

1027-187 Baseline Brachial Artery Diameter Is a Predictor of Endothelial Function Assessed by Brachial Artery Vasoreactivity Testing

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Background: Brachial artery vasoreactivity testing (BRT) is a non-invasive technique used to evaluate flow-mediated vasodilation (FMD), an endothelium-dependent function. **Methods:** To assess the impact of baseline brachial artery (BA) diameter on endothelial function, we prospectively assessed FMD in 289 consecutive healthy subjects (213 men, mean age 55±11 years) without coronary artery disease (CAD). After an overnight fast endothelium-dependent FMD and endothelium-independent nitroglycerin-mediated vasodilation (NTG) were assessed using high resolution (15 MHz) linear array ultrasound. Correlation analysis revealed a significant inverse association between baseline BA diameter and FMD (r=-0.74, p<0.00001). No association was found between systolic or diastolic blood pressure and BA diameter. Multivariate analysis demonstrated that baseline BA diameter was an independent predictor of FMD. Severe endothelial dysfunction (<6% FMD) was observed in 27% of the patients. We therefore divided the study population into 2 groups: Group A (n=78) with and Group B (n=211) without endothelial dysfunction.

Results: Both groups were comparable with regard to CAD risk factors, age, gender, body mass index, concomitant medications, lipids, resting heart rate and blood pressure (Table).

Conclusion: Baseline BA diameter in healthy subjects is inversely associated with FMD assessed by BRT independent of risk factors for CAD. The mechanism(s) responsible for this relationship warrant exploration.

	Group A (n=78)	Group B (n=211)	p-value
Brachial artery diameter (mm)	6.06±1.00	5.33±0.91	<0.00001
%FMD	1.6±3.2	14.7±3.1	<0.000001

1027-188 Relationship of Polymorphisms in the Oxidative Stress-Related Genes - Paraoxonase and p22phox - to Variant Angina and Coronary Artery Stenosis

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Background: Oxidative stress plays an important role in the pathogenesis of coronary atherosclerosis and spasm. We investigated whether the polymorphisms in two oxidative stress-related genes, paraoxonase and p22phox, are associated with risks of coronary artery spasm and stenosis. **Methods:** The study comprised of 116 patients with variant angina, 118 patients with coronary artery stenosis, and 117 control subjects, who were all classified by coronary angiography. In all three groups, the genotype frequencies of the Q192R polymorphism of the paraoxonase gene and C242T polymorphism of the p22phox gene were analyzed, and the serum thiobarbituric acid-reactive substance concentration was measured. **Results:** The frequency of the RR genotype of the paraoxonase Q192R polymorphism was significantly higher in patients with variant angina and coronary artery stenosis than in the control subjects (40.4% in variant angina and 37.8% in coronary artery stenosis vs. 24.7% in control, p=0.020 and 0.048, respectively). From the multivariate analysis, the odds ratio of the RR genotype was 2.240 for variant angina (95% confidence interval; 1.012-4.956), and 2.333 for coronary artery stenosis (95% confidence interval; 1.140-4.777), in relation to the control subjects. The thiobarbituric acid-reactive substance level was significantly higher in the RR type than in the QQ+QR types (RR vs. QQ+QR: 1.106 ± 0.420 nmol/mL vs. 0.949 ± 0.311 nmol/mL, p=0.028). There was no significant difference in the prevalence of C242T polymorphism of the p22phox gene between the three groups. **Conclusion:** The RR genotype of the paraoxonase gene Q192R polymorphism was found to be an independent risk factor of both coronary spasm and stenosis.

1027-189 Chronic Endothelin Receptor Antagonism Preserves Endothelial Function in a Transgenic Mouse Model of Alzheimer's Disease

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Background: Studies have demonstrated an association of Alzheimer disease (AD) with cerebrovascular dysfunction and a number of cardiovascular risk factors, and thus possibly with endothelial dysfunction. Endothelial dysfunction has been associated with an increased release of endothelin-1 (ET-1). The current study was designed to test the hypothesis that AD is associated with endothelial dysfunction and that chronic ET-1 antagonism improves endothelial function in a transgenic model of AD (Tg2576).

Methods: Three groups of mice were studied: C57BL/6 (normal control, n=6), Tg2576 (n=5), and Tg2576 fed Bosentan (100 mg/kg⁻¹/day⁻¹), a combined endothelin A and B receptor antagonist for 4 months (Tg2576+Bosentan, n=5). Mice were sacrificed at the age of seven months. Aortic artery vasorelaxation in response to the endothelium-dependent vasodilator acetylcholine (ACh) was determined in vitro.

Results: Maximum endothelium-dependent vasorelaxation of the aorta to ACh (10⁻⁵ mol/L) was significantly attenuated in Tg2576 mice. In contrast, in Tg2576+Bosentan mice endothelium-dependent vasorelaxation was similar to that observed in C57BL/6 mice (see figure). There was no difference between the 3 groups in response to the non-endothelial dependent vasodilator nitroprusside.

Conclusion: The current study demonstrates the presence of endothelial dysfunction in an established murine model of AD and suggests a pathophysiological role for the endogenous endothelin system in this disease process.

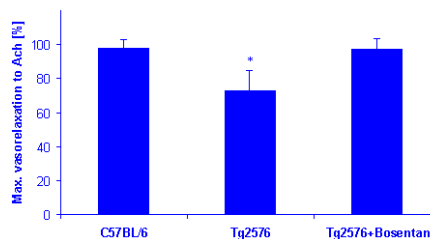


Figure. Maximal vasorelaxation of aorta to acetylcholine (ACh). *p<0.05 for other 2 groups.

1027-190 Whole-Body Insulin Resistance Precedes Vascular Insulin Resistance in a Murine Model of Diet-Induced Obesity

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Impaired nitric oxide (NO) bioactivity is a prominent feature of the vasculopathy associated with obesity and insulin resistance. Although insulin promotes endothelial NO production, the mechanistic relationship between insulin resistance and endothelial dysfunction is poorly defined. We tested the hypothesis that metabolic abnormalities precede endothelial dysfunction, using a model of diet-induced obesity in mice. Male C57b1/6 mice receiving an obesogenic diet (fat/carbohydrate -35%) from weaning were compared with chow-fed controls. Body weight, glucocopenance, fasting insulin and triglycerides, systolic blood pressure and vasomotor responses in aortic rings ex-vivo were assessed after 4 and 8 weeks of feeding.

Mice receiving an obesogenic diet developed a typical metabolic syndrome with obesity, hypertension, hyperglycemia, hyperinsulinemia and hypertriglyceridemia evident after 4 weeks. Whole-body insulin resistance, demonstrated by a blunted hypoglycemic response to exogenous insulin (0.75u/kg i.p) was apparent by 4 weeks. In aortic rings from control mice, preincubation with insulin (10mU/ml, 2 hours) significantly blunted the maximal constriction to phenylephrine (PE;10microM). This vascular effect of insulin was preserved in mice receiving an obesogenic diet for 4 weeks, but was lost after 8 weeks. In conclusion, these data indicate that the development of whole-body insulin resistance in a murine model of obesity, precedes insulin's NO dependent vasodilatory effects.

Results [mean]

Parameters	Weight (grams)	Epididymal Fat pad (mg)	Systolic BP (mmHg)	Fasting Blood sugar (mol/L)	Fasting Insulin (pg/ml)	Fasting Triglycerides (mol/L)	% Fall in blood sugar at 30 mins after insulin (i.p)	% Change in PE E-max after insulin preincubation
Control 4 weeks	24.1	11.6	116	6.4	0.55	0.7	70.2	-26.2
High Fat 4 weeks	29.0	24.3	123.0	12.0	1.03	5.3	54.2	-28.6
p value	<0.0001	<0.0001	<0.0001	<0.0001	<0.01	<0.0001	<0.0001	NS
Control 8 weeks	27.3	11.7	117.0	7.1	0.3	2.2	65.6	-18
High Fat 8 weeks	38.4	33.9	124.8	10.1	3.	5.4	48.4	+11.2
p value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.05

1027-191 Endothelial Dysfunction Accelerates Future Hypertensive Evolution and Causes Excess of Fatal Cardiovascular Events

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Introduction and hypothesis: We know little about the relationship between endothelial dysfunction (ED) and hypertensive evolution (HTE). This study assessed hypothesis that ED accelerates HTE. **Methods:** ED was graded by ultrasonic measured reactive changes in lumen diameter of brachial artery after transient forearm occlusion (FMD; flow-mediated endothelium-dependent vasodilation) in consecutive 518 patients with suspected coronary artery disease. The enrolled patients were categorized into 3 groups according to the values of FMD and we prospectively followed-up HTE and fatal cardiovascular events for 36 months or more. HTE was defined as two or more upstage of hypertension or new administration of an antihypertensive agent. **Results:** For a mean period of 57 months with 100% follow-up, the patients with severe endothelial dysfunction (FMD<4%; Group-L, n=174) more frequently manifested HTE compared to Group-M with mild endothelial dysfunction (4%≤FMD<8%, n=171) plus Group-H with preserved endothelial function (FMD 8% or more, n=173), and more frequently resulted in cardiovascular death. Cox proportional hazard model analysis including clinical variables showed that severe endothelial dysfunction was the strongest predictor for HTE and the only predictor for cardiovascular death. **Conclusion:** In conclusion, this is the first investigation demonstrating that endothelial dysfunction increases future hypertensive evolution and cardiovascular death.

	Group-L	Group-M	Group-H	Odds ratio	P value
HTE	44 (25.2%)	17 (9.9%)	9 (5.2%)	2.87	<0.001
Cardiovascular death	9 (5.2%)	1 (0.6%)	1 (0.6%)	10.34	0.022