9:45 a.m.

803-3 **The Interleukin–174G/C Polymorphism Is a Powerful Predictor for Restenosis After Coronary Stent Implantation**

Tanja Kottmann, Cornelia Piper, Martin Farr, Dieter Fassbender, Michael Schmidt, Christian Goetting, Dirk Welge, Knut Kleesiek, Dieter Horstkotte, Heart Center North Rhine-Westphalia, Bad Oeynhausen, Germany

Background: The influence of numerous polymorphisms on restenosis after coronary stent implantation is discussed controversially. However, there are no data regarding the impact of the interleukin-6 (IL-6) –174G/C polymorphism on restenosis.
Methods: Between 9/01 and 2/03 96 patients (85% men, mean age 64±9 years) were enrolled prior to coronary stent implantation. The genotypes of IL-6 (–174G/C), fibrinogen (-455G/A, -854G/A and HaeIII), factor VII (RQ353 and –323I/D), factor XIII (Val34Leu), PAI-1 (4G/5G) and TFPI (-399C/T) were determined. After 6 months, all patients underwent coronary angiography to quantify restenosis.
Results: Coronary in-stent restenosis (≥ 50%) was angiographically documented in 31% of all patients. In an univariate analysis, restenosis was correlated with the G allele of –174G/C polymorphism (45% in GG vs. 30% in GC vs. 11% in CC genotype; p<0.05). No evidence for a significant influence on restenosis was detected for any of the other polymorphisms analyzed.
When analyzing the different polymorphisms, age, sex, body mass index, length of endothelial lesion, stent length, morphology of lesion, duration of dilation and maximum balloon pressure in a multivariate analysis, the –174G/C polymorphism was the only parameter which turned out to be a significant predictor for coronary restenosis.
Conclusions: Of various polymorphisms only the –174G/C polymorphism is an independent predictor for restenosis after coronary stent implantation. The risk for restenosis in homozygous carriers of the G allele is about four times higher than in patients without G allele.

10:00 a.m.

803-4 **Analysis of Anti-apoptotic Intracellular Viral Serpins as Anti-atherosclerotic Agents**

Liyung Liu, Kasinath Viswanathan, Erbin Dai, Peter C. Turner, Jide Togonu-Bickersteth, Ben Pang, Yue Li, Richard W. Moyer, Grant McFadden, Alexandra Lucas, Robarts Research Institute, London, ON, Canada, University of Florida, Gainesville, FL

Rationale Serine proteinase inhibitors, serpins, regulate key stages in clot formation, clot lysis and inflammation. Two intracellular viral serpins, CrmA and Serp-2, with cysteine proteinase and granzyme B inhibitory activity have been proven to inhibit apoptosis when expressed inside virus infected cells. We have postulated that proteins released after virus induced cell lysis have extracellular activities. The effects of purified CrmA and Serp-2 proteins on early arterial apoptosis and later plaque growth after angioplasty injury in rats were assessed and the effects of Serp-2 and crmA on human monocytes and T-lymphocytes were also assessed.
Methods Sprague dawley rats had iliofemoral angioplasty with early (0, 12 and 72 hrs) follow up (N=155) for arterial apoptosis and late (28 days) follow up (N=108) for arterial plaque area. Rats were given a single intravenous (3ng-3ug) bolus of Saline, Serp-2, CrmA, or Serp-2 active site mutants, D294A and D294E (P_1 in reactive center loop altered to Alanine and Glutamic acid respectively) immediately after surgery. Apoptosis was measured using cell death ELISA immunoassay and substrate specific tetrapeptides for Caspase 3 and Granzyme B. Apoptosis was also induced in human atherogenic cells, monocytes and T-lymphocytes with Camptothecin and the anti-apoptotic activity of Serp-2 and CrmA was examined. Anti-apoptotic gene expression was evaluated using RT PCR.
Results Serp-2 and CrmA reduced plaque area with greater efficacy for Serp-2. Active site mutants D294A and D294E had no effect on plaque growth. Serp-2, CrmA, D294A and D294E reduced apoptosis and Serp-2 and CrmA reduced caspase 3 and Granzyme B significantly at 12 - 72 hrs. The active site mutant D294A reduced Granzyme B but not Caspase 3 while D294E reduced Caspase 3 but not Granzyme B. Crm-A effectively attenuated Caspase 3 in human monocytic THP-1 and Serp-2 in Jurkat T-lymphocytes.The anti-apoptotic activity of these proteins was in part by upregulation of the Bcl-2 family genes. **Conclusions** Intracellular viral Serpins with cysteine proteinase inhibitory activity displayed surprising anti-atherogenic and anti-apoptotic activity when applied extracellularly in a rat angioplasty model.

10:15 a.m.

803-5 **Dendritic Cells Contribute to In-Stent Restenosis: Recruitment in Early Neointima Formation After Porcine Aortic Stent Implantation and in Human In-Stent Restenosis**

Izabela Tuleta, Alexander Jabs, René Andrié, Dirk Skowasch, Matthias Peuster, Berndt Lüderitz, Gerhard Bauriedel, Heart Center University of Bonn, Bonn, Germany, Heart and Diabetes Center Nordrhein Westfalen, Bad Oeynhausen, Germany

Background: We recently reported presence of dendritic cells (DCs) in rat carotid neointima early post balloon angioplasty. Since DCs are a new cell type in context with neointima formation, in the current study, we sought to assess the presence of neointimal DCs in porcine arteries following stent implantation and in human in-stent restenosis (ISR).
Methods: Normal juvenile female domestic swine underwent stent implantation to abdominal aortic segments. Animals were sacrified at 7, 14, 30 or 90d post stenting (n=3 per time). S100 polyclonal antibodies were used to identify DCs by immunohistochemistry in cross sections of the injured arteries and in 10 atherectomy probes from patients with coronary ISR (time post stenting 5±3 months). Also in the porcine model, DC-motility associated fascin expression was analyzed. Labelling was quantified as % labelled cells per total count/mm^2.
Results: In porcine arteries, neointima at 7d consisted of 3 layers of cells, and a high percentage of these cells expressed the DC marker S100 (13.0±2.7%). Likewise, fascin immunoreactivity was seen in 10.5±5.3% of neointimal cells. Subsequently at 14d, S100+ and fascin+ cells were found predominantly in neointimal cells close to the luminal border (14.1±5.6% for S100; 11.0±3.9% for fascin). DC marker expression in neointima further decreased at both 30d (9.0±1.7% for S100; 2.9±1.1% for fascin) and 90d (3.1±1.2% for S100, p<0.001; 2.9±3.0% for fascin, p=0.01 vs. 7d), but consistently revealed luminal prevalence of this cell type. Media consistently showed no immunoreactivity of S100 or fascin. In human probes, frequency of DCs was high with 9.2±5.4% at the time of clinical ISR.
Conclusions: Dendritic cells contribute to neointima formation post stenting in a porcine coronary model, most at early time points, as well as in human clinical ISR. Given our previous findings of S100+ DCs in rat carotid neointima post balloon angioplasty, our present data conclusively identify DCs as novel cell type in early vascular repair post arterial traumatization.

ORAL CONTRIBUTIONS

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Guidance of Interventional Therapy

Monday, March 08, 2004, 11:00 a.m.-12:15 p.m.
Morial Convention Center, Hall A

11:00 a.m.

808-1 **Dose Threshold for Clinical Success in Coronary Brachytherapy: A Nested Case-Control Study**

Harsimran S. Singh, Ning Yue, Kenneth B. Roberts, Ravinder Nath, Steven Pfau, Yale University School of Medicine, New Haven, CT

Background: Intravascular brachytherapy is the primary treatment for coronary in-stent restenosis. We hypothesized that differences in dose delivered to target may contribute to treatment failures. We compared dose distribution between arteries that developed recurrent restenosis (treatment failures) and those that remained patent at nine-months (treatment success).
Methods: A cohort of 140 patients receiving brachytherapy for coronary in-stent restenosis with four radiation delivery devices was followed to identify treatment failures and successes. A nested case-control construct was used in which treatment failures (n=14) were compared 1:2 to treatment successes (n=28) matched by two variables: radiation delivery system and angiographic pattern of in-stent restenosis. At baseline, the groups had similar patient and lesion characteristics. The dose absorbed by 90% of the artery encompassed by the external elastic membrane (D_{90}EEM) was calculated using intravascular ultrasound (IVUS) images taken at 2-mm intervals along the treated lesion. Dose calculations were performed using dose kernel integration techniques; the dose kernels were generated from Monte Carlo simulations.
Results: The mean D_{90}EEM minimum dose in treatment failures was 7.46±1.98 Gy, while for treatment success the mean D_{90}EEM minimum dose was significantly higher: 8.87±1.13 Gy (p=0.007). Using a minimum dose threshold of 8.4 Gy, a D_{90}EEM minimum dose ≤ 8.4 Gy occurred in 13 (93%) patients with treatment failure, but in only 9 (32%) with treatment success (p≤0.001). No confounding variables were found to be statistically significant between the cases and controls.
Conclusions: Current brachytherapy dose prescriptions result in significant inter- and intra-lesion variation in dose at the EEM. Arteries that receive ≤ 8.4 Gy at any point along the external elastic membrane are more likely to be treatment failures. IVUS guided dosimetry may be critical to assure adequate dose regardless of radiation delivery system.

11:15 a.m.

808-2 **Creatine Kinase-MB Elevation After Coronary Stenting in Lesions With Ruptured Plaque**

Kenichi Fujii, Yoshio Kobayashi, Gary S. Mintz, David Jacoboff, Hideo Takebayashi, Takenori Yasuda, Issam Moussa, Roxana Mehran, George Dangas, Alexandra J. Lansky, Edward Kreps, Michael Collins, Gregg W. Stone, Martin B. Leon, Jeffrey W. Moses, Cardiovascular Research Foundation, New York, NY

Background: Elevation of serum creatine kinase MB fraction (CK-MB) after perctaneous coronary intervention is associated with early and late mortality. We undertook this study to evaluate the relation between CK-MB elevation and coronary stenting in lesions with ruptured plaque.
Methods: Intravascular ultrasound (IVUS) was performed in 50 lesions with ruptured plaque that were subsequently treated by coronary stenting. Patients with acute myocardial infarction and elevated baseline CK-MB were excluded. Patients were divided into 3 groups according to CK-MB elevation after stenting: 1) no elevation (n = 32), 2) 1 to 3 x CK-MB elevation (n = 9), and 3) >3 x CK-MB elevation (n = 9). CK-MB was measured at baseline, 6 and 24 hours after stenting. Remodeling index was calculated as lesion external elastic membrane (EEM) divided by reference EEM.
Results: CK-MB enzyme elevation was observed in 18 patients (36%). Baseline clinical characteristics were similar among the 3 groups. IVUS data are shown in the Table. Multivariate analysis indicated that remodeling index (p=0.04), post-stent cross sectional

area (p=0.03), and cavity size (p=0.04) were independent predictors of CK-MB elevation after stenting in lesions with ruptured plaque.
Conclusion: CK-MB elevation is frequent after coronary stenting in lesions with ruptured plaque. It is associated with coronary remodeling, aggressive stent expansion, and cavity size.

	No	1 to 3 x	>3 x	P value
Unstable angina (%)	69	67	56	NS
Pre-intervention				
EEM CSA (mm^2)	18.6±6.7	19.5±5.4	19.7±5.5	NS
Minimal lumen CSA (mm^2)	4.1±2.4	4.6±2.4	5.4±2.4	NS
Plaque & media CSA (mm^2)	12.2±4.6	12.6±3.5	10.6±3.5	NS
Cavity area (mm^2)	2.3±1.1	2.3±0.8	3.8±1.6	0.002
Remodeling index	1.06±0.17	1.14±0.17	1.14±0.14	NS
Thrombus (%)	50	22	33	NS
Final stent CSA (mm^2)	9.1±2.3	11.8±2.2	12.5±2.2	0.02

CSA = cross-sectional area.

11:30 a.m.

808-3 Impact of Periprocedural Plaque/Thrombus Reduction on Myocardial Injury After Stent Deployment

Mamoo Nakamura, Hideo Tamai, Tadanori Aizawa, Atsushi Hirohata, Yasuhiro Honda, Heidi N. Bonneau, William F. Fearon, Alan C. Yeung, Paul G. Yock, Peter J. Fitzgerald, Stanford University, Palo Alto, CA

Background: Larger plaque/thrombus (P/T) burden and its compression/embolization may be associated with an elevated creatine phosphokinase MB fraction (CK-MB) following percutaneous coronary intervention (PCI). The aim of this volumetric intravascular ultrasound (IVUS) study was to assess the impact of periprocedural P/T reduction on subsequent elevation of CK-MB following stenting.
Methods: Preintervention and poststent IVUS analyses were performed in 86 native coronary arteries treated by conventional stenting. Along the stented segment, IVUS parameters (volume/segment length: mm^3/mm) were measured. P/T volume was obtained as vessel volume minus lumen volume, since plaque and thrombus are difficult to distinguish. Absolute and percent P/T reductions from preintervention to poststent were also calculated. CK-MB elevation was defined as > 2 times normal, 24 hours after the PCI.
Results: Preintervention vessel and P/T volumes were significantly greater in the group with CK-MB elevation (see Table). There was no significant difference in lumen volume. Significant P/T reduction was also noted in cases with CK-MB elevation compared to those without CK-MB elevation.
Conclusions: After conventional stenting, native coronary artery lesions with large vessel and plaque/thrombus volume are prone to subsequent CK-MB elevation. The excessive plaque/thrombus reduction in this lesion subset may indicate embolism as a potential cause for the myocardial damage.

Comparison of Volumetric IVUS Parameters

	CK-MB >2 X (n=9)	CK-MB <=2 X (n=77)	p- value
Pre-intervention Vessel	18.64±4.24	13.60±3.33	<0.0001
Pre-intervention P/T	13.70±2.67	9.52±2.80	<0.0001
P/T reduction	3.00±1.56	1.12±1.20	0.0004
Percent P/T reduction	22±11	11±10	<0.0001

11:45 a.m.

808-4 Exaggeration of Neointimal Hyperplasia Following Stent Deployment in Type B Bifurcation Lesions

Atsushi Hirohata, Mamoo Nakamura, William F. Fearon, Yasuhiro Honda, Paul G. Yock, Peter J. Fitzgerald, Stanford University Medical Center, Stanford, CA

Background: Restenosis rates are considerably higher after bare metal stenting in typeB bifurcation lesions (stenosis in the main vessel, just distal to a side branch). The aim of this volumetric IVUS study was to assess the relative contribution of stent area and neointimal hyperplasia on late lumen loss in this lesion subset.
Methods: Serial IVUS analyses (pre, post-stent and 6 months follow-up) were performed in 101 left anterior descending coronary artery segments treated by bare metal stenting. Based on the location of the minimum lumen area in pre-interventional IVUS of the main vessel, segments were divided into two groups (Group I; lesions with the narrowest cross-sectional lumen area located within 3mm distal to the major side branch and Group II; lesions that did not meet this criteria). Along the stented segment, volumetric index (VI: volume/length) was calculated for the vessel, lumen, plaque, stent and neointima. Percent neointimal VI was calculated to standardize stent VI.
Results: Group I lesions were observed in 42 and Group II in 59 stented segments. At baseline, all IVUS measurements were similar between two groups. However, at 6 months follow-up, neointimal and percent neointimal VI were significantly larger in Group I lesions(Table1).
Conclusion: These observations suggest that following bare metal stent deployment, exaggeration of neointimal hyperplasia occurs more frequently in typeB bifurcation lesions, regardless of the original vessel morphometry and mechanical scaffolding.

	Group I (n=42)	**Group II** (n=59)	**p-value**
Pre-Intervention			
Lumen VI (mm^3/mm)	3.92±1.35	4.16±1.49	ns.
Vessel VI (mm^3/mm)	13.8±3.18	13.87±3.91	ns.
Plaque VI (mm^3/mm)	9.91±2.91	9.68±3.01	ns.
Post-Stent			
Lumen (stent) VI (mm^3/mm)	8.18±1.75	8.22±2.02	ns.
Vessel VI (mm^3/mm)	16.73±3.32	16.7±4.11	ns.
Plaque VI (mm^3/mm)	8.58±2.23	8.57±2.71	ns.
6-months Follow-up			
Lumen VI (mm^3/mm)	5.13±2.17	5.75±2.04	ns.
Vessel VI (mm^3/mm)	17.5±3.54	17.36±4.11	ns.
Plaque VI (mm^3/mm)	12.38±2.49	11.6±2.78	ns.
Stent VI (mm^3/mm)	8.13±1.85	8.19±1.98	ns.
Intimal VI (mm^3/mm)	3.01±1.41	2.46±1.14	0.03
% Neointimal VI (%)	38±19	31±14	0.02

Noon

808-5 Findings of Intravascular Ultrasound During Acute Stent Thrombosis

Fernando Alfonso, Alfonso Suarez, Dominick J. Angiolillo, Manel Sabate, Javier Escaned, Raul Moreno, Camino Bañuelos, Rosana Hernández-Antolín, Carlos Macaya, Cardiovascular Institute-San Carlos University Hospital, Madrid, Spain

Background: Intravascular ultrasound (IVUS) is useful to guide stent (ST) implantation, but its role in patients experiencing an episode of acute stent (ST) thrombosis has not been established. ***Methods:*** A total of 50 consecutive patients with angiographically demonstrated acute ST thrombosis were studied over a 3-year period (incidence of 1.2% of all patients treated with ST). IVUS was used in 12 patients undergoing coronary interventions for ST thrombosis to gain further mechanistic insights and to guide therapy. The remaining 38 patients were excluded due to logistic reasons, severe hemodynamic derangement or persisting angina/ECG changes after crossing the ST with the guidewire. IVUS studies were obtained before and after intervention using a motorized pull-back device. Qualitative and volumetric IVUS analyses were performed. ***Results:*** Angiographically, 10 patients had occluded vessels and 2 patients showed intraluminal filling defects within the ST. IVUS demonstrated an occlusive thrombus in all patients. Thrombus volume was 90±77 mm^3 which represented 51±21% of total ST volume. Most patients showed evidence of severe ST under-expansion and no patient fulfilled standard criteria for optimal ST implantation. ST malapposition was detected in 4 patients, edge dissections were seen in 2 patients and significant inflow-outflow disease was present in 11 patients. During interventions IVUS findings led to the use of higher pressures or larger balloons than those used during initial stenting in 10 patients. In addition, 4 patients required additional stenting whereas a thrombectomy device “alone” was selected in 1 patient. After the procedure final minimal ST area (7.1±2.1 vs 5.3±2 mm^2, p<0.005) and ST expansion (83.2±17 vs 62.1±15%, p<0.005) improved as compared with pre-interventional values. However, residual lining thrombus could still be visualized in 8 patients (25±19 mm^3 accounting for a 17% of final ST volume). ***Conclusions:*** IVUS provides an attractive technique to fully characterize the pattern of ST thrombosis, to readily identify underlying mechanical predisposing factors and to guide repeated coronary interventions.