819-4 Obesity Predicts Coronary Endothelial Dysfunction Independently of Inflammation, Atherosclerosis, and Conventional Risk Factors

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Background: Obesity is a well recognized modifiable risk factor for coronary artery disease (CAD) that is associated with insulin resistance, dyslipidemia, hypertension and low-grade inflammation. We investigated the relationship between coronary vascular endothelial dysfunction, obesity and its metabolic correlates.

Methods: Coronary vascular function testing was performed in 418 patients (203 with normal coronary arteries). Change in coronary blood flow (dCBF) was measured using a Doppler flowwire during intra-coronary acetylcholine (15mg/min), and adenosine (2.2mg/min) infusion to test endothelium-dependent, and independent coronary microvascular function. Patients were grouped according to body mass index (BMI): group 1 (<25kg/m^2, n=90), group 2 (25-30kg/m^2, n=163), group 3 (>30kg/m^2, n=164).

Results: Prevalence of diabetes and hypertension, as well as total cholesterol, low density lipoprotein, and triglyceride levels were increased, whereas high density lipoprotein was lower with increasing BMI. C-reactive protein (CRP) was elevated in group 3 compared with 1 and 2 (1.15±0.73 versus 0.74±0.67 and 0.74±0.57mg/dl respectively, p<0.001). During acetylcholine administration, dCBF was reduced with increasing BMI (13.3±11.9% versus 8.3±4.9% in group 1 and 3 respectively, p=0.009). Atorvastatin was similar during adenosine infusion (377±152, 363±173, and 358±186% in groups 1-3 respectively p=0.67). The association between BMI group and dCBF with acetylcholine was independent of CAD and its risk factors, including CRP, by multivariable analysis (p=0.05). Furthermore, reduced dCBF with acetylcholine was also observed in the cohort of obese subjects with normal coronary arteries (135±85, Versus 102±84% in groups 1 and 3 respectively, p=0.01).

Conclusion: The relationship between obesity and coronary vascular endothelial dysfunction remains independent of the associated adverse CAD risk profile factor. Thus, weight loss may improve CAD risk over and above the observed benefits on conventional risk factors.

3:00 p.m.

819-5 Atorvastatin Restores Endothelial Function in Normocholesterolemic Smokers

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Cigarette smoking impairs endothelial function and is a major cause of atherosclerosis. Research suggests that statins benefit vascular function independent of their lipid lowering effects. We hypothesized that statin therapy would improve endothelial function in normocholesterolemic smokers. We performed a randomized, double-blind, crossover, placebo-controlled study of atorvastatin (Atorva), 40 mg daily, in 20 smokers (S) and 20 healthy subjects (H). Subjects had vascular function testing and skin biopsy after each 30 day treatment period. Ultrasonography was used to measure brachial artery flow-mediated endothelium-dependent vasodilation (EDV) and nitric oxide-induced (0.4 mg) endothelium-independent vasodilation (EIV). To determine mechanisms of the findings skin endothelial NO synthase (eNOS) mRNA expression was assessed by RT-PCR and normalizing to GAPDH. Skin nitrosyline concentration, an intracellular marker of oxidative stress, was determined via enzyme immunosorbent assay. The mean age (42±38 years), total cholesterol (188±176 mg/dL), LDL (103±95 mg/dL), and HDL (54±54 mg/dL) (all p>0.1) were similar in S and H, respectively. EDV was less in S compared with H (8.0% vs. 12.1%, p=0.03), but there was no difference in EIV (18.6% vs. 21.0%, p=0.34). Atorva restored EDV in S (8.0% to 10.5%, p=0.017), but had no effect in H (12.1% vs. 14.5%, p=0.003), but there was no difference in EIV (18.6% vs. 21.0%, p=0.34). Atorva restored endothelial function in normocholesterolemic smokers, independent of LDL lowering. Improved NO bioavailability in statin, may result from eNOS activity changes, since it cannot be ascribed to changes in eNOS content or reduction in oxidative stress.

3:15 p.m.

819-6 Inducible Nitric Oxide Synthase Activity Does Not Contribute to the Maintenance of Peripheral Vascular Tone in Patients With Symptomatic Congestive Heart Failure

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Background: There have been previous reports of inducible nitric oxide synthase (iNOS) activity in the peripheral vasculature of patients with symptomatic congestive heart failure (CHF). However, these studies used the poorly selective inhibitor, aminoguanidine, which has considerable action on endothelial nitric oxide synthase (eNOS). For the first time, we have used the highly selective iNOS inhibitor, 1400W (<10,000-fold more selective for iNOS than for eNOS) to determine whether iNOS activity contributes to the maintenance of vascular tone in patients with symptomatic CHF.

Methods: Bilateral forearm blood flow was recorded using strain-gauge plethysmography in 10 patients with CHF (New York Heart Association Class II-IV) during intra-brachial infusion of 1400W (0.1-1 µmol/min), Nω-nitro-L-arginine (L-NMMA, a non-selective NOS inhibitor; 2-8 µmol/min) and norepinephrine (as a control vasodilator; 60-480 µmol/min).

Results: There were no changes in heart rate, mean arterial pressure or non-infused forearm blood flow during infusions. Intra-brachial infusion of L-NMMA and norepinephrine caused dose dependent reductions in infused forearm blood flow (p<0.05 for both): peak reductions of 28±4% and 48±6% respectively. In contrast, 1400W had no effect on blood flow: +2±3% change with 1400W at 1 µmol/min (95% confidence intervals, -7 to 3%, p=NS).

Conclusion: In contrast to earlier reports, we have found that selective NOS inhibition does not affect forearm blood flow in patients with CHF. These findings suggest that the effects on vascular tone seen after administration of poorly selective NOS inhibitors may be largely due to inhibition of eNOS. Inducible NOS activity does not appear to contribute to the maintenance of peripheral vascular tone in patients with symptomatic CHF.