1197-12 **Cerebral Hyperperfusion and Intracranial Hemorrhage Following Internal Carotid Artery Stenting**

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Background: The rate of hyperperfusion hemorrhage following carotid endarterectomy is 0.3-1.5%. Little is known about the frequency and risk factors for intracerebral hemorrhage and the cerebral hyperperfusion syndrome following internal carotid artery stenting (CAS).
Methods: We reviewed the prospective computerized database of all CAS procedures performed in the peripheral interventional laboratory to identify patients who developed intracerebral hemorrhage.
Results: A total of 205 consecutive patients with a mean stenosis of 83.4% ±12.4% underwent CAS over a three-year period. There were three (1.5%) cases of intracerebral hemorrhage, one immediate and two delayed (mean 4 ±1.4 days). All three patients had correction of a severe (mean 96% ±5.2%) internal carotid artery stenosis with a concomitant >80% stenosis or occlusion of the contralateral carotid artery. All three patients had hypertension preoperatively and the two patients with delayed hemorrhage developed hypertension postoperatively. Aspirin, clopidogrel, and heparin were given to all three patients, additionally one received eptifibatide and one received abciximab during the procedure. Two of the three patients died and one recovered with persistent neurological deficits.
Conclusion: The cerebral hyperperfusion syndrome occurs infrequently following CAS but is a cause of significant morbidity and mortality when it does occur. Patients with severe, bilateral internal carotid artery stenosis and perioperative hypertension may be at particular risk. Vigilant postoperative monitoring and blood pressure control, in-hospital as well as after discharge, may be critical preventative measures. The role of antiplatelet and antithrombotic agents in the pathogenesis of hyperperfusion hemorrhage is unclear.

POSTER SESSION

1198 Restenosis: Promising Experimental Therapy

Tuesday, March 19, 2002, 3:00 p.m.-5:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: 3:00 p.m.-4:00 p.m.

1198-1 **Sonodynamic Therapy Reduced Neointimal Hyperplasia After Stenting in Rabbit Iliac Artery**

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Background:In-stent restenosis remains a pivotal problem after coronary and peripheral stenting. Sonodynamic therapy inhibits tumor growth by means of cytotoxicity after the activation of sonochemical sensitizers by ultrasound. PAD-S31 is known to be a water-soluble chlorin derivative sonochemical sensitizer. We assessed the efficacy of sonodynamic therapy using this sensitizer on neointimal hyperplasia in a rabbit stent model.
Methods:Stents were implanted in the iliac arteries of 16 rabbits. Thirty-two stented arteries were randomized to sonodynamic therapy, control, ultrasound exposure, and PAD-S31 groups. One hour after the intravenous administration of PAD-S31 of 25mg/kg, ultrasound energy (1MHz, 0.3W/cm2) was delivered transdermally to the sonodynamic therapy group. At 28 days, all stent sites were analyzed morphometrically. Results:The size of the intimal cross sectional area was smaller in the sonodynamic therapy group than in the control, ultrasound, and PAD-S31 groups (0.31±0.07 versus 1.38±0.47, 1.66±0.71, and 1.61±0.42 mm2, p<0.05). The ratio of the intimal and media cross sectional area was smaller in the sonodynamic therapy group than in the control, ultrasound, and PAD-S31 groups (0.71±0.22 versus 2.53±1.39, 2.48±0.60, and 3.45±1.42 mm2, p<0.05). The percent area stenosis was also significantly smaller in the sonodynamic therapy group than in the control, ultrasound, and PAD-S31 groups (23±7 versus 58±11, 53±14, and 65±9 %, p<0.05).
Conclusions:Sonodynamic therapy with PAD-S31 is considered to be a feasible treatment modality for non-invasively inhibiting neointimal hyperplasia in a rabbit iliac stent mode

1198-2 **Local Motexafin Lutetium Delivery With Subsequent Photoangioplasty Reduces Macrophages and Atheroma Burden in a Rabbit Postballoon Injury Model**

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Background: Motexafin lutetium (MLu, Antrin® Injection) is a phototherapeutic agent that selectively accumulates in atheromatous plaque where it can be activated by far-red light. In this study, we assessed the feasibility and impact of local MLu administration with subsequent endovascular illumination on the intima/media ratio and macrophage burden in a rabbit post-balloon injury model. **Methods**: New Zealand white rabbits (n=20) were fed a 1% cholesterol diet. After 2-3 weeks, bilateral iliac artery lesions were induced by balloon denudation, followed by continued feeding of the high cholesterol diet for a further 5-6 weeks. A local drug delivery catheter (3mm, Dispatch®, Scimed) was introduced into the specified iliac artery to deliver 2.2 ml volumes of MLu (0.5 or 2.0 mg) or vehicle (5% mannitol). Photoactivation with endovascularly delivered light (photoangioplasty) was performed 15 minutes after sensitizer delivery (781 Joules/cm^F at 830 mW/cm^F). Two weeks post treatment, vessels were harvested and hematoxylin and eosin (H&E) and RAM11 (macrophages) staining was performed. **Results:** Local administration of 2.0 mg MLu and subsequent photoactivation led to a significantly lower intimal/media ratio compared with those animals receiving drug alone (1.44±0.17SEM versus 2.01±0.28, P=0.006). Quantitative planimetric analysis using RAM11 positive cells revealed significant reduction of macrophages in treated lesions in the 0.5 (6.74±1.50 versus 15.06±1.92%, P<0.001) and 2.0 mg MLu (7.46±1.73 versus 15.06±1.92%, P=0.001) phototherapy groups, compared with animals receiving only light treatment. **Conclusions:** Photoactivation of MLu within atheroma, after local delivery resulted in a significant decrease in macrophages and a small decrease in atheroma burden. These findings have implications for a possible effect of MLu photoangioplasty on plaque regression and stabilization.

1198-3 **Estrogen Reduces Neointima Formation Independent of iNOS Expression in Mouse Carotid Ligation Model of Vascular Injury**

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Background: Estrogen is vasoprotective in animal models of vascular injury, yet the mechanisms involved are incompletely understood. Many lines of evidence indicate that inducible nitric oxide synthase (iNOS) plays a role in neointima formation after arterial injury and that 17β-estradiol (E_2) modulates iNOS expression. This study tested the hypothesis that E_2 reduces neointima formation after vascular injury via a mechanism that is dependent on modulation of iNOS expression.
Methods: Male and female wild type (iNOS+/+) mice and mice with homozygous deletion of iNOS (iNOS-/-) were studied intact (INT) or following ovariectomy (OVX) and implantation of E_2 or vehicle (V). Mice were randomized to 8 groups based on gender, iNOS status, OVX, and treatment with E_2 or V (n=5-8 per group). Mice were sacrificed 28 days after carotid ligation, and injured vessels were examined for cross-sectional neointimal areas. Results are expressed as means ± SEM.
Results: There was a marked sexual dimorphism in neointima formation in both the iNOS +/+ mice and the iNOS -/- mice. iNOS +/+ INT females had a > 90% reduction in neointima formation compared to iNOS +/+males ($0.17\pm0.03\times10^4$ μm^2 vs $2.88\pm0.41\times10^4$ μm^2; p<0.05), and iNOS -/- INT females had a 65% reduction in neointima formation compared to iNOS -/- males ($0.42\pm0.10\times10^4$ μm^2 vs $1.20\pm0.28\times10^4$ μm^2; p<0.05). The sexually dimorphic response was attenuated by OVX and restored by E_2 replacement in both iNOS +/+ and iNOS -/- mice. Female iNOS +/+ OVX + E_2 mice had an 82% reduction in neointima formation compared to female iNOS +/+ OVX + V mice ($0.34\pm0.13\times10^4$ μm^2 vs $1.94\pm0.49\times10^4$ μm^2; p<0.05), and female iNOS -/- OVX + E_2 mice had a 70% reduction in neointima formation compared to iNOS -/- OVX + V ($0.32\pm0.04\times10^4$ μm^2 vs $1.07\pm0.19\times10^4$ μm^2; p<0.05).
Conclusions: These results demonstrate that the vasoprotective effects of E_2 following vascular injury are, at least in part, independent of iNOS expression.

1198-4 **Intracoronary Administration of Acetyl-Tyrosinyl-Valyl-Alanyl-Aspartyl-Chloro-Methylketone (Ac-YVAD-cmk) Reduces Neointimal Hyperplasia After Stenting of the Porcine Coronary Artery**

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Background. The irreversible caspase-1 inhibitor acetyl-tyrosinyl-valyl-alanyl-aspartyl-chloro-methylketone (Ac-YVAD-cmk) inhibits apoptosis and proinflammatory cytokine release. In contrast to apoptosis inhibition, the chloromethylketon chain of Ac-YVAD-cmk increases smooth muscle cell apoptosis through elastase inhibition. The aim of the present study was to reduce neointimal proliferation after coronary stent implantation using Ac-YVAD-cmk. Methods. After general anaesthesia, domestic pigs received intracoronary infusion of 50 mg Ac-YVAD-cmk (dissolved in 1 ml dimethylsulfoxid /DMSO/ and 59 ml phosphate buffer /PBS/, infusion rate 6ml/min) into the left coronary artery (group 1, n=10), while 8 animals served as untreated controls (group 2) and 6 further pigs as vehicle controls (DMSO+PBS) (group 3). One coronary stent was then implanted in the left anterior descending or circumflex coronary artery. After 4 weeks, control angiography and intravascular ultrasound (IVUS) were performed. IVUS parameters were measured using computer-assisted 3D analysis system. Results. Ac-YVAD-cmk reduced in-stent neointimal volume (29.1±12.5 vs 80.5±24.9 and 67.4±22.3mm3, p<0.005) and maximal area stenosis (38.6±8.0 vs 71.0±6.4 and 67.0±9.9%, p<0.001) assessed by IVUS in group 1 vs groups 2 and 3, but did not influence vessel remodeling (maximal vessel area 12.4±3.3 vs 13.5±2.1 and 12.3±2.7mm3, nonsignificant). Smaller maximal neointimal thickness (0.38±0.19 vs 0.94±0.37 and 0.97±0.44mm, p<0.01) and decreased maximal neointimal area (1.73±1.53 vs 3.66±1.54 and 4.03±0.86mm2, p<0.01) assessed by histology (computerized planimetry) were found in pigs in group 1 vs groups 2 and 3. IVUS results (maximal neointimal area and neointimal thickness) correlated significantly with histological data (r=0.774, p<0.001 and r=0.699, p<0.001, respectively). Injury score did not differ significantly between the groups. Conclusions. Our data indicate that caspase-1 inhibitor Ac-YVAD-cmk reduces in-stent neointimal proliferation. IVUS allows a quantitative 3D analysis of experimental neointimal proliferation and vessel remodeling and is able to guide targeted histological analysis.