effect of Inflammation on Blood Pressure Reduction Following Therapeutic Lifestyle Change via Cardiac Rehabilitation and Exercise Training

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Background: Inflammation promotes the development and progression of atherosclerosis and is associated with several traditional CV risk factors including hypertension, diabetes, and dyslipidemia. We evaluated the impact of inflammation on insurance in risk factors following 12 weeks (36 sessions) of therapeutic lifestyle change (TLC) via cardiac rehabilitation and exercise training (CRET) in 635 patients (mean age ±64±6±10 years).

Methods: Patients were dichotomized based on baseline median hs-CRP (median = 3.2 mg/l) values. At baseline there were no differences in age, gender, systolic and dia-

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