transcriptional control of e-NOS (i.e. mRNA) is not impaired and appears to be upregulated in the presence of vascular dysfunction. Measurement of tissue expression of mRNA for e-NOS is a novel indicator of vascular dysfunction that may be helpful in mechanistic studies.

1056-81   The Combination of Renin-Angiotensin System Inhibitors and HMG-CoA Reductase Inhibitors in Atherosclerosis: Effects on Vascular Endothelial Function

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Background: Endothelial dysfunction plays a fundamental role through which cardiovascular risk factors contribute to atherosclerosis. Several pharmacological agents, including HMG-CoA reductase (HMGR) inhibitors and renin-angiotensin system (RAS) inhibitors, appear to possess cardioprotective effects via mechanisms that may reverse vascular endothelial dysfunction in atherosclerosis.
Methods: We studied 124 normotensive and hyperlipidemic patients with stable coronary artery disease on a medical regimen including aspirin (CON). The patients were treated with the HMGR inhibitor atorvastatin (ATO, 10-40 mg/day) to obtain a serum LDL cholesterol of <100 mg/dl. The subjects were then randomized to either of two RAS inhibitors: the angiotensin converting enzyme inhibitor quinapril (QUI, n=65, 20 mg/day) or the angiotensin II type 1 receptor inhibitor irbesartan (IRB, n=59, 150 mg/day) for 12 weeks.
**Results:** Using ELISA analysis, treatment with ATO slightly reduced serum soluble vascular cell adhesion molecule-1 (sVCAM-1) levels from CON (CON: 433±72; ATO: 382±58 ng/ml, p<0.05). Moreover, the addition of QUI or IRB reduced sVCAM-1 further by 33% and 36% respectively (both p<0.01 from CON and ATO). Also, treatment with ATO reduced serum soluble interleukin-6 (sIL-6) by 17% (CON: 25.3±3.3; ATO: 21.5±2.3 ng/ml, p<0.045); additional therapy with QUI or IRB reduced sIL-6 by 29% and 40%, respectively (both p<0.01 from CON and ATO). Treatment with ATO did not significantly affect the adhesion of monocytes to the monoclonal antibody CD11b, a protein with high binding affinity to human monocytes (CON: 75±11; ATO: 78±14 percent binding, NS). However, the addition of QUI or IRB to ATO therapy dramatically suppressed monocyte binding to CD11b (QUI: 34±8; IRB: 27±9 percent binding, both p<0.01 from CON or ATO).
Conclusions: These findings suggest that HMGR inhibitors and RAS inhibitors have functions in addition to reductions in serum cholesterol and blood pressure. Furthermore, the combination of these agents may significantly reduce the effects and expression of vascular inflammatory and oxidative mechanisms in the pathogenesis of atherosclerosis.

1056-82   Prediction of Sites of Progression of Native Coronary Disease In-Vivo Based on Identification of Sites of Low Endothelial Shear Stress

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Background: Endothelial shear stress (ESS) plays a critical role in atherogenesis: Low ESS increases production of inflammatory, growth, and adhesion molecules, and correlates with atherosclerosis. It has previously not been possible to predict sites of coronary disease (CAD) progression in vivo. The purpose of this study was to determine if CAD progression could be predicted in vivo based on ESS. Methods: We studied 4 patients at baseline and after 6 mos. The 3-D anatomy of an arterial segment with luminal obstruction < 50% was determined using intracoronary ultrasound, biplane angiography, and coronary flow measurements. The lumen was reassembled in accurate 3-D space; local ESS was calculated using computational fluid dynamics. Outer vessel dimensions (external elastic lamina [EEL]) and the plaque (difference between EEL and the lumen) were similarly reconstructed. The techniques are highly reproducible. Changes in the artery at 6 mos were assessed by general linear regression accounting for repeated measurements. Results: Baseline ESS ranged from 3-71 dynes/cm2. Low ESS was inversely associated with subsequent plaque progression (p<0.001); high ESS was associated with outward remodeling (p<0.01). Conclusions: These results show, for the first time in man, that sites of CAD progression over 6 mos can be identified in vivo. This methodology can detect minute changes in the coronary lumen, wall, and plaque and may be used to identify the natural history of CAD and the vascular response to therapies.
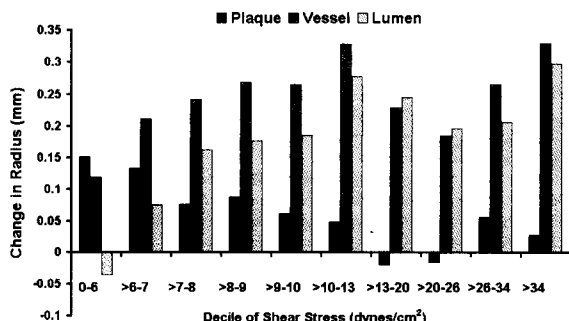
1056-83   Bradykinin B1 Receptor Gene Polymorphism is Associated With Impaired Coronary Reactivity in Women: A Report From the NHLBI WISE Study

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Background: Bradykinin and related peptides (terminal kinins) promote vasodilation, endothelial NO production, and vascular permeability. Kinin fragments interact with bradykinin B1 receptors (B1R), which couple to G-proteins. We hypothesized that the kinin system's protective effect on the coronary circulation may be reduced in patients with polymorphic (deficient) alleles of the B1R gene.
Methods: We studied 148 women enrolled in the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE). Women underwent quantitative coronary angiography (QCA) and genetic analysis for the G to C polymorphism at position -699 of the gene. Seventy women underwent intracoronary Doppler flow studies. Volumetric flow was calculated from coronary cross sectional area (CSA) and flow velocity. Measurements were made at baseline and in response to adenosine, acetylcholine, and nitroglycerin. Flow ratios with each agent to flow at baseline were calculated.
Results: Twenty-five women (20.3%) carried the B1R gene polymorphism. Women carrying the polymorphism (CG genotype) showed a significant decrease in response to adenosine. Their mean flow ratio was 2.05 ± 0.30, while "wildtype" women (GG genotype) had a mean ratio of 2.78 ± 0.15 (p=0.047). This change in flow ratio was due to a decrease in velocity (p=0.022), rather than to a change in CSA (p=0.78). Similar results were obtained in response to nitroglycerin. Women with the polymorphism had flow ratio of 2.47 ± 0.24 versus 3.36 ± 0.14 for the wildtype genotype (p=0.029). When acetylcholine (an endothelial mediator) was tested, no difference was seen by genotype (p=0.55). No difference by genotype was seen for age, severity of angiographic coronary artery disease (CAD), hypertension, diabetes, dyslipidemia, or smoking.
Conclusion: A polymorphism in the bradykinin B1R gene is associated with impaired coronary reactivity in women. This association occurs independently of angiographic CAD, coronary risk factors, and endothelial mediated response. While some have suggested that impaired coronary reactivity may be a feature of early atherosclerosis, our data suggest that intrinsic genetic factors contribute to coronary smooth muscle reactivity, as well.

1056-84   Determination of Shear Stress in Patients Confirms That Lumen Preservation in Atherosclerosis Is Associated With Shear Stress Regulation

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BACKGROUND: Previous studies showed that atherosclerotic plaques preferentially develop at average low shear stress (SS) locations. SS is known to control lumen dimensions under physiological variations. We hypothesized that in the development of atherosclerosis outward remodeling, while preserving the lumen, is controlled by SS.
METHODS: In 12 atherosclerotic patients, interventionally treated for coronary lumen narrowing, a non-treated angiographically normal coronary artery (lumen stenosis <50%) was investigated with a combined ANGiographic and ivUS technique (ANGUS) to provide true 3D lumen and vessel wall geometry. Segments in between side branches were selected, resulting in 22 segments. The 3D reconstruction served to calculate SS by computational fluid dynamics. Inflow for the segments was selected to deliver an average SS of 15 dynes/cm2 in normal reference (ref) cross sections (minimal plaque area). Lumen area (LA) stenosis (AS) was defined as (LA -LAref) / LAref * 100%. SS and wall thickness (Th) data were measured at 16 different circumferential locations. For each segment, data were averaged over all cross sections. Linear regression analysis was used to relate Th to SS (Th=a+b*SS). Two groups were compared based on AS (AS <-10% and AS >-10%).
RESULTS: For preserved lumen areas (AS>-10%, average AS = 0.01 being not different from 0, p=0.8) the slope (b) of the relationship between Th and SS was negative, indicating shear stress control (N=14, b = -6.1*10-4 ±9.8*10-4 m3/N : p=0.036). For AS<-10% no relationship was observed (N=8, b = 0.9*10-4± 5.2*10-4 m3/N, p=0.6). The slopes of both groups were also different (p=0.038).
CONCLUSION: These data show for the first time in coronary arteries of patients that lumen preservation is obtained by SS regulation.