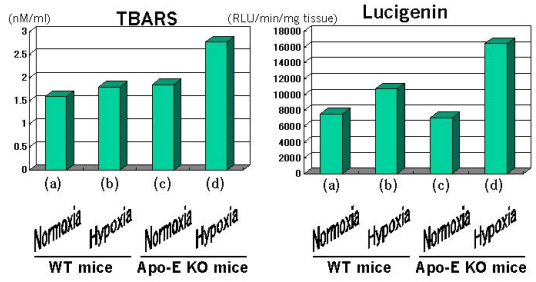
(MMP) activity and superoxide production in apolipoprotein E-knockout mice (ApoE-KO mice).
Methods and Results: Female apoE-KO mice and wild-type (WT) mice at 6 weeks of age were exposed to hypoxia (10.0±0.5% oxigen) for 3 weeks. Following 4 groups (5 mice each) were studied :(a) WT mice in normoxia, (b) WT mice under hypoxia, (c) apoE-KO mice in normoxia, and (d) apoE-KO mice under hypoxia. Low-density lipoprotein (LDL), total cholesterol (TC) and thiobarbituric acid-reactive substances (TBARS) increased in apoE-KO mice. The MMP activity by zymography and vascular superoxide production assessed by lucigenin chemiluminescence in aorta were increased both in apoE-KO mice and WT mice under hypoxia.
Conclusion: The increase of oxidative stress in aorta and serum caused by hypoxia was more prominent in atherogenic apoE-KO mice than WT mice in female.



1140-176 **Expression of HMG-1, a Novel Mediator of Inflammation, by Human Smooth Muscle Cells of Atherosclerosis and Percutaneous Transluminal Coronary Angioplasty-Restenosis Lesions**

Katsumi Inoue, Masakiyo Nobuyoshi, Kazuaki Mitsudo, Kouichi Kawahara, Ikuro Maruyama, Kokura Memorial Hospital, Kitakyushu, Japan, Kagoshima University School of Medicine, Kagoshima, Japan

Background : High mobility group-1 (HMG-1) protein is an ubiquitous and abundant chromatin component with chemoattractant effects leading to neuronal and tumor cell migration. HMG-1 is also secreted by activated macrophages (MACs), acting as a mediator of inflammation and endotoxic lethality (Wang H et al. Science, 285: 248, 1999). However, HMG-1 expression under various pathophysiological conditions of vascular lesions, is still unknown. We investigated the expression of HMG-1, particularly by smooth muscle cells (SMCs) of human atherosclerotic and restenotic coronary arteries after balloon angioplasty (PTCA).
Methods: Specimens were obtained at the time of directional coronary atherectomy of 26 restenotic (2.5 to 4 months post-PTCA) and 15 primary lesions tissue samples. All specimens were immunohistochemically stained with antibodies against HMG-1, MACs, C-reactive protein (CRP), nuclear factor kappa B (NF-KB), plasminogen, matrix metalloproteinases (MMP-3 and MMP-9) and 3 types of SMC myosin heavy chains (SM1, SM2 and SMemb).
Results: Intense HMG-1 immunoreactivity was observed in nuclei and/or cytoplasm of lipid-laden foamy SMCs and MACs from the intima of atherosclerotic plaques. HMG-1 positive SMCs expressed both NF-KB and CRP immunoreactivities. Co-expression of HMG-1 and plasminogen and/or MMPs was also observed in these SMCs by immunodouble staining. These immunohistochemical findings were clearly observed in polymorphic SMemb-positive SMCs from coronary restenotic neointima, but could not be observed in atrophic and spindle-shaped SMCs from fibrous plaques with scanty cellularity and normal medial SMCs.
Conclusions: HMG-1 is expressed by MACs and activated SMCs. Thus, it may play important roles in progression and vulnerability of primary coronary atherosclerotic lesions by enhancing inflammatory responses, and in induction of restenosis post-PTCA by increasing SMC migration.

POSTER SESSION

1141

Pharmacologic Interventions in Cardiovascular Diseases

Tuesday, March 09, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1141-189 **Limited Antiplatelet Effect of Aspirin and Clopidogrel in Patients With Stable Coronary Artery Disease: The Platelet Glycoprotein Ia/IIa and Glycoprotein IIb/IIIa Genetics and Female Sex**

Aino Lepantalo, Jussi Mikkelsson, Julio Resendiz, Pekka J. Karhunen, Riitta Lassila, Wihuri Research Institute, Helsinki, Finland, University of Tampere, Tampere, Finland

Impaired antithrombotic effect of aspirin has been suggested to be a risk factor for coronary events in stable coronary artery disease (CAD). In the current series, we have analysed functional platelet phenotypes in stable CAD patients using aspirin as well as combined aspirin and clopidogrel. These phenotypes were related to patient characteristics as well as platelet GPIa/IIa, GPIb-IX-V and GPIIb/IIIa genotype status.
We took samples from 101 patients with stable CAD on aspirin at baseline and again after a 300mg loading dose of clopidogrel. The antiplatelet effect of the treatment was studied in whole blood with PFA-100 and in platelet-rich plasma with turbidometric aggregations. We used 170s. cut-off limit for epinephrine closure time (CT-CEPI) and aggregation slope >10%/min for arachidonic acid (AA) (1.5mmol/L) as predetermined cut-off points to identify aspirin non-responders. Clopidogrel response was determined by percentual inhibition of ADP (5 µmol/L)-induced aggregation from the pre-clopidogrel value by aggregometry.
7% (AA) to 22% (CT-CEPI) of patients were defined as poor aspirin responders. 41% of these aspirin non-responders were GPIIIa A2/A1 heterozygotes as opposed to 17% among aspirin responders (p=0.02) using the PFA cut-off values. In addition, 45% of poor aspirin responders were women as opposed to 20% of aspirin responders (p=0.02) with PFA. Genotype and sex were not associated with aspirin response defined by AA-induced aggregation.
24% of patients were poor responders to clopidogrel (with the 10% cut-off). The mean inhibition of ADP-induced aggregation in GPIIIa A2/A1 heterozygotes was 16% and in GPIIIa A1/A1 22% (p=0.04). The mean inhibition was 33% in GPIa/IIa A1A1 homozygotes as opposed to 21% in other GPIa/IIa genotypes (p=0.02).
We conclude that poor response to aspirin and clopidogrel is common among individuals with angiographically proven severe CAD. Female sex and the common platelet GPIIb/IIIa receptor A2 allele are associated with a poor response to aspirin and the GPIIIa A2 allele and the rare GPIa A1/A1 genotype associate with clopidogrel response.

1141-190 **Current Enoxaparin Dosing Strategies Yield Supratherapeutic Anti-Xa Activity in Many Elderly Patients**

Frederick Leri, Stephen J. Voyce, Salvatore Scialla, William Glavich, Moses Taylor Hospital, Scranton, PA

Background: Enoxaparin (E) is used to treat a wide range of thromboembolic disorders. Therapeutic anti-Xa activity has been defined as 0.5 -1.0 IU/ml with increased hemorrhagic risk reported at anti-Xa activity ≥1.5 IU/ml. Current dosing recommendations (1 mg/kg subcutaneous every 12 hours) do not adjust for age, gender, or creatinine clearance (CrCl) >30 ml/min. Accordingly, we sought to determine anti-Xa activity in a cohort of elderly patients receiving E.
Methods: We identified 36 consecutive patients greater than 65 years old (12 male, 24 female)admitted to our institution and treated with E for various clinical indications. All patients had CrCl ≥ 30ml/min. Blood samples for peak Anti-Xa activity were obtained at steady state.
Results: Subjects had a mean age of 79 ± 6 years, mean weight of 81.3 ± 17.4 kg, mean serum creatinine of 1.0 ± 0.3 mg/dl and mean CrCl of 46 ± 11 ml/min.Fifty-nine percent of patients were treated for acute coronary syndome, 22% for atrial fibrillation and 11% for deep venous thrombosis/pulmonary embolism. The mean anti-Xa activity for these study patients was 1.3 ± 0.4 IU/ml. Anti-Xa activity was >1.0 IU/ml in 25/36 patients (69%) and >1.5 IU/ml in 10/36 patients (28%). Analysis by gender revealed 18/24 (75%) of female patients with anti-Xa activity >1.0 IU/ml and 8/24 (33%) with anti-Xa activity ≥1.5 IU/ml. Values for male patients were 7/12 (58%) and 2/12 (17%) respectively.
Conclusion: Current E dosing recommendations lead to supratherapeutic anti-Xa activity in a high percentage of elderly patients. Twenty-eight percent of elderly patients demonstrate Anti-Xa activity >1.5 IU/ml. Elderly female patients are more likely to exhibit elevated anti-Xa activity.

1141-191 **Beneficial Effect of Oral Acetylcysteine for Prevention of Contrast-Induced Nephropathy in Patients With Renal Insufficiency: A Meta-Analysis**

Ramin Ebrahimi, Christopher Wolf, Jahandar Saleh, West Los Angeles VA, Los Angeles, CA

Background: Contrast Induced Nephropathy (CIN) is a well known complication of coronary angiography and angioplasty in patients with renal insufficiency. Prophylactic use of Acetylcysteine in such patients has been reported to ameliorate CIN in multiple small studies. The purpose of this report is to evaluate the cumulative evidence from reported

studies for this therapeutic effect of acetylcysteine.
Methods: The initial electronic search queried both the Medline database and the Cochrane Library for the perior of January 1996 ttrough May 2003. Furthermore a manual inspection of articles published in New England Journal of Medicine, Circulation, Journal of the American College of Cardiology was conducted for the years 1998-2002. Bibliographies of the identified articles were searched for additional pertinent articles as well as the bibliographies of three prominent cardiovascular textbooks. A meta-analysis of the data meeting specific criteria for inclusion was performed.
Results: Five studies with a total of 641 patients were identified that evaluated the effect of oral prophylactic administration of acetylcysteine on CIN in randomized controlled trials vs. placebo. The baseline serum creatinine concentrations varied from 1.4+/_ 0.4 mg/dlto 2.8+/_ 0.8 mg/dlin the five trials. Contrast dose ranged from< 80 ml to > 375 ml. Acetylcysteine dosage was 400 mg or 600 mg bid started the day prior to or on the day of the procedure and continued thereafter for two days. All patients received hydration with 0.45% normal saline or 0.9% normal saline pre and post procedure. Acetylcysteine administration reduced the incidence of CIN (defined as a 0.5 mg/dl or a 25% increase in creatinine concentration) from 11%-45% in the placebo group to 2%-8% in the acetylcysteine group. The combined risk ratio of the treated group was 0.19 with a combined 95% confidence interval of 0.093 to 0.379 and a p-value of <0.0001.
Conclusions: Based on this meta-analysis, prophylactic administration of oral acetylcysteine significantly reduces the risk of CIN in patients with mild to moderate renal insufficiency.

1141-192 Genetic Variation in Cyclooxygenase-1 Associates With the Antiplatelet Effect of Aspirin in Stable Coronary Artery Disease

Aino Lepantalo, Jussi Mikkelsson, Julio Resendiz, Leena Heinonen, Pekka J. Karhunen, Riitta Lassila, Wihuri Research Institute, Helsinki, Finland, University of Tampere, Tampere, Finland

Impaired antithrombotic effect of aspirin may be a risk factor for coronary events in stable coronary artery disease (CAD). The pharmacogenetics of the COX-1, the target of the antithrombotic effect of aspirin, have not been studied previously. In the current series, we have analysed platelet responses in stable CAD patients on aspirin. The platelet responses were determined with optical aggregometry as well as PFA-100. The phenotypes were related to patient characteristics as well as COX-1 haplotype.
We took blood samples from 101 patients with stable CAD on aspirin (100mg/day). The antiplatelet effect of the treatment regimen was studied in whole blood with PFA-100 and in platelet-rich plasma with turbidometric aggregations using arachidonic acid (AA)-induced (1.5mmol/L) aggregation to identify the aspirin response. We used 170s. closure time (CT-CEPI) for PFA-100 and aggregation slope of 10%/min for AA as predetermined cut-off points for aspirin response.
7% (AA) and 22% (CT-CEPI) of patients were defined as poor aspirin responders. Individuals carrying the rare (20%) COX-1 haplotype had shorter mean CT-CEPI (222s., SD 81s.) compared to carriers of the common (80%) haplotype (261s., SD 67s.) (p=0.03). In addition, platelets of individuals from the rare haplotype group showed more preserved mean AA-induced maximal aggregation (31% +-6.5) compared to the common haplotype (21%+-1.3) (p=0.02).
We conclude that impaired response to aspirin measured with PFA-100 and aggregometry is common among individuals with angiographically proven severe CAD and is associated with common genetic variation of COX-1.

1141-193 Short Burst Oral Amiodarone Improves Cardioversion Success Rates for Patients in Persistent Atrial Fibrillation

Christopher J. Boos, Eric Clark, Ranjit S. More, Eric Clark, St. Mary's Hospital, Portsmouth, United Kingdom

Background: Increasing efforts have been made to improve the success rates for external direct-current cardioversion (EDC) for patients in persistent atrial fibrillation, without exposing them to prolonged toxic side effects of antiarrhythmic treatment.
Methods: 35 patients with rate controlled persistent atrial fibrillation (>1month), listed for EDC, were randomized to 2 groups. Group A received 4 weeks of oral amiodarone: 200mg Tds for 1 week prior to DCCV, then 200mg Tds week 2, 200mg Bd week 3 and then 200mg daily for week 4. Group B did not receive amiodarone. The cardioversion protocol of up to 5 synchronized shocks, was the same for the 2 groups (anterior-anterior 200J, 360J, 360J then anterior-posterior 360J and 360J).
Results: All results are expressed as mean ± standard deviation. The 2 groups, A and B respectively, were demographically well matched: age (61.2 ± 12.3 vs. 61.6 ± 7.6 years, p=0.96), weight (85.4 ± 8.90 vs. 85.4 ± 12.5 kg, p=1.0), left ventricular ejection fraction (50.2 ± 13.5 % vs. 51 ± 13.0 %, p=0.9), left atrial size (4.4 ± 0.6 cm vs. 4.1 ± 0.8 cm, p=0.55), mean duration of AF (7.2 ± 4.2 months vs. 10.2 ± 6.0 months, p=0.16), and heart rate pre-cardioversion (90.8 ± 14.7/min vs. 88.1 ± 18.0/min, p=0.64). The initial cardioversion success rate was 17/17=100% for group A vs. 17/18=94% for group B, p=1.0). There was a non-significant trend to the use of fewer shocks (1.7 ± 0.9 vs. 2.2 ± 1.4, p=0.42) and less total shock energy (454 J ± 331.1 vs. 620J ± 497.8, p=0.42) in the amiodarone group. The number of patients remaining in sinus rhythm at 6 weeks and 6 months respectively was significantly higher in group A than group B (15/17=88% vs. 3/18= 16.7%, p=<0.0001 and 11/17=65% vs. 3/18= 17%, (p=0.0016) respectively. However, by a mean follow-up of 16.2 (± 4.1) months there was only a non-significant trend to a higher rate of sinus rhythm in the amiodarone group as compared with the control group (8/17, 47.1% vs. 3/18, 16.7%; p=0.075).
Conclusion: For patients in persistent AF, a short course of oral amiodarone appears to improve 6 week and 6 month sinus rhythm rates following external direct-current cardioversion. This interesting data needs to backed up by a larger randomized study.

1141-194 Chronic Therapy With Phospodiesterase 5 Inhibitor Tadalafil Has a Sustained Effect on Endothelial Function

Giuseppe M. Rosano, Antonio Aversa, Cristiana Vitale, Andrea Fabbri, Massimo Fini, Giovanni Spera, San Raffaele Roma, Roma, Italy, University of Roma "La Sapienza", Roma, Italy

Erectile dysfunction (Ed) is often associated with a cluster of risk factors for coronary artery disease and with a reduced endothelial function. Acute administration of phosphodiesterase-5 inhibitors (PDE5) improves endothelial function in patients with ED. Tadalafil is a newer PDE5 inhibitor with a long half life that allows chronic administration and chronic therapy with Tadalafil has been suggested to be beneficial in patients with ED.
We hypothesized that chronic therapy with T may improve endothelial function in patients with ED and increased cardiovascular risk. To this end we randomized 32 patients with ED to receive either T 20 mg on alternate days or matching placebo (P) for 1 month. Brachial artery flow-mediated dilation (FMD) was assessed at baseline, at 1 month and at 6 weeks. At 1 month FMD was significantly improved by T (from 4.2±3.2 to 9.3±3.7%, p=0.01 vs. baseline), but was not affected by PL (from 4.1±2.8 to 4.0±3.4%, p=0.09 vs. baseline). At 6 weeks the benefit in FMD was sustained in patients that received T (9.1±3.9% vs 4.2±3.2%, p=0.01 vs. baseline; 9.1±3.9% vs 9.3±3.7%, vs 1 month, p=NS) while no changes in FMD were observed in patients randomized to P.
In conclusion, chronic therapy with T improves endothelial function. The benefit of this therapy seems to be sustained after discontinuation of therapy. Larger studies are needed in order to assess the clinical implications of this scheme of therapy.

1141-195 Chromium Supplementation Shortens QTc Interval Duration in Patients With Type 2 Diabetes

Matjaz Vrtovec, Bojan Vrtovec, Alenka Briski, Andreja Kocijancic, Richard A. Anderson, Division of Endocrinology, Diabetes, and Metabolic Diseases, Ljubljana University Medical Center, Ljubljana, Slovenia, Nutrient Requirements and Functions Laboratory, Beltsville Human Nutrition Research Center, Beltsville, MD

Background. QTc interval duration is predictive of mortality in diabetic patients. Since hromium supplementation has been shown to improve insulin sensitivity, lower plasma insulin levels, and improve glucose homeostasis, we sought to investigate the potential effects of chromium on QTc interval duration in patients with type 2 diabetes.
Methods. We performed a double-blind, randomized, placebo-controlled cross-over trial enrolling 60 patients with diet-treated type 2 diabetes, who were randomly assigned to either Group A or Group B. Group A (n=30) received 1 mg of chromium picolinate (CrPic) daily for 12 weeks, followed by placebo in the next 12 weeks; Group B (n=30) was treated with placebo for the first 12 weeks and CrPic in the next 12 weeks. At each visit, QT interval was measured on a standard surface ECG by averaging 3 consecutive beats in leads II, and V4, and corrected for heart rate with the Bazett formula. QTc interval shortening was defined as a difference between two consecutive QTc interval measurements of at least 10 ms.
Results. Baseline QTc interval was similar in both group (422±34 ms in Group A vs. 425±24 ms in Group B, p=0.77). Within first 12 weeks, QTc interval shortened in Group A, but not in Group B, which led to a significant difference in QTc interval duration between the groups (406±35 ms in Group A vs. 431±26 ms in Group B, p=0.01). In the following 12 weeks, QTc interval shortened in Group B but not in Group A, which resulted in a comparable QTc interval duration of both groups at the end of the study (414±28 ms in Group A vs. 409±22 ms in Group B, p=0.50). Overall, QTc interval shortening (>10 ms) with CrPic therapy was observed in 62% of patients. Except for body mass index (31.4±4.2 kg/m^2 in patients with QTc shortening vs. 28.7±4.2 kg/m^2 in patients without QTc shortening, p=0.03) none of the clinical and laboratory variables were predicitve of QTc shortening in our patient cohort.
Conclusions. Short-term chromium supplementation shortens QTc interval duration in patients with type 2 diabetes. These effects appear to be especially pronounced in diabetic patients with a higher body mass index.

1141-196 Effect of Atorvastatin and Sildenafil on Endothelial Function in Patients With Erectile Dysfunction and Increased Cardiovascular Risk

Giuseppe M. Rosano, Cristiana Vitale, Giuseppe Mercuro, Roberto Patrizi, Giuseppe Marazzi, Elena Cerquetani, Massimo Fini, San Raffaele Roma, Roma, Italy, University of Cagliari, Cagliari, Italy

Erectile Dysfunction is often associated with an increased cardiovascular risk and with a decrease in endothelial function. In patients with increased cardiovascular risk statin therapy reduce cardiovascular events and improves endothelial function. Oral therapy with phosphodiesterase-5 inhibitors improves erectile function through an amelioration of endothelial function.
Aim of the present study was to compare the effects of Sildenafil (S, 25 mg tds), Atorvastatin (A, 20 mg od) and their combination (CT) on endothelium-dependent flow mediated vasodilation (FMD), plasma nitrite, nitrate and endothelin-1 in 16 male with increased cardiovascular risk and erectile dysfunction in a double-blinded double-crossover study. Patients were randomized and treated for 1 weeks with either S, A or CT. Brachial artery diameter, FMD, endothelin-1 and plasma nitrite and nitrate levels were measured at baseline and after each treatment phase.
Brachial artery diameters remained unchanged after each treatment phase. All treatments significantly improved FMD compared to baseline.
In conclusion chronic therapy with S improves endothelial function by a similar extent of statin therapy. Combination of Sildenafil and Atorvastatin is more effective that either therapies alone in improving endothelial function and reducing plasma levels of endothelin-1 in male patients with increased cardiovascular risk.