	Sham (n=10)	Radiated (n=12)	p Value
Plaque Area (mm^2)	1.05 ± 0.6	1.6 ± 0.5	< 0.02
Macrophages (% RAM 11)	14.6 ± 9.8	35.1 ± 9.1	< 0.0001
SMC (% α-actin)	19.9 ± 15.2	8.7 ± 10.6	< 0.001
MMP-1 (% area)	41.2 ± 23.4	26.5 ± 9.4	0.01

Conclusion: In this atherosclerotic rabbit model, radiation was associated with decreased smooth muscle cell density, increased infiltration of macrophages and increased plaque burden. Metalloprotease 1 was also over-expressed in the radiated arteries. Thus, special care should be taken in hypercholesterolemic patients treated with VBT.

1152-126 Angiotensin Converting Enzyme Inhibitor Therapy Reduces the Vascular Oxidative State in Normotensive Patients With Newly Diagnosed Type 2 Diabetes Mellitus

Bobby V. Khan, Rekha G. Menon, Stamatios Lerakis, Emory University School of Medicine, Atlanta, GA

Background: The increase in the vascular oxidative state and production of reactive oxygen species are significant in the pathogenesis of atherosclerosis. The therapeutic use of renin-angiotensin system (RAS) antagonists, including ACE inhibitors, results in a significant reduction of cardiovascular events in patients with coronary artery disease. Recent outcome studies demonstrate that these agents may have vascular benefits independent of blood pressure reduction. Methods: We followed 33 normotensive subjects (female:18, male:15) with newly diagnosed (less than one year) type II diabetes mellitus. These patients were under fair metabolic control (glycosylated hemoglobin < 7.5%) and with normal renal function and no evidence of overt proteinuria. The subjects were started on the ACE inhibitor quinapril 20 mg/day for 4 weeks. Serum samples were drawn. The erythrocyte superoxide dismutase (E-SOD) activity and lag time for LDL oxidation were measured.
Results: Treatment with quinapril significantly increased E-SOD activity (pre: 543±70; post: 812±98 U/gHb, p<0.05). Furthermore, quinapril therapy significantly enhanced lag time for LDL oxidation in these subjects (pre: 63±11; post: 88±10 sec, p<0.05), suggesting an increased resistance of LDL modification in the vasculature. No changes in systolic blood pressure (pre: 118±11; post: 116±8 mm Hg, NS), LDL cholesterol, or metabolic control were noted with quinapril therapy. Conclusions: Administration of ACE inhibitor therapy improves the vascular oxidative state in patients with newly diagnosed Type II diabetes mellitus. Furthermore, these effects appear to be independent of blood pressure reduction or changes in the metabolic control of diabetes mellitus.

1152-127 Roxithromycin Inhibits Plaque Formation Induced by Recurrent Lipopolysaccharide Inflammation In Vivo

Markus G. Engelmann, Constanze V. Redl, Sigrid Nikol, University of Munich, Klinikum Grosshadern, Munich, Germany, University Hospital, University of Muenster, Muenster, Germany

Aims: Recently we demonstrated increased plaque formation occurred after repetitive LPS application in cholesterol-fed animals. Thus, repeated local infection by microorganisms may contribute to atherogenesis through specific bacterial products such as LPS. In the current study we assessed the effect of macrolide treatment on prevention of LPS-induced atherogenesis in the absence of a bacterial infection.
Methods and results: Rabbits (n=14) were fed a cholesterol-enriched diet. All animals were treated with a single perivascular injection of bacterial lipopolysaccharide (LPS) placed next to auricular, carotid and femoral arteries and sodium chloride placed next to the contralateral arteries with repeated perivascular injections over 90 days. 5 days after initial LPS or sodium chloride treatment the animals were randomized to two groups. Group A animals were treated with roxithromycin 40 mg/kg/d, group B animals served as control. Vascular tissues (n=41 treated segments) were analyzed using morphometry at histology, and using immunohistochemistry to detect macrophages, lymphocytes, vascular smooth muscle cells. Repeated LPS application resulted in significant plaque formation compared with control (Group B, plaque-area index 0.122±0.05 vs 0.029±0.02, p=0.02). The plaque induction effect of LPS was inhibited by long term roxithromycin treatment (Group A, plaque-area index 0.045±0.02, LPS treatment, vs 0.017±0.01, control, p=0.049).
Conclusion: The significant increase in plaque formation after repeated perivascular LPS application in cholesterol-fed animals can be inhibited by long term treatment using roxithromycin. The anti-inflammatory effect of macrolides may contribute to reduced atherogenesis through specific bacterial products such as LPS.

1152-128 Enhancement of Inhibitory Effects of Glycoprotein IIb/IIIa Antagonists in Patients With Diabetes: Effects of Glycation on the Kinetics of Fibrinogen Binding

Friederike K. Keating, Burton E. Sobel, David J. Schneider, University of Vermont, Burlington, VT

Background: Glycoprotein (GP) IIb-IIIa antagonists reduce subsequent cardiac events to a greater extent in patients with diabetes. To identify mechanisms potentially responsible, we characterized inhibitory effects of GP IIb-IIIa antagonists and the kinetics of fibrinogen binding to platelets from patients with and without diabetes.
Methods: Blood was incubated with tirofiban or eptifibatide in vitro for 15 minutes. The capacity of platelets to bind fibrinogen was determined with the use of flow cytometry. Kinetics of binding of I^{125}-labeled fibrinogen to platelets were characterized in response to 10 μM ADP. Glycation of platelet membrane proteins was determined with the fructosamine assay. Results were compared in patients with HbA1c ≥ 6.5% (diabetes), and those with HbA1c < 6.5% (no diabetes).
Results: The capacity of platelets to bind fibrinogen was inhibited to a greater extent by either tirofiban (50 ng/ml) or eptifibatide (1.5 μg/ml) in blood from 34 patients with compared with 38 without diabetes. Tirofiban inhibited fibrinogen binding by 67 ± 17 % in blood from patients with and by 53 ± 19 % in blood from those without diabetes (p = 0.002). Eptifibatide inhibited fibrinogen binding by 64 ± 21% in blood from patients with and by 52 ± 23% in blood from those without diabetes (p = 0.024). Total stimulated binding of fibrinogen assessed with the use of flow cytometry or I^{125}-fibrinogen was similar 10 minutes to 60 minutes after addition of ADP. By contrast, after 5 minutes, platelets from patients with diabetes bound 39% less I^{125}-fibrinogen (% bound I^{125}-fibrinogen, diabetes = 0.44 ± 0.22, n=11; no diabetes = 0.72 ± 0.31, n=10; p = 0.03). Increased platelet membrane protein glycation was seen with samples from patients with diabetes.
Conclusions: Greater clinical benefits associated with GP IIb-IIIa antagonists in patients with diabetes appear to reflect augmented inhibitory effects in those with diabetes. The augmentation is mediated, at least in part, by glycation of membrane proteins that slows the rate of binding of fibrinogen.

1152-129 Identification of Apoptosis-Inducing Factor Expression in Human Coronary Artery Endothelial Cells and Its Upregulation by Ox-Low-Density Lipoprotein

Wenquang Zhang Madhu Shokeen, Dayuan Li, Jawahar L. Mehta, University of Arkansas for Medical Sciences, Little Rock, AR, Central Arkansas Veterans Healthcare System, Little Rock, AR

Background: Apoptosis-inducing factor (AIF) is a potent caspase-independent pathway of cell death, initially characterized in HeLa cells (Nature 1999; 397:441-6). Since caspase inhibitors do not completely block apoptosis in human coronary artery endothelial cells (HCAECs), we hypothesized that AIF may be another pathway of apoptosis in these cells. This study was designed to examine the presence of AIF in HCAECs and its regulation by ox-LDL.
Methods & Results: Cultured HCAECs were pre-treated with ox-LDL in different concentrations (0-50μg/ml) and for different time points (1-24 h). Western blot analysis was used to determine AIF expression using anti-human AIF goat antibody. Reverse transcription-polymerase chain reaction with β-actin as internal standard was performed (primers: sense-5'-GGATCCTGGGGCCAGGGTACTGAT-3' and antisense- 5'-CTCGGGGAAGAGTTGAATCACTTC-3'). We also sequenced AIF gene by ABI 377 DNA Sequencer. In the resting cells, faint but distinct AIF bands were detected in all HCAEC preparations. The gene sequence had 99% homology with neuronal and HeLa cell AIF gene. Ox-LDL treatment of HCAECs cells significantly induced the expression of AIF (mRNA and protein). Exposure of HCAECs cells to 50μg protein/ml ox-LDL resulted in maximal increase. Induction of expression was evident at 1 h, and became maximal at 24 h. Treatment of HCAECs with actinomycin-D blocked ox-LDL-mediated increase in AIF expression. Z-VAD.fmk, the inhibitor of caspase did not affect the expression of AIF induced by ox-LDL.
Conclusions: This study shows that HCAECs express AIF, and ox-LDL upregulates the expression of this novel pathway of cell death.

1152-130 Increased Concentrations of Interleukin-1 Receptor Antagonist Associated With Diabetes Mellitus and in the Vicinity of Coronary Plaques: A Sensitive Marker of Inflammation

Atul Aggarwal, David J. Schneider, Edward F. Terrien, Deborah A. Whitaker, Burton E. Sobel, Harold L. Dauerman, University of Vermont, Burlington, VT

Background: Inflammation portends adverse outcomes after percutaneous coronary interventions (PCI). Interleukin-1 receptor antagonist (IL-1Ra) accompanies release of interleukin-1 by macrophages associated with atherosclerotic plaques. Interleukin-1 stimulates release of interleukin-6 (IL-6) and C-reactive protein (CRP). To determine whether local inflammation could be detected in coronary blood, the concentrations of IL-1Ra, IL-6, and CRP were measured in blood simultaneously from the coronary and femoral arteries.
Methods: Concentrations of CRP (μg/ml), IL-6 (pg/ml), and IL-1Ra (pg/ml) were determined by ELISA in blood obtained in 75 patients before PCI from the femoral artery and from a guide catheter after engagement of the culprit coronary artery. Results were compared with the use of paired Student's t-tests.
Results: The majority (88%) of the patients studied had acute coronary syndromes (ACS), and 36% had elevation of cardiac markers. Despite substantial inter-individual variability, IL-1Ra was consistently greater (by 50) in coronary compared with peripheral blood (coronary = 595±388, peripheral=545±378; p=0.003). IL-1Ra was greater in coronary blood from those with marker positive ACS (by 47), marker negative ACS (by 48), and stable symptoms (by 44). Similar concentrations of CRP (coronary = 9.0±15, peripheral=9.5±14; p=0.4) and IL-6 (coronary = 6.4±9.9, peripheral=6.9±10; p=0.1) were seen in coronary and peripheral blood. The concentration of IL-1Ra was greater in patients with diabetes (n=21), both in coronary blood (diabetes = 748±492, no diabetes = 538±325; p =0.02) and peripheral blood (diabetes = 709±510, no diabetes = 482±294; p =0.02).
Conclusions: Concentrations of IL-1Ra are greater in blood obtained from the culprit coronary artery and in samples from patients with diabetes mellitus. IL-1Ra may be useful for detecting and assessing the magnitude of local inflammation associated with culprit lesions. Greater concentrations of IL-1Ra in patients with diabetes mellitus suggests a heightened inflammatory state that may contribute to accelerated atherogenesis in diabetes.