1027-192 The Assessment of Arterial Compliance Using Noninvasive Techniques: A Comparison of Radial and Ocular Measures of Arterial Pressure and Flow

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Background: Nitric Oxide (NO) plays a pivotal role in controlling the tone of arteries.Modulation of NO, by using the donor Glyceryl Trinitrate (GTN) or the inhibitor N^G-Nitro-L-arginine methyl ester (L-NAME) alters arterial tone.Changes in vascular tone have traditionally been assessed in terms of steady-state haemodynamics.These ignore the importance of the pulsatile element of the circulation.The latter can be derived from analysis of the arterial pressure pulse contour recorded non-invasively. In this study we have compared the use of radial tonometry with novel ocular measures of arterial pressure and flow. Methods:10 healthy male volunteers had baseline radial artery pressure recorded using the HDI/ Pulsewave^{TM}CR-2000. Doppler ultrasound measures of flow in the ocular arteries was made, using the ATL^{TM}-HDI 3500 device. Ocular pressure was recorded directly using the OBF Pneumotonometer.0.5 milligrams GTN was administered sublingually. The above were then repeated after 3 minutes.A rest period of ten minutes ensued after which L-NAME was infused intravenously at a dose of 0.25 mg/kg/min for 8 minutes. The dose was then increased to 0.5 mg/kg/min for a further 8 minutes. All measures were repeated after the dose increment and at the end. Results:No significant change in Cardiac Output (CO) occured with GTN.Large arterial compliance was significantly improved as was small arterial compliance. The radial and ocular waveshapes changed significantly and consistently.CO was significantly decreased with L-NAME but this was confounded by the reduction in heart rate. Small arterial compliance was significantly reduced in a dose dependent fashion. A marked alteration in the pulse waveforms was detected with L-NAME. These changes were found at both the radial and ocular sites. Conclusions:Non-invasive measures of arterial tone can track changes in the vasculature in a sensitive manner. Pronounced changes occured in both the derived pulsatile parameters and the waveshapes in response to changes in NO. Ocular measures of arterial flow and pressure are comparable to radial studies and provide a unique and novel method for assessing the microirculation non-invasively.

1027-193 Influence of Genetic and Nongenetic Factors on Endothelium-Dependent Microvascular Reactivity in the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE)

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Background: Endothelial dysfunction is a known contributor to coronary disease. It is unclear what the additive contribution of traditional risk factors and genetic polymorphisms is on vascular reactivity in women with ischemic symptoms, and through what mechanisms.
Methods: We studied 79 WISE women who underwent coronary angiography for suspected ischemia. Average peak velocity ratio (APV-R) response to acetylcholine (Ach), which produces endothelium-dependent vasodilation, was measured. Linear regression was used to determine the joint effects of covariates on APV-R. Variables analyzed for inclusion in the model were: age, race, β_1-adrenergic receptor (AR), β_2AR, and Gsα genotypes, SBP, DBP, BMI, diabetes, hypertension, dyslipidemia, coronary artery disease, CAD severity score, smoking status, ever oral contraceptive (OC) use, ever HRT use, ACE inhibitor use, statin use, and menopausal status.
Results: The model of best fit (R^2 = 0.34, <0.0001) included the non-genetic variables history of hypertension (p=0.065), current smoker (p=0.0004), SBP (p=0.046), and ever OC use (p=0.061). The β_2AR Arg/Arg genotype at codon 16 (Arg16Arg) attenuated the microvascular response to Ach (parameter estimate -0.396, p=0.0903). In white women only, β_2AR Gln27Gln genotype improved APV-R by 0.535, while β_1AR Gly49 carrier status diminished the response by 0.515, suggesting a race-by-genotype interaction. Polymorphisms at β_1AR codon 389 and Gsα codon 131 had no effect.
Conclusion: Polymorphisms in the β_2AR and codon 49 of the β_1AR, and other non-genetic factors are associated with endothelium-dependent microvascular reactivity in women with ischemic symptoms. Consideration of these variables offers possible insights into mechanisms of microvascular dysfunction. The risk conferred by these variables on clinical outcomes should be investigated in a broad population.

1027-194 Effects of Irbesartan and Lipoic Acid on Endothelial Function and Serum Inflammatory Markers in Patients With the Metabolic Syndrome

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Background: The metabolic syndrome is associated with an increased incidence of early or accelerated atherosclerosis. An increased activity of angiotensin II, induction of the vascular oxidative state, and endothelial dysfunction are significant factors in the pathogenesis of atherosclerosis. We wished to investigate the effects of irbesartan, an angiotensin receptor blocker, and lipoic acid, an antioxidant, on endothelial function in patients with the metabolic syndrome.
Methods: We enrolled 32 subjects that met the criteria for the metabolic syndrome into the study. The subjects were randomized to placebo (Group A, n=8), 150mg/day irbesartan (Group B, n=8), 1 g/day lipoic acid (Group C, n=8), or irbesartan and lipoic acid (Group D, n=8) for 4 weeks. Serum levels of isoprostane and interleukin-6 (IL-6) were measured. Endothelial dependent flow mediated vasodilation (FMD) was also determined.
Results: The FMD was significantly increased in Group B (39.6±7.3 to 66.6±10.0%, p<0.005), Group C (42.5±6.4 to 61.6±8.0%, p<0.005), and Group D (40.8±8.1 to 72.2±8.4%, p<0.005). Serum levels of isoprostane were reduced in Group B (44.3±5.6 to 37.6±4.5 pg/ml, p<0.005) and Group D (46.1±6.5 to 36.0±5.3 pg/ml, p<0.005); no significant changes were noted in Groups A or C. There was a reduction in serum IL-6 in Group B (11.1±1.0 to 9.7±1.2 pg/ml, p<0.01), Group C (11.8±1.5 to 10.6±1.2 pg/ml, p<0.01), and Group D (11.5±0.8 to 9.5±0.8 pg/ml, p<0.01). No significant changes in blood pressure were noted in any of the study groups.
Conclusions: These findings suggest that administration of irbesartan and/or lipoic acid to patients with the metabolic syndrome improves endothelial function and reduces pro-inflammatory markers, factors which are implicated in the pathogenesis of atherosclerosis.

1027-195 Coronary Artery Disease Extent and Severity Is Associated With Pulse Wave Velocity, but Not Central Aortic Augmentation Index

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Background: Although it is proposed that central aortic pressure waveform characteristics, particularly augmentation index, influence cardiovascular disease progression and may predict cardiovascular risk, nothing is known of the relationship between central waveform characteristics and the severity and extent of coronary artery disease. We tested the hypothesis that coronary artery disease extent and severity are associated with central aortic pressure waveform characteristics in 40 patients (24 male).
Methods: Central aortic waveforms (2F Millar pressure transducer-tipped catheters) were acquired at the time of coronary angiography for suspected native coronary artery disease. The severity and extent of disease were assessed using 2 previously described scoring systems (Modified Sullivan's stenosis and extent scores). Relationships between disease scores, aortic waveform characteristics, aorto-radial pulse wave velocity (PWV) and subject demographic features and cardiovascular risk factors were assessed by regression techniques.
Results: Both extent and severity scores were associated with increasing age and male gender ($P < 0.001$), but no other risk factors. Both scores were independently associated with PWV ($P < 0.001$), which entered a multiple regression model prior to age and gender. This association was not related to mean, diastolic or systolic blood pressure. Neither score was associated with any central aortic waveform parameter, including augmentation index, by either simple linear regression or multiple linear regression techniques including heart rate and subject demographic features and cardiovascular risk factors.
Conclusion: Aorto-radial PWV, but not central aortic augmentation index, is associated with both the extent and severity of coronary artery disease.

1027-196 Tetrahydrobiopterin Corrects Escherichia Coli Endotoxin-Induced Endothelial Dysfunction

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Background. Acute inflammation causes endothelial dysfunction, which is partly mediated by oxidant stress and inactivation of nitric oxide (NO). The contribution of depletion of tetrahydrobiopterin (BH4), the cofactor required for NO generation, is unclear.
Methods. In this randomized, double blind, three-way cross-over study, forearm blood flow (FBF) responses to acetylcholine (ACh) and glyceryltrinitrate (GTN) were measured before and 4 hours after administration of Escherichia coli endotoxin (LPS, 20 IU/kg i.v.) in 8 healthy males. The effect of intra-arterial BH4 (500 µg/min), placebo, or vitamin C (24 mg/min) was studied 4 hours after LPS, respectively.
Results. ACh and GTN caused dose-dependent forearm vasodilation. LPS decreased FBF responses to ACh by 23 ± 6 % (p<0.05), which was restored to baseline responsiveness by BH4 and vitamin C. FBF responses to GTN were not affected by BH4 or Vitamin C. LPS increased leukocyte count, high sensitivity C-reactive protein, heart rate and body temperature and decreased platelet count and vitamin C concentrations. Vitamin C increased forearm plasma concentrations of BH4 from 17.3 ± 3.1 to 23.6 ± 4.2 nmol/l after LPS (p<0.02).*Conclusions.* Impaired endothelial function during acute inflammation can be restored by BH4 or vitamin C. Vitamin C may exert some of its effects by increasing BH4 concentrations.

1027-197 Endothelial-Dependent Vasodilation Does Not Improve With the Atkins' Diet in Diabetic Subjects

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Background: Vascular endothelial dysfunction has been associated with high-fat diets. We tested the hypothesis that the Atkins' diet will not improve endothelial function despite potential improvement in metabolic parameters. **Methods:** Eight obese (BMI> 30) diabetic subjects were admitted to our Clinical Research Center for 21 days. Subjects received their usual diet for 7 days, then received 14 days of the high fat/low-carbohydrate induction phase of the Atkins' diet. Flow-mediated dilation was assessed (n=7) before and after 2 weeks of the Atkins' diet using brachial artery ultrasound to measure artery diameter and blood velocity at baseline, during post-cuff occlusion reactive hyperemia (endothelium-dependent vasodilation (EDV)), and after 0.4 mg of sublingual nitroglycerin (endothelium-independent vasodilation (EIV)). **Results:** The 2-week Atkins' diet resulted in an average weight loss of 6.9 ± 2.4 lbs, p<0.05. There was no significant change in total cholesterol, LDL or HDL cholesterol. Triglycerides decreased 25%, from 150 ± 21 to 113 ± 23 mg/dl (p=0.007). Fasting glucose fell 23%, from 140 ± 9 to 108 ± 5 mg/dl (p=0.004). Despite these favorable metabolic changes EDV remained unaltered.