two groups as 62 nondiabetic and 51 diabetic patients. Simvastatin 10 mg/d was given for 24 weeks . Fasting glucose (FG), glycohemoglobin (HbA1c) fasting insulin (FI), total cholesterol (total-c), high density lipoprotein-cholesterol (HDL-c), triglyceride and low density lipoprotein-cholesterol (LDL-c) were measured before and after treatment. IR and βcf are assessed with homeostasis model assessment method (HOMA). The formulas are as follows; IR = FI x FG / 22.5 and βcf = 20 x FI /FG-3.5, where FG (mmol/lt) and FI (mU/l).
Results: Total-c and LDL-c levels were significantly reduced in both groups. IR non-significantly increased in nondiabetic patients (3.33±2.1 vs 3.40±2.5; p>0.05), and non-significantly improved in diabetics patients (7.43±13.9 vs 5.52±5.3; p>0.05). βcf increased in both groups (180±100 vs 241±168; p<0.005 and 62±69 vs 106±90; p<0.005) respectively. In order to rule out possible positive effects of antidiabetic therapy, results of 31 diabetic patients whose oral antidiabetic drug (OAD) doses are increased (group I) compared with 82 patients who are use only simvastatin or OAD doses were not changed (group II). Total -c and LDL -c levels reduced in both groups. IR changed with treatment from 3.55 ±3.3 to 3.67±3.4; p<0.0005 in group I and from 9.50±17.1 to 6.20±5.7; p<0.0005 in group II, respectively. No correlations were found between change in IR with changes in total-c, LDL-c and triglyceride levels.
Conclusion: Simvastatin treatment has neither negative nor positive effects on IR and has positive effect on βcf in diabetic and non-diabetic hypercholesterolemic patients.

1059-76 Simvastatin Lowers C-Reactive Protein by 14 Days: An Effect Independent of That on LDL Cholesterol

Julie K. Plenge, Kathleen M. Weil, Gary Grunwald, Jeri Forster, Paul Poirier, Robert H. Eckel, *The University of Colorado Health Sciences Center, Denver, Colorado.*

Introduction: Highly sensitive C-Reactive Protein (hsCRP) is an independent predictor of myocardial infarction. HMG Co-A reductase inhibitors (statins) decrease hsCRP levels over time. The early response of hsCRP to statins is unknown. The aims of this study were: 1) to determine the rate at which hsCRP levels change after initiation of simvastatin, and 2) to determine whether changes in hsCRP levels occur independently of change in LDL.
Methods: Cross-over, double-blind study of 40 subjects with elevated LDL. Subjects were randomly assigned to one of two groups: (A) simvastatin followed by placebo or (B) placebo followed by simvastatin (each for 14 days). HsCRP levels were measured on days 0, 1, 3, 7, and 14. Levels of acute phase reactants lipoprotein(a) (Lp(a)) and fibrinogen were also measured. Fasting LDL was calculated at baseline, day 7 and day 14.
Results: Baseline levels of hsCRP were not significantly different between groups A and B (group A log(hsCRP) = 0.83+/-0.15 [mean +/- SEM] versus group B log(hsCRP) = 0.72 +/- 0.15 (p=0.34)). Baseline LDL levels were similar (163 +/- 44 in group A and 166 +/- 38 in Group B). After initiation of simvastatin mean log(hsCRP) fell to 0.71 +/- 0.15 at day 7 (p=0.57) and to 0.52 +/- 0.15 at day 14 (p=0.011). LDL cholesterol fell with simvastatin treatment (108 +/- 31at day 7 vs. 98 +/- 31 at day 14). By repeated measures ANOVA, there was a significant treatment-time effect of simvastatin on hsCRP over 14 days(F=2.50, p=0.011). This effect was not seen with placebo. There was no correlation between treatment-related change in LDL and change in hsCRP. Fibrinogen levels did not change significantly. Lp(a) increased slightly (p=0.03).
Conclusions: While recent studies have shown that statins decrease hsCRP over the long term, this is the first study to show that the effect of simvastatin on hsCRP occurs early in the treatment course. The effect on LDL cholesterol occurs even earlier (7 days) than the fall in hsCRP (14 days), but the change in hsCRP is independent of the change in LDL cholesterol. In addition, this early effect on hsCRP appears to occur independently of changes in other acute phase reactants.

POSTER SESSION

1080 Endothelial Function: Effects and Effectors

Monday, March 18, 2002, 9:00 a.m.-11:00 a.m.
Georgia World Congress Center, Hall G
Presentation Hour: 9:00 a.m.-10:00 a.m.

1080-82 Activity of Endothelin-1 Is Increased in the Forearm Resistance Vessels of Subjects With Hypertension

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Background: Endothelin-1 (ET-1) is a potent vasoconstrictor peptide produced by endothelial cells. ET-1 has been postulated to increase vasoconstrictor tone in subjects at risk for atherosclerosis, particularly those with hypertension. Vasoconstriction to ET-1 is mediated principalty by the endothelin A (ET_A) receptor on vascular smooth muscle cells. Accordingly, we used an ET_A specific antagonist, BQ-123 to test the hypothesis that ET-1 increases vascular resistance selectively in subjects with hypertension compared to people with other risk factors.
Methods: BQ-123 was infused at 100 nmol/min for 80 minutes into the brachial artery of 10 subjects whose only risk factor was hypertension (mean arterial pressure = 106± 15; mean±SD), 12 subjects with only dyslipidemia (total cholesterol = 273±22 mg/dl), 10 active smokers (32±15 pack years), and 11 healthy, age-matched controls. None of the subjects had clinical evidence of atherosclerosis. Forearm blood flow (FBF) was measured by venous occlusion plethysmography.
Results: BQ-123 induced significant vasodilatation in the hypertensive subjects compared to controls. FBF increased by 38% from 2.1±0.7 to 2.9±1.2 ml/dl/min (p<0.05). FBF did not change in response to BQ-123 in subjects with dyslipidemia, smokers or healthy controls. Similarly, BQ-123 reduced forearm vascular resistance only in hypertensive subjects (from 55.9±19.8 to 40.4±13.9 mm Hg per ml/dl/min).
Conclusion: ET-1, acting via the ET_A receptor, increases the tone of resistance vessels in subjects with hypertension, but not in subjects with dyslipidemia or smokers. These results indicate that endothelin contributes to the pathophysiology of hypertension. Endothelin antagonists may be beneficial for the treatment of hypertension, but not for vascular dysfunction associated with other risk factors for atherosclerosis.

1080-83 Heme Oxygenase Antagonism Inhibits Endothelium-Dependent Vasodilation in the Normal Human Forearm Circulation

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Background: Carbon monoxide (CO) mediates smooth muscle relaxation via generation of cyclic GMP in a manner analagous to nitric oxide. CO is generated from heme in endothelial cells by the constitutive enzymatic action of heme oxygenase. We hypothesized that endogenous CO contributes to endothelium-dependent vasomotor function in the human forearm circulation.
Methods: In 5 healthy volunteers, we studied the effect of the heme oxygenase inhibitor tin mesoporphyrin (SNMP, 112.5nmol/min) on endothelium-dependent forearm vasodilation by acetylcholine (7.5 - 30 μg/min). In a further 10 healthy subjects, the effect of SNMP on the response to acetylcholine was also determined during inhibition of nitric oxide synthase and cyclooxygenase by L-NMMA (4μmol/min) and aspirin (1g by mouth), respectively. Sodium nitroprusside (1.6-6.4 μg/min) was also administered before and after SNMP to test endothelium-independent function. Drugs were infused into the brachial artery and forearm blood flow (FBF) and vascular resistance (FVR) were measured by plethysmography.
Results: SNMP did not affect basal forearm vasomotor tone or the dose response curve to acetylcholine. When the study was performed during co-administration of L-NMMA and aspirin, basal FBF and FVR were also unchanged after SNMP. However, the FBF and FVR dose response curves with acetylcholine (ANOVA p=0.025 and p=0.026, respectively), but not with sodium nitroprusside (ANOVA p=0.22 and p=0.29 respectively) were attenuated after SNMP; thus FVR was 21% greater at the peak dose of acetylcholine after SNMP.
Conclusions: Our findings suggest that inhibition of heme oxygenase attenuates endothelium-dependent but not -independent vasodilation in the normal human forearm microvasculature after inhibition of nitric oxide and prostanglandin synthesis. Thus, CO may contribute to endothelium-dependent vasodiiation in conditions characterized by reduced nitric oxide bioavailability.

1080-84 Endothelial Dysfunction Accelerates Hypertensive Evolution

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Background: Although hypertension has great impact to develop cardiovascular diseases, evolutional mechanism of hypertension remains partially clarified. On the other hand, endothelial dysfunction (ED) is thought to affect atherogenic processes, there has been little clinical evidence for the relationship between clinical manifestation of cardiovascular disease and ED. This study investigated whether noninvasively evaluated ED has clinical influences on hypertensive evolution (HTE). **Methods:** Vasomotor dysfunction was graded by noninvasively measured reactive changes in lumen diameter of right brachial artery following transient occlusion for 5 minutes (FMD; flow-mediated endothelium-dependent vasodilation), and after sublingual administration of (300μg) glyceril trinitrate (TNG; endothelium-independent vasodilation) using high resolution ultrasonography in consecutive 365 ambulatory patients who underwent the above vasomotor function tests. The enrolled patients were categorized into three groups according to the values of FMD and TNG, and their blood pressure was followed-up for no less than 36 months. We prospectively followed-up HTE defined as more than two stage upgrade of hypertension defined by world health organization or new administration of an antihypertensive agent. **Results:** For a mean follow-up period of 54 months (range; 36 to 73) with 100% follow-up, the patients with severe endothelial dysfunction (FMD<4%; Group-L, n=121), more frequently manifested HTE [Group-L versus Group-M with mild endothelial dysfunction (4%≤FMD<8%, n=121) plus Group-H with preserved endothelial function (FMD 8% or more, n=123): 28 (23.1%) versus 12 (9.9%) plus 5(4.2%), p<0.001, by Kaplan-Meier analysis]. There was no significant association between TNG and HTE. Cox proportional hazard model analysis showed that severe endothelial dysfunction (odds ratio=3.29, 95%confidential interval; 1.57-7.28, p<0.01) was independently associated with future HTE. **Conclusion:** These results suggest noninvasive ultrasonic evaluated endothelial dysfunction is a great practical predictor for future hypertensive evolution.

1080-85 Physical Activity in Patients With Coronary Artery Disease: Effects on Endothelial Function and NAD(P)H Oxidase-Expression

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For patients (pts) with coronary artery disease (CAD), coronary endothelial function, and particularly nitric oxide-mediated vasodilation are clearly enhanced by physical exercise training (ET). The molecular basis for this improvement is still unclear. To address this issue we examined the effect of ET on endothelial function of the left internal mammarial artery (LIMA) in vivo and in vitro and determined whether ET affects the expression level of the subunit gp91phox of the NAD(P)H oxidase, which is known to play an important role in O2-. formation.
Thirty-two symptomatic pts with CAD, who were scheduled for elective coronary artery