APV by acetylcholine (10 microg/kg/min) injection into MA. The endothelium-independent vascular function (EDVF) was determined as a ratio of basal to peak of APV by nitroprusside (10 microg/kg/min) injection into MA. Simultaneously, the plasma isoprostane F2alpha-Ill was measured by ELISA kit (Oxford Biomedical). Results: The infusion of isoprostane F2alpha-Ill significantly attenuate EDVF in CH rabbits (1.8 ± 0.3 vs. 2.3 ± 0.1, p < 0.01). The treatment by ramipril can improve the EDVF in CH rabbits (3.8 ± 1.2 vs. 2.5 ± 1.1, p < 0.05). There was no significant difference in the EDVF among the four groups. The plasma isoprostane F2alpha-Ill levels in CH or CH + APV was significantly higher than NL rabbits (884 ± 44, 858 ± 59 vs. 258 ± 17 ng/ml, both p < 0.01). Conclusion: This study suggested that isoprostane F2alpha-Ill synthesis induced by experimental hypercholesterolemia may be due to impaired endothelial function in rabbits. This effect may be due to TXA2 receptor stimulation.

Differential Effects of Cyclooxygenase and Nitric Oxide Inhibition on Endothelium-Dependent Responses in Coronary Arteries From Juvenile and Adult Male Pigs

Methods: Rings from right coronary artery with and without endothelium from 6 juvenile (2-3 mo; testosterone 67 ± 17 mg/dL) and 8 adult (2-6 mo; testosterone 625 ± 148 mg/dL) male pigs were suspended in organ chambers for measurement of isometric force. During contractions to prostaglandin F2alpha (50 nM), cumulative concentration-response curves to UK-4, 14, 204 (α-adrenergic agonist) and bradykinin (50 nM) were obtained in the absence and presence of either indomethacin or indomethacin plus β2-agonist (L-NMMA) inhibited nitric oxide and nitric oxide synthase, respectively. Blood was collected for measurement of nitric oxide (NO).

Results: Plasma NO was significantly higher in juvenile compared to adult males (48.7 ± 28.3 vs. 16.8 ± 6.7 μMol/L, p < 0.0001). UK-4, 14, 204 caused similar concentration-dependent relaxations only in rings with endothelium from juvenile and adult pigs. With indomethacin, relaxations were significantly enhanced in arteries from adult pigs (EC50 = 7.9 ± 0.27 μMol/L) and reduced in arteries from juvenile pigs (EC50 = 6.7 ± 0.37 μMol/L, p = 0.02). L-NMMA significantly inhibited relaxations in arteries from both groups. Relaxations to BK also were similar in rings with or without indomethacin from juvenile and adult pigs. In arteries from juvenile but not adult pigs, indomethacin caused a rightward shift of the dose response curve (p = 0.08). Whereas, L-NMMA in the presence of indomethacin caused significant rightward shift of dose-response curve (p < 0.01) in arteries from adult but not juvenile pigs.

Conclusion: Endothelium-dependent responses are selectively modulated by cyclooxygenase and nitric oxide inhibition in coronary arteries from male pigs. At immaturity, inhibition of cyclooxygenase reduces relaxations which is reversed with maturation. Nitric oxide synthase is increased with maturity and associated with relaxations to BK. Shifts from inhibition to contractile prostanoids and decreases in plasma NO may be related to production of testosterone.

Short-Term Therapy With Gatifloxacin or Azithromycin Prevents the Acceleration of Atherosclerosis After Infection With Chlamydia Pneumoniae in a Rabbit Model but Does Not Eradicate the Organism From Plaque

Background: Chlamydia pneumoniae (Cpn) is associated with atherosclerosis in human and animal studies, and short-term (5-7 months) antibiotic therapy has prevented Cpn-induced atherosclerosis in rabbits. However, short-term antibiotic therapy has not demonstrated lasting clinical benefit in recent secondary prevention trials. It is proposed that these poor long-term results may be due to inability of the antibiotic to eradicate the organism. Both azithromycin (A) and gatifloxacin (G) are agents presently being tested for the secondary prevention of atherosclerosis. Whether either is able to eradicate Cpn from atherosclerotic plaque is unknown.

Methods: Forty-five rabbits received a 2.5% dietary supplement of cholesterol and were randomized 2:1 to Cpn infection or placebo and then randomized 1:1 to A or 20 mg/kg/day X 1 week followed by 30 mg/kg twice weekly for 6 weeks, G 50 mg/kg/day for 7 weeks, or placebo. One untreated rabbit died spontaneously, and the rest were euthanized 3 months after initial infection. Blinded sections of the aortas were examined to calculate plaque percent area stenosis (PAS) (plaque area / total area within the internal elastic lamina). The presence of Cpn within aortic sections was evaluated by direct immunofluorescence (DIF) (Bartels).

Results: PAS was greater for infected, untreated arteries (39±12%) than the other groups (non-infected = 21±12%, infected + A = 20±11%, infected + G = 22±14%, all p-values <0.05 vs. infected-untreated). UT was positive in the aortas of 1/4 infected, 1/6 infected A, and 5/10 infected G rabbits. Conclusion: Although a seven-week course of either antibiotic significantly prevented Cpn-induced atherosclerosis in the rabbit, neither was able to eradicate the organism by three months. This finding may help to explain the disappointing long-term results in recent clinical trials. We propose that the differences in microbial therapy may be required to eradicate Cpn and provide lasting clinical benefit in the setting of primary or secondary prevention for atherosclerosis.

Comparison of Effect of Thiazolidinediones on Atherosclerosis in Apolipoprotein E-Deficient Mice

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Background: Thiazolidinediones are peroxisome proliferator-activated receptor-gamma agonists and are used to improve insulin resistance in type 2 diabetes mellitus. It is controversial whether thiazolidinediones promote or inhibit atherosclerosis in vivo. The purpose of this study is to compare the effect of thiazolidinediones on atherosclerosis in apolipoprotein E- (apoE)-deficient mice. Methods: At 4 weeks of age, male apoE-deficient mice were weaned from mother and fed a powdered 2-C-freon diet alone (control group) or Cpn-infected (Cpn+) or A (180 mg/kg) or G (240 mg/kg) or placebo. Results: There were no significant differences among the 4 groups in body weight, fasting blood sugar or HDL levels at 24 weeks. The atherosclerotic lesion of thiazolidinedione group was significantly smaller than that of control group (control; 0.22±0.052 mm2 vs. rosiglitazone; 0.48±0.061 mm2 vs. pioglitazone; 0.52±0.046 mm2, or glibenclamide; 0.62±0.074 mm2, p < 0.05). Conclusion: Thiazolidinediones have a protective effect on atherosclerosis in apoE Deficient mice, whereas pioglitazone and rosiglitazone do not.

The Cardiac Peptide BNP is Superior to ANP and the Renally Derived Peptide Urokinase in Enhancing Renal Function in Overt Experimental Congestive Heart Failure

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Background: Recent studies have reported that improving renal function is the most important predictor of survival in congestive heart failure (CHF). A hallmark of overt CHF is attenuated GMP production to ANP with renal resistance. BNP is FDA approved for the management of acute CHF and is synthesized and released by cardiomyocytes. Urokinase (Uro) is from the kidney and has been isolated from human urine with an amino acid (AA) sequence identical to ANP except for N-terminal extension of four AA residues. Studies have reported that the cardiac peptide, BNP, results in greater renal effects as compared to ANP but to date no comparison has been made with BNP nor ANP to BNP.

METHODS: We determined the cardiac and renal hormones of equimolar infusion of (10 pmol/kg/min) ANP (n=6), BNP (n=5) and Uro (n=6) in 3 separate group of dogs with rapid ventricular pacing induced overt CHF (240 bpm for 10 days). RESULTS: BNP caused a significant increase in urinary sodium excretion with BNP (2.2±0.7 to 184±7.6 μg/min, p < 0.05) and glomerular filtration rate (GFR) (27±4 to 52±11 min/m2, p < 0.05) which were greater as compared to ANP (p < 0.05) or Uro (p < 0.05). However, there was no significant change with ANP. Cardiac filling pressures were reduced similarly in all three groups. CONCLUSION: In this model of experimental overt CHF, infusion of BNP produced greater increases in Urinary GFR compared to ANP or Uro, while ANP did not result in significant changes. These favorable renal effects were associated with increases in both plasma cGMP and urinary cGMP excretion which were similar with BNP and Uro, however there was no significant change with ANP. These studies also support the conclusion that in CHF renal resistance to natriuretics in increasing rank order is ANP>Uro>BNP. These results may have clinical implications when considering the therapeutic efficiency of these peptides in the management of overt CHF.

PROTEIN NUTRITION AND FUNCTION IN OVEFT EXPERIMENTAL CONGESTIVE HEART FAILURE

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In this study, we examine the relationships of select inflammatory mediators in the atherogenic superfamily (TNFRSF) with body mass index (BMI) and other agents. Methods: One hundred and twenty-nine stable heart transplant recipients, aged 56.7±10.1 years (mean±SD) and 77.9±42.5 months post-op, were randomized to continue on Neoral (n=64) or switch to Prograf (n=65). Comprehensive lipid profile was measured at baseline (bsl) and after 1, 3, and 6 months (6 mo). Hemostatic parameters (fibrinogen, factor VIII, von Willebrand factor) and proatherogenic markers (hsCRP, homocysteine, sICAM, sVCAM, MCP-1, TPA, PAI-1) were measured at baseline and after 6 mo. Results: The Prograf-treated group exhibited a significantly greater decrease in total cholesterol (-5.1±1.6 (bsl) versus -4.8±1.3 mmol/L (6 mo); Prograf, versus -4.8±1.5 mmol/L (6 mo): 5.3±0.67 mmol/L (6 mo); Neoral, p=0.0021). The Prograf group also yielded a significantly greater decrease in LDL-cholesterol [3.10±0.8 (bsl) versus 2.72±0.8 mmol/L (6 mo); p=0.009], and cholesterol/HDL ratio [4.7±3.1 (bsl) versus 4.15±1.36 (6 mo) p=0.017]. The decrease in cholesterol was maximal at one month post-switch. For patients treated with Prograf, the change in plasma creatinine from baseline to month 6 [mean=-2.88 ± 2.35 (6 mo)] was significantly greater than for patients who remained on Neoral [mean=1.13±4.30 (6 mo); p=0.014] (Table 1). Plasma glucose remained stable in the Prograf-treated patients [5.9±1.0 versus 6.1±1.7 mmol/L]. Conclusions: These large prospective controlled studies show that Prograf-based immunomodulation provides a significant decrease in total, LDL cholesterol and homocysteine/HDL ratio as well as an improvement in renal function. These provide a rationale for the use of Prograf in cardiac transplant patients treated with but persisting dyslipidemia.

1156-118 Elevated Soluble Tumor Necrosis Factor Receptor Levels in Nonobese Adults With the Atherogenic Dyslipoproteinemia

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Background: Human adipocyte expression and protein levels of TNF-α and TNF receptor superfamily (TNFRSF) 1A and 1B are positively correlated with body mass index (BMI) and insulin levels, and inversely correlated with adipose tissue triglyceride lipase activity. In this study, we examine the relationships of select inflammatory mediators in the atherogenic dyslipoproteinemia (ADL) and the effects of statistical therapy on soluble TNF receptors.

Methods: 60 non-smoking, normoglycemic (HbA1c ~8%) subjects participating in a randomized 8 week trial comparing statin or placebo. ADL (TG ≥1.00 mmol/L, HDL-C ≤1.04 mmol/L, VLDL ≥4.0 mg/dL) in men and ≤1.30 mmol/L in women, and/or small LDL (≤2.05 mm) was present in 42 subjects. Results: ADL subjects were younger (mean = 55.2 ± 12.9 vs 74.2 ± 9.7, p = 0.019) and had higher levels of both TNF-α (7.9 ± 18.1 vs 21.6 ± 0.5 ng/mL, p = 0.013) and TNFRSF1B (3.8 ± 0.6 vs 2.7 ± 0.5 ng/mL, p = 0.026) compared to the 18 non-ADL subjects. After adjustment for age and gender, TNF-α (p = 0.047), sTNFRSF1A (p = 0.060) and sTNFRSF1B (p = 0.024) were predictive of ADL. There were no age and gender adjusted associations between IL-6 (μg/mL) Cox-2 (μg/mL) and ADL status. Statin therapy reduced TNF-α levels more in ADL subjects (7.9 ± 18.1 to 6.2 ± 11.9 ng/mL, p = 0.088) than in non-ADL subjects (2.1 ± 0.5 ng/mL to 2.4 ± 0.2 ng/mL, p = 0.55), whereas sTNFRSF1A or sTNFRSF1B levels did not change.

Conclusions: High levels of TNF-α and TNFRSF1A and TNFRSF1B are markers of the proinflammatory state in ADL.

1156-119 Impact of Multiple Cardiovascular Disease Risk Factors on Brachial Artery Distensibility In Young Adults: The Bogalusa Heart Study

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Background: Cardiovascular (CV) disease risk factors have been associated with global abnormalities in vascular function and structure, as quantified by increased arterial stiffness. Arterial distensibility decreases with age and the extent of atherosclerosis. The subsequent rise in pulse pressure increases left ventricular work, thereby promoting left ventricular hypertrophy, a risk factor for CV morbidity. However, atherosclerosis may affect segments of the vascular tree non-uniformly. The effect of CV risk factors on focal areas of the vascular tree is less well studied. Therefore, vascular function in the brachial artery and relationships with multiple CV disease risk factors were examined.

Methods: Brachial artery distensibility was measured using pulse waveform analysis (DynaPulse 2000A, Pulse Metric, Inc.) (precision = 0.009543 mmHg−1; coefficient of variation = 14.7%; reliability = 0.58). CV risk factors evaluated included serum total and HDL cholesterol, serum triglycerides, glucose, body mass index, and systolic blood pressure. Data were collected on 803 young adults from a community-based population (42% female, 72% white, 19-37 years). Subjects were defined to have an abnormality in risk factor levels if they ranked in the highest quintile for this population (lowest quintile for HDL). The results. Approximately 30% of subjects had elevated levels in one or fewer risk factors, 18% had clusters of two risk factors, and 24% had clusters of three or more risk factors. Results showed distensibility was significantly lower in blacks than in whites (0.063 vs. 0.089 mmHg−1, p < 0.0001). An inverse linear relationship was found between distensibility and the number of risk factors clustering in an individual (r = 0.001 for trend analysis).

Conclusions: These observations show that clustering of risk factors is associated with decreased brachial distensibility in young adults and non-invasive measures of brachial artery function are useful in measuring sub-clinical vascular changes related to atherosclerosis.

1156-152 Acute Effects of Low-Density Lipoprotein Apheresis (HELP Procedure) on Cholesterol Oxidation Products and Novel Vasoactive Substances Urotensin and Relaxin


Introduction: LDL apheresis according to HELP (APH) is used to treat severe hypercholesterolemia in patients (pts.) with coronary artery disease. It has been argued that either hypercholesterolemia or extracorporeal treatment may enhance oxidative stress. Our study aimed to investigate the influence of a single APH on plasma concentrations (PC) of cholesterol oxidation products, oxidative stress, and atherothrombotic markers. Ratios of cholesterol oxidation products and advanced glycation end products in ADL were compared to healthy controls (HC).

Methods: PC of oxidized LDL (oxLDL), superoxide dismutase (CuZnSOD), relaxin and urostenol were determined by ELISA, matzolacontaepitope (MUA) by HPLC, the antioxidant capacity (ImAnOx) by photometric method. Samples of 12 pts. (6 F, 57 ± 10) were collected before (pre), immediately after (post1), and prior to the next APH (post2) after APH.

Results: Pts. with heterogeneous familiar hypercholesterolemia showed higher PC of oxLDL than healthy controls (n=30), 11.4±8.6 vs 7.7 µmol/L (p<0.05) propritional to LDL-chol. (n=8, p<0.001). APH reduced LDL-chol. and oxLDL by 52% and 45%, respectively. However, MDA declined by 30%. CuZnSOD was not changed. Relaxin and urostenol decreased significantly.

Conclusions: Single APH reduces cholesterol oxidation products as well as the vasoconstrictor urostenol without having an influence on plasma CuZnSOD. The antioxidative capacity tends to decline after APH.

1156-153 Withdrawal of Statin Treatment Abrogates Its Beneficial Effects in Humans

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Background: Statins exert beneficial effects on the vascular wall beyond cholesterol (C) lowering. Changes of these pleiotropic effects after discontinuation of statin remained unknown.

Methods: Fourteen patients (6 M, 8 F, age 50-70, treated with statins for 6 months) were enrolled. The following 5 sets of serum lipid and 3 serum markers including vascular cell adhesion molecule-1 (VCAM-1), 8-iso-prostaglandin A2 (8-iso-PGXA) for each cutout were assessed: (1) at baseline; (2) 12 weeks after stovastatin (10mg/day); (3) at day 1; (4) at day 2; (5) at day 3 after withdrawal of A.