9:30 a.m.

875-5   Antiinflammatory and Antiangiogenetic Effect of Ramiprilat: Angiotensin Converting Enzyme Inhibition in Monocytes Prevents Their Angiotensin II- and Hypoxia-Induced Cytokine Expression by Downregulation of AT-1 Receptor Expression and NF-kappaB Activation

Alexander Schmeisser, Oliver Soehnlein, Thomas Illmer, Christoph Garlichs, Hannes Lorenz, Gerhard Ehninger, Werner G. Daniel, Ruth H. Strasser, Technical University of Dresden, Dresden, Germany, University Erlangen-Nuernberg, Erlangen, Germany

Background: There are several controversal reports regarding the effects of ACE inhibitors on the plaque angiogenesis in atherosclerosis and tumor growth. An antiinflammatory and antiangiogenic effect of ACE-inhibition might be of major relevance in acute coronary syndromes. Because the Angiotensin II (ATII)-AT1-receptor(R)- and hypoxia-derived angiogenesis is induced by supporting mononuclear cell (MNC) infiltration and angiogenic cytokine expression we examined the effects of ACE inhibition on the stimulation of Monocytes by ATII and hypoxia.
Methods: Human Mo were stimulated in vitro 1. with 100 and 500 nM ATII and 2. with hypoxia (O2:3%). In 1. Mo were pretreated with 1,5,10microM ramiprilat (Ra), AT1-R inhibitor (I) Losartan (1microM) or AT2-RI PD123,319 (1microM) and in 2. with 1,5,10microM Ra. Analysis of monocytic AT1/2-R expression was performed by western blotting, NF-kappaB by EMSA, IL-8 and MCP-1 by RT-PCR and ELISA, statistics by students t-test (sign: p<0.05). In 10 samples of advanced human atherosclerotic carotid plaques (AHP) immunohistochemic staining for ACE, IL-8 and MCP-1 was performed.
Results: In 100% of inflammatory shoulder regions of AHP colocalization of MNC-ACE with MCP-1 and IL-8 could be demonstrated. In vitro, hypoxia stimulated Mo IL-8 and MCP-1 expression was inhibited with Ra by 65+/-13% and 48+/-11% (P<0.01), respectively. Mo ATII-AT1-R induced IL-8 and MCP-1 expression was inhibited by 49+/-4% and 71+/-5% with Ra in dose-dependent manner. Ra (10microM) reduced the hypoxia- and ATII-induced NF-kappaB activation only slightly (p=0.6). But, Ra (10microM) reduced the monocyte AT1-R expression by 50+/-12% and 83+/-13% after 12 and 24h highly significant (p<0.001). The AT2-R expression remained unchanged.
Conclusion: For the first time, it could be demonstrated that antiinflammatory effects of ACE inhibition could be derived by a marked downregulation of monocytic AT1-R expression, and by an inhibition of the hypoxia-induced proinflammatory and angiogenic MCP-1 and IL-8 production. These effects of Ra might be of major relevance in atherosclerotic plaque vulnerability.

9:45 a.m.

875-6   Effect of Exercise Training in Patients With Coronary Artery Disease on Circulating Endothelial Progenitor Cells

Karsten Lenk, Volker Adams, Marcus Sandri, Atila Tarnok, Dominik Lenz, Andrej Schmidt, Dirk Scheinert, Dirk Scheinert, Gerhard Schuler, Rainer Hambrecht, University of Leipzig, Heart Center, Leipzig, Germany

In patients with coronary artery disease (CAD) exercise training (ET) is regularly associated with a decrease in exercise-induced myocardial ischemia. Recently it has been shown that a symptom-limited exercise test is sufficient to increase circulating endothelial progenitor cells (EPC) in patients with symptomatic CAD. Until now, however less is known about the impact of regular ET on the amount of circulating EPCs. Aim of this study was to investigate the effects of ET on the number of EPCs in patients with symptomatic CAD. To define the role of ischemia during ET we also analyzed the effect of treadmill training in patients with peripheral artery occlusive disease (PAOD) beyond the ischemic threshold. 14 patients with CAD and 14 patients with PAOD were randomly assigned either to (ET) or an inactive control group (C). Ergometer and treadmill training was performed 6 times daily for a period of 4 weeks. The concentration of EPCs was analyzed by FACS-analysis of CD34+/KDR+ cells. In cell culture the amount of EPCs was determined by analyzing Di-LDL and FITC-Lectin double positive stained cells using Laser Scanning Cytometry. After 4 weeks of ET circulating EPCs showed no significant differences in IP in comparison to baseline levels (cell culture: 1.6±0.5fold increase ; n.s. vs. baseline and C ; FACS: 1.3±0.3fold increase , n.s. vs. baseline and C). In PAOD patients regular ET leads to a significant increase of EPC during the training period with a peak after 3 weeks (cell culture: 8.2±3.4fold increase ; p<0.01 vs. baseline and C ; FACS: 3.2±1.8fold increase , p<0.01 vs. baseline and C). In conclusion, the present study demonstrates that exercise training in symptomatic CAD patients below the ischemic threshold is insufficient to induce an increase in the number of circulating EPCs. In contrast treadmill training in PAOD patients beyond the ischemic threshold seems to be a potent trigger for an EPC release.

ORAL CONTRIBUTIONS

876   Aggressive Lipid Intervention: Beyond Low-Density Lipoprotein Cholesterol

Wednesday, April 02, 2003, 8:30 a.m.-10:00 a.m.
McCormick Place, Room S101

8:30 a.m.

876-1   Aggressive Treatment Aimed at Raising High-Density Lipoprotein Cholesterol in Stable Patients With Angiographically Evident Coronary Disease Prevents Stenosis Progression and Reduces Cardiovascular Events

Richard A. Krasuski, Ara M. Maranian, Edwin J. Whitney, Bradley E. Personius, B. Greg Brown, Antonio M. Gotto, Jr., Wilford Hall Medical Center, San Antonio, TX

Background: Overwhelming evidence supports that lowering low-density lipoprotein cholesterol (LDL-c), particularly with statins, leads to a reduction in cardiovascular events. High-density lipoprotein cholesterol (HDL-c), despite being a stronger predictor of events in epidemiologic studies, has been mostly neglected as the focus of therapy.
Methods: We performed a randomized double-blind, placebo-controlled trial assessing the effect of gemfibrozil, niacin, and cholestyramine on a baseline of aggressive dietary and lifestyle intervention. Patients <76 years of age with angiographically-evident coronary disease in the absence of recent instability were consented and followed over a period of 30 months. Quantitative angiography was performed at baseline and at the completion of the study.
Results: In the 143 randomized patients, mean age was 63 ± 7 years and 8% were women. Baseline characteristics included total cholesterol 195 ± 31 mg/dl, LDL-c 127 ± 27 mg/dl, HDL-c 34 ± 6 mg/dl, triglycerides 169 ± 82 mg/dl, systolic blood pressure 139 ± 16 mm Hg, and fasting blood sugar 80 ± 14 mg/dl. No difference in baseline characteristics was seen between the 2 groups. Median weight loss during the study was 1% in the placebo group and 4% in the drug group, p<0.001. Total cholesterol increased by 3% in the placebo group but was reduced by 16% in the drug group, p<0.001. LDL-c increased by 21% in the placebo group but dropped by 5% in the drug group, p<0.001. HDL-c increased by 2% in the placebo group and by 37% in the drug group, p<0.001. Triglycerides increased by 3% in the placebo group but were reduced by 45% in the drug group, p<0.001. Fasting blood sugar increased by 8% on placebo group and by 18 % on drug therapy, p=0.006. Focal coronary stenosis increased by 1% on placebo but decreased by 1% in the drug group, p=0.043. A combined endpoint of unstable angina, transient ischemic attack and stroke, percutaneous intervention, coronary bypass, or death was reached in 19 placebo patients and 9 drug patients, p=0.039.
Conclusion: A combination of agents aimed at increasing HDL-c dramatically improves cholesterol profiles, arrests angiographic progression, and results in a significant reduction in cardiovascular events.

8:45 a.m.

876-2   Statin Therapies for Elevated Lipid Levels Compared Across Dose Ranges to Rosuvastatin: Low-Density Lipoprotein Cholesterol and High-Density Lipoprotein Cholesterol Results

Peter H. Jones, for the STELLAR Study Group, Baylor College of Medicine, Houston, TX

Background: The primary objective of this large, multicenter trial was to compare the effects of rosuvastatin (RSV) versus atorvastatin (ATV), simvastatin (SIM), and pravastatin (PRA) across dose ranges on percent changes in low-density lipoprotein-cholesterol (LDL-C).
Methods: After discontinuation of lipid-lowering drugs and a 6-week dietary lead-in period, 2431 adults with hypercholesterolemia (LDL-C≥160 mg/dL and <250 mg/dL; triglycerides <400 mg/dL) were randomized to 15 parallel, open-label treatments for 6 weeks. Treatments in this trial (4522IL/0065) included RSV 10, 20, 40, or 80 mg; ATV 10, 20, 40, or 80 mg; SIM 10, 20, 40, or 80 mg; and PRA 10, 20, or 40 mg. Prospectively planned analyses for each lipid included log-dose-response curve analyses and 25 selected pair-wise comparisons of RSV doses with corresponding or higher doses of comparators (with a statistical significance level adjustment to 0.002 to account for multiple comparisons).
Results: The table shows dose-to-dose comparisons. Baseline LDL-C means were 187 to 194 mg/dL. The curves analysis showed that RSV produced a mean 8.2% greater LDL-C reduction (p<.001) than ATV across the dose ranges. Greater differences in LDL-C reduction were observed between RSV and PRA or SIM.