The Assessment of Arterial Compliance Using Noninvasive Techniques: A Comparison of Radial and Occlusive Measures of Arterial Pressure and Flow

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Background: Nitric Oxide (NO) plays a pivotal role in controlling the tone of arteriess.Modulation of NO, by using the donor Glycerol Trinitrate (GTN) or the inhibitor N5-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 component of the circulation. The present study examined the analysis of the arterial pressure pulse contour recorded non-invasively. In this study we have compared the use of radial tonometry with novel occlusive measures of arterial pressure and flow.

Methods: 10 healthy male volunteers had baseline radial artery pressure recorded using the NDDPulsewave 3CR™. Doppler ultrasound measures of flow in the ocular arteries was made, using the ATL™HD 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 earlier (p<0.05). Coronary artery disease severity score, smoking status, ever oral contraceptive (OC) use, ever HRT use, was explored in the model. Polymorphisms in the 

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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 criteria and extent scores). Aortic arterial disease severity 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.

Tetrahydrobiopterin Corrects Escherichia Coi Endothelin-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 GTN were measured. Linear regression was used to determine the joint effects of covariates on ACh-FBF. Variables analyzed for inclusion in the model were: age, race, 16-adrenergic receptor (AR), 2AR and Gs genotypes, SNP, DBP, BMI, diabetes, hypertension, dyslipidemia, coronary artery disease, CAD severity score. EIV, age of onset (CO) use, ever HRT use, ACE inhibitor use, statin use, and menopausal status.

Results: The model of best fit (R^2 = 0.34, <0.001) included the non-genetic variables history of hypertension (p=0.065), current smoker (p=0.0004), BP (p=0.046), and ever Q10 use. (p=0.008). ACh (p=0.08) and GTN (p=0.08) caused dose-dependent forearm vasodilation. FBF responses to GTN were attenuated by BH4 concentrations.

Conclusion: Polymorphisms in the 2AR and codon 49 of the 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 variants on clinical outcomes should be investigated in a broad population.

Effects of Ibsentaran and Lipic 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 ibsentaran, an angiotensin receptor blocker, and lipic 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 ibsentaran (Group B, n=8), 1 g/day lipic acid (Group C, n=8), or ibsentaran and lipic acid (Group D, n=8) for 4 weeks. Serum levels of interleukin-6 and interleukin-8 (IL-6) were measured. Endothelial dependent flow mediated vasodilation (FMD) was also determined.

Results: The FMD was significantly increased in Group B (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 isoprostanes were reduced in Group B (43.7±6.5 to 37.6±4.0, p<0.005) and Group C (43.7±6.5 to 36.0±3.0, 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 9.9±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 ibsentaRan and/or lipic acid to patients with the metabolic syndrome improves endothelial function and reduces proinflammatory markers, factors which are implicated in the pathogenesis of atherosclerosis.

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 criteria and extent scores). Aortic arterial disease severity 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.

Endothelial-Derpend Vasodilatation Does Not Improve With the Atkins’ Diet in Diabetic Subjects

Helene L. Gissberg, Joseph R. Libonati, III, Xuyu Zhang, Randi DeSilva, Karin Sargrad, Alfred A. Bove, Guenther Boden, Temple University School of Medicine, Philadelphia, PA

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 arterial 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 (EVI)).

Results: The 2-week Atkins’ diet resulted in a significant weight loss of 6.8 ± 2.4 lbs. 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.

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The Effect of Body Weight Change on Arterial Wall Properties

Christos Papamichael, Georgia Varnavou, Kimon Stamatakopoulos, Konstantinos Annacourdis, Paraskevi Katsichi, Ignatios Oikonomidis, Emmanouil Karatzis, Vasilios Sideris, John Lekakis, Myron Mayrikis, Alexandra University Hospital, Athens, Greece

Background: Excess weight gain in adulthood increases the risk for CAD, hypertension and diabetes mellitus and is associated with higher intima-media wall thickness (IMT) of the carotid artery.

Objective: To examine the effect of weight gain since adolescence on vascular wall properties.

Methods: Seventy-one healthy individuals (26 men, age 36.5 ± 9 years) with a wide range of body-mass index (BMI, 28.8 ± 6.9, 19.3 – 57.9 kg/m²) without any risk factors for CAD were examined. Weight change was calculated as the difference between weight at the baseline examination and self-reported weight at age 18. Each participant was examined for flow-mediated dilation (FMD) of the brachial artery, IMT at 3 sites of the carotid artery and compliance and distensibility in the common carotid artery.

Results: Mean weight gain was 15.9 ± 15.1 kg (range -15 to 86 kgs). Weight gain was significantly correlated with IMT (r=0.339, p<0.005), FMD (r=-0.250, p<0.05) and pulse pressure (r=0.284, p<0.05). Weight gain was stronger predictor of combined and carotid bulb IMT when compared to waist to hip ratio (WHR) and BMI. When adjusted for gender, current BMI, WHR and systolic and diastolic blood pressure, weight gain was still an independent predictor of carotid bulb IMT. Individuals with more than 10 kgr weight gain had significantly lower FMD (p=0.05), carotid distensibility and compliance (p<0.05) and higher IMT in the internal carotid artery (p<0.05).

Conclusion: Weight gain in adulthood is an important parameter which significantly affects vascular wall properties independently of current BMI and body fat distribution.

POSTER SESSION

1028

Inflammation, Insulin Resistance, and Cardiovascular Risk I

Sunday, March 07, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1028-T155

Obesity Is the Major Determinant of Elevated C-Reactive Protein in Subjects With the Metabolic Syndrome

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Introduction: Elevated C-reactive protein (CRP) is strongly associated with characteristics of the metabolic syndrome (MS). However, the relative importance of various components of the MS in promoting the inflammatory state is unclear.

Subjects: We conducted a population-based cross sectional study of 1929 apparently healthy subjects (age 50 ± 10 years; 63% males). Diagnosis of the MS was based on the ATP III Criteria. The relationship between CRP and the MS was assessed using general linear models adjusting for age, gender, physical activity, HRT, smoking, BMI, triglycerides, HDL, fasting glucose, and hypertension.

Results: Subjects with obesity (Ob+) had markedly higher CRP level compared to subjects without obesity (Ob-) regardless of whether they had the MS (Figure A). There was no significant difference in CRP levels between obese subjects without the MS (MS-, Ob-) and subjects in whom the diagnosis of the metabolic syndrome was based on criteria other than obesity (MS+, Ob-) (P=0.79). Similarly, CRP levels did not differ among obese subjects with (MS+, Ob+) and without (MS-, Ob+) the metabolic syndrome (P=0.99). There was a linear increase in CRP levels with an increase in the number of metabolic disorders (Figure B). However, the relationship substantially diminished after controlling for BMI.

Conclusion: Obesity is the most important contributor to the chronic subclinical inflammation associated with the metabolic syndrome.

1028-185

Association of Coronary Heart Disease With Interleukin-1 Gene Variants in the Atherosclerosis Risk in Communities Study

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Background: Current evidence supports the hypothesis that proinflammatory variants of the interleukin-1 (IL-1) gene cluster are associated with elevated levels of C-reactive protein and may confer an increased risk of coronary heart disease (CHD).

Introduction: To investigate further the role of IL-1 in the pathogenesis of CHD, we analyzed variations IL-1A(+4845), IL-1B(+3954), IL-1B(-511), and IL-1RN(+2018) in the genes for IL-1α, IL-1β, and IL-1ra. A subset of the Atherosclerosis Risk in Communities (ARIC) Study comprising a case sample of 955 with incident CHD (myocardial infarction, fatal CHD, or cardiac procedure) and a 918-person cohort random sample was used. Proportional hazards regression was done using SAS Proc PHREG with Barlow macro to adjust for stratified sampling.

Results: Adjusting for age, gender, race, diabetes, smoking, cholesterol, and hypertension, statistically significant associations in CHD hazard ratio (HR) were demonstrated for IL-1A(+4845), IL-1B(+3954), IL-1B(-511), and IL-1RN(+2018). The strongest genetic association was found in a subset with total cholesterol <200 mg/dl, a population considered to be at relatively low risk for CHD. In these 261 cases and 325 non-cases, HR for IL-1B(+4845) 2.2 vs 1.1, 1.0 to 1.2 p=0.0034. Similar results (HRR=4.95, p<0.005) were obtained for a sensitivity analysis of 2.2 vs. 1.1, indicating that inclusion of heterozygotes in the reference group is not pivotal. Significance was achieved in both racial groups, but the effect in African Americans (HRR=20.3, p<0.0005) is intriguingly large compared to that in Caucasians (HRR=3.27, p=0.025). The modest number of African Americans with a 2.2 genotype (n=7) may play some role in this finding, but bona fide population differences may also be responsible.

Conclusion: These findings suggest that certain IL-1 gene variants impart an increased risk for CHD that behaves independently of traditional risk factors such as diabetes and smoking. Moreover, the importance of IL-1 genes is most apparent in those who are not already at high risk due to elevated cholesterol.