1007-179 Exercise Training Increases the Number of Endothelial Progenitor Cells in Patients With Coronary Heart Disease and Cardiovascular Risk Factors

Sabine Steiner, Alexander Niessner, Bernhard Richter, Sophie Ziegler, Martina Penka, Erich Minar, Christoph William Kopp, University of Vienna, Vienna, Austria, Austria

Background – Endothelial Progenitor Cells (EPCs) circulating in peripheral blood defined by the surface antigens CD34, KDR and CD133 were shown to contribute to neovascularization and rejuvinate arteries. Vascular function and cardiovascular risk were inversely correlated with the number of EPCs. As regular physical exercise improves endothelial dysfunction and promotes cardiovascular health we studied the effect of exercise in patients with coronary heart disease and cardiovascular risk factors.
Methods - 15 patients with documented coronary heart disease and/or cardiovascular risk factors joined a 12-week supervised endurance training. The number of circulating EPCs was determined before and after the exercise period by whole blood flow cytometry.
Results – A significant increase in exercise frequency (pre 1.5±1.5 versus post 3.7±1.7 weekly training episodes; *P*<0.0001) and duration (pre 74±88min versus post 186±87min weekly training time; *P*<0.0001) was observed in the study group (mean age±std; 52.9±10.1). The proportion of EPCs defined as $CD34^+/KDR^+/CD133^+$-positive peripheral blood mononuclear cells ($BM^{CD34+/KDR+/CD133+}$; pre:0.7±0.8% versus post:2.7±2.2%; *P*=0.006) as well as $CD34^+/KDR^+$-positive cells ($BM^{CD34+/KDR+}$; pre:1.3±1.1% versus post:3.3±2.6%; *P*=0.02) and $CD34^+/CD133^+$-positive ($BM^{CD34+/CD133+}$; pre:45.5±14.8% versus post:59.8±11.9%; *P*=0.01) significantly increased with exercise. In contrast, the total number of $CD34^+$-positive cells (BM^{CD34+}) did not increase in response to exercise training (pre:0.09±0.05% versus post: 0.09±0.05%; *P*=0.95).
Conclusions – Endurance training increases the number of EPCs in patients with CHD and cardiovascular risk factors which may contribute to the atheroprotective effect attributed to regular physical activity.

1007-180 The Effect of Losartan Versus Atenolol on Circulating Adhesion Molecules in Essential Hypertension: A LIFE Substudy

Michael H. Olsen, Peter Clausen, Kristian Wachtell, Ulrik Andersen, Keld Neland, Hans Ibsen, Harriet Dige-Pedersen, Glostrup University Hospital, Copenhagen, Denmark, Rigshospitalet, Copenhagen, Denmark

Background: Hypertension and diabetes are associated with disturbances in circulating adhesion molecules. We wanted to investigate a) the relation of adhesion molecules to blood pressure and metabolic disturbances and b) the effect of a losartan vs. an atenolol based antihypertensive regime on adhesion molecules.
Methods: In 43 LIFE patients with stage II-III hypertension and electrocardiographic left ventricular hypertrophy we measured insulin sensitivity (M/IG) by a three-hour isoglycemic hyperinsulinemic clamp, ambulatory 24-hour blood pressures (BP), plasma levels of VCAM, ICAM, E-selectin and glucose and serum insulin and lipids after two weeks of placebo treatment and after one year of anti-hypertensive treatment with either an atenolol- or a losartan-based regime reducing BP equally. Identical analyses were performed in 26 age and gender matched normotensive controls.
Results: At baseline VCAM, ICAM and E-selectin was not elevated in the patients as compared to the controls. In patients, VCAM (r=0.39* and r=-0.24), ICAM (r=0.45** and r=-0.34*) and E-selectin (r=0.41** and r=-0.39*) were related to serum insulin and M/IG, but not to ambulatory or office BP or serum lipids. VCAM (484±127 mg/l to 448±97 mg/l*) and ICAM (236±46 mg/l to 217±44 mg/l*) were reduced significantly without any difference between the two groups. E-selectin decreased insignificantly in patients receiving losartan (64.5±34 mg/l to 50.7±19 mg/l) and the relative change was closely related to the relative change in 24-hour systolic BP (r=0.88***) and in serum insulin (r=0.61*) in patients receiving losartan. Although M/IG decreased in patients treated with atenolol as compared to losartan we were not able to demonstrate any significant relationship between changes in insulin sensitivity and concentrations of adhesion molecules. *P<0.05,**P<0.01,***P<0.001.
Conclusion: Circulating VCAM and ICAM decreased during anti-hypertensive treatment with losartan as well as atenolol based regimens. The decrements were independent of concomitant changes in insulin resistance, although the levels of these circulating adhesion molecules were related to insulin resistance rather than high BP at baseline.

1007-181 Oral Folic Acid Does Not Reduce Plasma Concentrations of the Endogenous Nitric Oxide Synthase Inhibitor Asymmetric Dimethylarginine in Hyperhomocysteinemic Subjects

Markus C. Stuehlinger, Bernhard Paulweber, Jan Schirnhofer, Otmar Pachinger, Olaf Stanger, University Clinic of Innsbruck, Innsbruck, Austria, Landeskrankenhaus Salzburg, Salzburg, Austria

Endothelial function is impaired in hyperhomocysteinemic subjects, however, the mechanism for endothelial dysfunction in hyperhomocysteinemia remains unclear. We could previously show that homocysteine (Hcy) inhibits NO production by accumulating asymmetric dimethylarginine (ADMA), an inhibitor of NO synthase (NOS), in endothelial cells. We also found that hyperhomocysteinemia after oral methionine leads to elevations of ADMA in humans. Accordingly a randomized, placebo-controlled, double-blind study design was chosen to investigate the effect of folic acid on Hcy and ADMA plasma concentrations.
29 hyperhomocysteinemic study subjects (16m/14f; 57±4y; Hcy>12μM) were randomized into 4 different groups: each individual was treated with either 0.4mg (n=7), 1mg (n=7) or 5mg of folic acid (n=8), or placebo (n=7) for 8 weeks. Every 2 weeks blood was drawn for measurements of Hcy and ADMA plasma concentrations. Additionally 5 healthy control subjects with normal Hcy concentrations were included to compare baseline ADMA and Hcy values.
At baseline Hcy (13.36±0.40 vs. 6.91±1.27μM, p<0.001) as well as ADMA (1.67±0.86μM vs. 0.55±0.03μM, p<0.001) plasma concentrations were significantly higher in hyperhomocysteinemic subjects. All doses of oral folate significantly reduced Hcy plasma concentration after 8 weeks of treatment: with 5mg from 13.08±0.57 to 10.30±0.95 (p=0.009), with 1mg from 12.63±0.79 to 9.88±1.45; (p=0.07) and with 0.4mg of folate from 13.94±0.75 to 10.28±0.73 (p=0.001), whereas placebo did not affect plasma Hcy (from 14.40±1.01 to 14.38±0.59; p=n.s.). ADMA plasma concentrations however were not affected by placebo (from 1.66±0.19 to 1.61±0.17; p=n.s.) or folate at any dose: with 5mg from 1.59±0.10 to 1.77±0.16, with 1mg from 1.86±0.21 to 1.98±0.30 and with 0.4mg from 1.58±0.22 to 1.56±0.20 (all p=n.s.).
In this randomized, placebo-controlled, double-blind trial oral folate caused significant reductions of plasma Hcy within 8 weeks of treatment. The decline of Hcy however was not accompanied with decrements of plasma ADMA concentrations. Our results suggest that the beneficial effects of folate on endothelial function and the NOS pathway are not mediated by ADMA.

1007-182 Aldosterone and Plasma Renin Activity Influence Plasma Plasminogen Activato Inhibitor-1 Levels in Overweight Subjects

James A. S Muldowney, III, Barbara C. Roberts, Joseph W. Covington, John A. Schoenhard, Nancy J. Brown, Douglas E. Vaughan, Vanderbilt University Medical Center, Nashville, TN

Plasminogen activator inhibitor-1 (PAI-1) is an important predictor of mortality in myocardial infarction, and serves as a key regulator of the fibrinolytic system. We have previously shown that plasma PAI-1 correlates with body mass index (BMI), plasma renin activity (PRA), and aldosterone levels in hypertensive subjects. In order to better understand the relationship between PAI-1 and these associated factors, we investigated a more diverse population of subjects. In the present study, 54 subjects were studied, (33% Male, 37% African-American, 56% hypertensive, 82% overweight or obese, mean age 49 ± 8). Height, weight, blood-pressure, plasma renin activity, aldosterone and PAI-1 were measured. The mean blood pressure of our population was 135/88 ± 15/12 mmHg, BMI 30 ± 5 kg/m^2, PRA 0.85 ± 0.65 ng Angl/ml/hr, plasma aldosterone 6.0 ± 3.4 pg/dl, and plasma PAI-1 18 ± 17 ng/ml. While BMI correlated with plasma PAI-1 in the composite group, BMI is a particularly strong predictor of plasma PAI-1 levels in low renin subjects (**R = 0.676**, *P = 0.002*). This correlation did not hold true in subjects with a PRA >/= 0.5. In addition, in overweight and obese subjects (BMI >/= 25), there is a correlation between plasma aldosterone and PAI-1 levels (**R = 0.376**, *P = 0.012*), but not in lean subjects. This relationship was gender-specific, with a strong correlation between aldosterone and PAI-1 in men(**R = 0.602**, *P = 0.008*), but not women (**R = –0.001**, *P = 0.993*). We conclude that BMI predicts PAI-1 in low renin individuals. Plasma aldosterone levels also correlate with PAI-1 levels in men and overweight individuals. Although BMI is widely recognized as a strong predictor of plasma PAI-1, clearly this relationship is influenced and confounded by gender and the relative activation state of the renin-angiotensin-aldosterone system.

POSTER SESSION

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Statin Therapy: Beyond Lipids

Sunday, March 07, 2004, 9:00 a.m.-11:00 a.m.
Morial Convention Center, Hall G
Presentation Hour: 9:00 a.m.-10:00 a.m.

1008-183 Effects of Ezetimibe, Simvastatin, and Ezetimibe-Simvastatin on Noncholesterol Sterol

Gerd Assmann, Frank Kannenberg, Wayne Weng, John Erbey, Ani John, Diane Tribble, Thomas Musliner, Leslie J. Lipka, Enrico P. Veltri, University of Munster, Munster, Germany, Merck/Schering-Plough, North Wales, PA

Background*:* Emerging interest in elevated phytosterols as a potential risk marker for coronary artery disease (CAD) is based on clinical findings in patients with hereditary lipid storage disorders (e.g. sitosterolemia) and observational studies in cohorts of CAD patients.
Methods: A post-hoc analysis of a randomized, double-blind, placebo-controlled trial of primary hypercholesterolemia patients (LDL-C 145-250 mg/dl and TG <350 mg/dl) was conducted to examine the effects of 12 weeks of daily treatment with ezetimibe (EZE) 10 mg, simvastatin (Simva) pooled doses 10-80 mg, or ezetimibe 10 mg/simvastatin pooled doses 10-80 mg (EZE/Simva) coadministration on concentrations of phytosterols (sitosterol and campesterol) and cholesterol precursors (lathosterol and desmosterol). Baseline and endpoint plasma samples of 578 patients were analyzed by GC-mass spectrometry.
Results:

EZE significantly lowered concentrations of phytosterols and increased the cholesterol precursor-lathosterol. Simva significantly lowered concentrations of cholesterol precursors but did not affect phytosterol concentrations. EZE/Simva coadministration lowered both concentrations of phytosterols and cholesterol precursors. Results for the sterol:cholesterol ratios were similar to those for concentrations, except that Simva increased ratios of phytosterol:cholesterol ratios