ORAL CONTRIBUTIONS

865

Determinants of Endothelial Function and Arterial Stiffness

Wednesday, March 10, 2004, 8:30 a.m.-10:00 a.m.
Morial Convention Center, Hall E-1

8:30 a.m.

865-1 Endothelium-Derived Hyperpolarizing Factor Is Involved in Flow-Dependent Dilation of Peripheral Conduit Arteries in Healthy Volunteers

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Background: Experimental data suggest that the endothelium-mediated, flow-dependent vasodilation of peripheral arteries (FDD) is not only mediated by nitric oxide (NO) but also by other relaxing factors, such as the cytochrome-p450-dependent endothelium-derived hyperpolarization factor (EDHF). However, the contribution of EDHF for the endothelium-mediated vasodilation of peripheral arteries in humans is unknown.
Methods: FDD of the radial artery was determined in 12 healthy volunteers by high resolution ultrasound. To inhibit vascular cyclooxygenase dependent vasodilation, we injected 500 mg acetylsalecyl acid 30 min before FDD-measurements. FDD was analyzed during control conditions and after intra-arterial infusion (5 min) of sulfaphenazole, a specific inhibitor of the isoenzyme 2C9 of the cytochrome-p450(4 mg/min), following L-NMMA (NO-synthase-inhibitor, 7 µmol/min) and after co-infusion of both, each 5 min. Furthermore, endothelium-independent vasodilation was characterized after intra-arterial infusion of SNP (9 µg/min, 5 min).
Results: FDD at baseline was 11.5±3%, following sulfaphenazole 7.4±3.3% (p<0.01 vs. control), after L-NMMA 6.0±2.4% (<0.01 vs. control), after co-infusion of L-NMMA and sulfaphenazole 3.9±2.5% (p<0.01 vs. control, p<0.05 vs. L-NMMA, p<0.01 vs. sulfaphenazole). Sulfaphenazole had no effect on endothelium-independent vasodilation (SNP: 19.6±6.2%, SNP+sulfaphenazole:20.2±6.8, p=n.s.).
Conclusion: FDD of the radial artery was substantially reduced In healthy volunteers after inhibition of cytochrome-p450 2C9 or NO-synthase. Co-infusions of both inhibitors for NO-synthase and EDHF had incremental inhibitory effects on FDD. Thus, our results support the concept that EDHF contributes to flow-dependent dilation of peripheral conduit arteries in normal human volunteers *in vivo*.

8:45 a.m.

865-2 1166 A/C Polymorphism of the Angiotensin AT1 Receptor Gene Alters Simvastatin-Induced Change in the Endothelial Function

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Background: Angiotensin AT1 receptors (AT1R) may influence function of vascular endothelium via stimulation of free radicals production. We examined relationship between 1166A/C polymorphism of the AT1R gene and statin related changes in endothelial function and AT1R density.
Methods: In 17 pts with coronary artery disease (not on hypolipemic treatment) lipid profile, platelet AT1R density and endothelial function (brachial artery flow mediated dilation FMD, NO metabolites: nitrate&nitrite concentration) were performed at baseline and after treatment with simvastatin 40mg/24h for 12 weeks. All subjects were genotyped for the 1166A/C polymorphism.
Results: At baseline there were no differences between pts carrying AA allele (n=9) vs. C allele (AC and CC; n=8) in LDL cholesterol, AT1R density and FMD. Pts carrying AA allele had at baseline lower nitrate&nitrite concentration (13,84±4,43 vs. 21,39±9,45uM; p=0,048). After simvastatin AA pts had significant improvement in endothelial function while AC or CC pts had no improvement in endothelial function (table). There were no differences between AA homozygotes and all C allele carriers in simvastatin-induced reduction in LDL cholesterol and AT1R density.
Conclusions: Influence of statin on endothelial function is modulated by 1166A/C polymorphism of the angiotensin AT1R gene. This polymorphism does not affect (i) the baseline AT1R density and baseline LDL (ii) simvastatin induced reduction of LDL and AT1R density.
Table:

Index of endothelial function	Patients carrying AA allele			Patients carrying AC or CC allele		
	Before simvastatin Mean(SD)	After simvastatin Mean(SD)	p	Before simvastatin Mean(SD)	After simvastatin Mean(SD)	p
FMD (%)	8,27(2,30)	11,25(2,79)	0,012	10,15(7,86)	9,26(4,68)	0,65
nitrate&nitrite concentration	13,84(4,43)	22,21(8,53)	0,01	21,39(9,45)	20,00(9,13)	0,44

9:00 a.m.

865-3 Improvement of Endothelium-Dependent Vasodilation by Simvastatin Is Potentiated by Combination With L-Arginine in Patients With Elevated Asymmetric Dimethylarginine Levels

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Background. Statins stimulate the expression of endothelial NO synthase (eNOS) in vitro and enhance endothelium-dependent, NO-mediated vasodilation in vivo. Asymmetrical dimethylarginine (ADMA) is an endogenous, competitive inhibitor of eNOS. The presence of elevated plasma ADMA levels is associated with endothelial dysfunction. We investigated the hypothesis that simvastatin may enhance endothelial function in patients with elevated ADMA only if the inhibitory effect of ADMA is overcome by supplemental L-arginine.
Methods. 15 clinically asymptomatic, elderly subjects with elevated ADMA levels received, in a randomised order, simvastatin (40 mg/day), L-arginine sustained-release (3 g/day), or a combination of both, each for 3 weeks, in a three period crossover design with at least three weeks of wash-out between treatments. Endothelium-dependent vasodilation was assessed by brachial artery ultrasound using computer-assisted image analysis; ADMA and L-arginine plasma concentrations were determined by a validated HPLC method.
Results. Analysis of 12 subjects who completed the study revealed that simvastatin had no effect on endothelium-dependent vasodilation when administered alone (6.2±1.2% vs. 6.1±0.9%). L-arginine significantly improved endothelial function (8.7±0.7 vs. 4.9±0.8%; p<0.02). When given in combination with L-arginine, simvastatin had a significant beneficial effect on endothelial function (9.8±1.5 vs. 5.3±0.8%; p<0.01). Endothelium-independent vasodilation by glyceryl trinitrate was not affected by any of the treatments.L-arginine, either alone or in combination with simvastatin, significantly improved plasma L-arginine/ADMA ratio (baseline, 82.3±4.0 vs. 102.8±9.2 and 102.6±10.8, respectively, each p<0.05).
Conclusions. Simvastatin does not enhance endothelial function in subjects in whom eNOS is blocked by elevated ADMA levels; combination of simvastatin with oral L-arginine has a synergistic effect on endothelial function. As NO-mediated effects may play a major role in therapeutic effects of statins, combination with L-arginine should be considered in patients with elevated ADMA concentration.

9:15 a.m.

865-4 Tetrahydrobiopterin Prevents Vascular Injury After Ischemia-Reperfusion in Humans

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BACKGROUND: Vascular inflammation and subsequent endothelial dysfunction are pivotal steps in the initiation of ischemia-reperfusion injury. Ischemic preconditioning is well known to have protective effects although the mechanism through which it occurs remains incompletely understood. We hypothesized that tetrahydrobiopterin (BH4) plays a critical role in ischemic preconditioning, and its administration prevents reperfusion injury. **METHODS:** Baseline endothelial function of the radial artery was measured in 21 healthy volunteers (mean age 36.2±2.9 years) using flow-mediated dilation (FMD). Subjects were divided into 3 groups: A) arm ischemia induced by a 20 minute cuff inflation B) preconditioning with three 5-minute cuff inflations followed by 20 minute cuff inflation and C) administration of BH4 (500µg/min) into the brachial artery followed by 20 minute cuff inflation. FMD was measured in all groups after 15 minutes of reperfusion. **RESULTS:** Twenty minutes of cuff inflation followed by reperfusion induced ischemic vascular injury as evidenced by impaired FMD (pre 7.4±0.6%, post -0.5 ±0.9%, p<0.001). In addition, ischemic preconditioning preserved endothelial function (FMD pre 6.8±0.6%, FMD post 7.4±1.0%, p=0.6, NS). Importantly, administration of BH4 also reduced the development of endothelial dysfunction (FMD pre 7.32±0.8%, FMD post 4.8±0.7%, p=0.03; p=0.002 compared with post-FMD of the ischemia-reperfusion group). **CONCLUSIONS:** Ischemia-reperfusion produces significant endothelial dysfunction in humans that can be prevented by ischemic preconditioning. Reperfusion injury is also dramatically attenuated by the administration of BH4. These findings suggest that reperfusion vascular injury occurs secondary to BH4 depletion and the uncoupling of eNOS.

9:30 a.m.

865-5 Six Months of Weight Loss Improves Metabolic and Vascular Indices in Overweight Adults

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Background: Obesity is a risk factor for cardiovascular disease and is characterized by metabolic and vascular abnormalities.We examined the effects of weight loss on metabolic and cardiovascular parameters. **Methods:** Twelve (F=9, M=3) overweight (BMI 30.3±3.7) adults (54.9±3.9 yr) without diabetes or vascular disease were counseled by a registered dietician to lose weight over six months. Vascular structure, function, and wall mechanical properties were measured via ultrasound. Insulin sensitivity (IVGTT), body composition (dual-energy x-ray absorptiometry), and lipids were also assessed. **Results:** There were significant reductions in body mass (86.3±14.2 vs. 79.5±13.8 kg, p<0.0001) and percent fat (44.3±7.0 vs. 41.0±8.5%, p<0.01) after weight loss. There were significant improvements in total cholesterol (230.9±33.9 vs. 194.8±30.7 mg/dl, p<0.0001), LDL-C (149.3±27.2 vs. 123.7±24.0 mg/dl, p<0.0001), triglycerides (131±88.6 vs.