ABSTRACTS - Hypertension, Vascular Disease, and Prevention

JACC
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240A

Selective Expression of Tenasin in the Coronary Artery and Its High Affinity Interaction With LDL May Account for Lipid Retention Capacity of Coronary Vessels and Their Susceptibility to Atherosclerosis


Background: Several studies have shown that internal mammary artery (IMA) in its native position as well as when grafted into coronary circulation is resistant to atherosclerosis even in patients with extensive atherosclerosis elsewhere. To understand the molecular basis for this anti-athero-protective nature of the coronary artery and artery-protective properties of mammary artery.

Methods: We have used porcine coronary and mammary arteries, and suppression subtractive hybridization (SSH) to generate profile of artery-specific gene expression. From a 3000 clones SSH-DNA repertoire, we have screened the libraries by dot blot array and sequenced 2000 promising artery-specific clones. Northern blot and in-situ hybridization confirmed the differential gene expression pattern identified by the array. Cluster analysis of the sequences revealed that extracellular matrix genes that are involved in lipid retention and metabolism are predominantly expressed in the coronary artery. We hypothesized that, unlike IMA, the extracellular matrix of the coronary artery retains lipids.

Therefore, we examined the interaction between tenasin, a coronary-specific gene, and LDL and minimally oxidized LDL (mo-LDL).

Results: Both LDL and mo-LDL exhibited concentration-dependent saturable binding to tenasin with similar Kd values of 4.2 ± 2.6 and 5.1 ± 1.8 mM, respectively. The Bmax for ox-LDL was about 55% less than that for LDL. 28 ± 4 and 65 ± 8 kDa, respectively. Additional experiments showed that at physiologic concentrations, CoA and Mgp increased mo-LDL binding to tenasin 2.3- and 6.2-fold, respectively.

Conclusion: Taken together with the preferential expression of other lipid binding proteins in the coronary artery, tenasin and its high affinity binding to LDL may raise a possibility that unlike mammary artery, coronary arteries have an intrinsic capacity to retain lipids. This may partly explain the artery-protective nature of coronary arteries.

1128-91

Insulin Resistance Impairs Endothelial Function by Enhancing Oxidation of Low Density Lipoprotein in Healthy Young Men

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Background: Both insulin resistance and LDL oxidation play important roles in the pathogenesis of atherosclerosis. Recent studies have suggested that there is a significant correlation between these factors and endothelial function in healthy young men, because endothelial dysfunction is regarded as an early step in the development of atherosclerosis.

Methods: Thirty-three men (aged 28.0±2.5 years), who had no history of any chronic diseases including diabetes mellitus, were enrolled in this study. We evaluated endothelial function estimated by flow-mediated vasodilation and by insulin sensitivity estimated by homeostasis model assessment insulin resistance (HOMA-IR).

Results: The plasma oxLDL level was significantly correlated with the body weight (r=0.436, P<0.05), body mass index (r=0.459, P<0.01), and HOMA-IR function (r=0.396), respectively. Furthermore, HOMA-IR cell function was significantly correlated with endothelium-dependent flow-mediated vasodilation (r=-0.375, P<0.05). When we divided these subjects into two subgroups according to HOMA-IR level (insulin-resistant group with a HOMA-IR of 0.386, P<0.05, and insulin-sensitive group with a HOMA-IR of 0.093, P=0.96), respectively. In insulin-resistant group, in contrast, insulin-sensitive group showed no significant relationship between these parameters and flow-mediated vasodilation. A stepwise multiple regression analysis showed that the relationship between endothelium-dependent flow-mediated vasodilation (P<0.503).

Conclusions: These results suggest the possibility that insulin resistance enhances oxidation of circulating LDL particles and thus impairs endothelial function even in healthy young men.

1128-80

Immunization With a Novel Human Apo B100 Related Peptide Reduces Atherosclerosis in Apo E Null Mice

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Background: Immunization with homologous LDL reduces atherosclerosis in animals. To develop a clinically testable strategy, we sought to design and test human apoB100 related peptides as immunogens.

Method: A polypeptide library of 20 amino acid peptides covering the human apoB sequence was screened. Two peptides were subsequently identified using patient and normal sera, and identified as potential immunogens. Day-week old apoB null mice were then immunized with 33 μg of P1 (t=10) or P2 (t=10) with Alum as adjuvant, followed 3 weeks later by a booster. Control mice received Alum alone (N=9). Mice were fed a high cholesterol diet for 12 weeks of age. After sacrifice 25 mice of the day 30 and 20 mice of the day 45 groups were used for the experiments.

Results: The plasma cholesterol was decreased in both groups (0.102±0.055% and 0.124±0.086% lesion area) as compared to controls given adjuvant alone 0.287±0.071%; p<0.0001), immunization with peptides A did not influence lesion area. In the coronary arteries, the expression of tenasin and its high affinity interaction with LDL may account for lipid retention in tenasin with similar Kd values of 4.2 ± 2.6 and 5.1 ± 1.8 mM, respectively. The Bmax for ox-LDL was about 55% less than that for LDL.

Conclusion: Immunization with specific human apoB100 related peptide P2 markedly reduced aortic atherosclerotic lesions, reduced inflammation, and altered plaque composition in apoE null mice despite severe hypercholesterolemia raising the possibility of future clinical testing.

1128-89

Immunization With a MDA-Modified Apo B Peptide Sequences

Gillina Nordstrom, Friskman, Marie Lindholm, Ingrid Soderberg, Paul Dmuyaka, Jan Nilsson, Department of Medicine, Malmo, Sweden.

LDL oxidation is believed to have an important role in the development of atherosclerosis. Oxidized LDL has been shown to activate antibody-mediated immune responses. Experiments in which animals have been immunized with oxidized LDL suggest that these immune responses inhibit atherosclerosis. Epitopes in oxidized LDL that induce antibody formation in man was identified by ELISA using a library of native and MDA-modified polypeptides covering the complete apo B sequence. The ability of these epitopes to induce atherosclerosis was examined in apoE(null) mice. Mice were immunized at 8 and 9 weeks of age with 100 μg of (A) MDA-modified peptides against which high IgG levels were detected in CHD patients, (B) native peptides against which high IgG levels were detected in healthy controls and (C) MDA-modified peptides against which high IgG levels were detected in healthy controls.

Conclusions: These results suggest the possibility that insulin resistance enhances oxidation of circulating LDL particles and thus impairs endothelial function even in healthy young men.
with the blocking antibody to LOX-1 (10 mg/ml) prevented the expression of MMPs (both P<0.01 vs. ox-LDL group) and TIMP2 in response to ox-LDL. PKC inhibitor blocked the affects of ox-LDL on the expression of MMPs (all P<0.01 vs. ox-LDL group) and TIMP2. 

Conclusion: These observations indicate that expression of LOX-1 may affect the stability of atherosclerotic plaques by modulation of MMP1, MMP3 and TIMP2 expression. In this process, the effect of LOX-1 is associated with activation of PKC pathway.

POSTER SESSION

1129 Aortic and Peripheral Arterial Disease: Clinical Assessment and Treatment

Monday, March 18, 2002, 3:00 p.m.-5:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: 3:00 p.m.-4:00 p.m.

1129-69 Excess Mortality of Type A Aortic Dissection in Women: Impact of Delayed Diagnosis
Barbara M. Richartz, Jeanea V. Cooper, Dean E. Smith, Rajendra M. Mehta, Kim A. Eagle, Christopher A. Nienaber, on Behalf of International Registry of Acute Aortic Dissection (IRAD), Ann Arbor, Michigan.

Background: Acute type A aortic dissection (AAD) is associated with a high mortality and morbidity and delayed diagnosis and treatment leads to excess mortality. The present analysis from the International Registry of Acute Aortic Dissection (IRAD) focuses on in-hospital mortality and gender differences in relation to the delay in diagnosis/treatment.

Methods: 599 patients with AAD were enrolled in the IRAD database. In-hospital mortality and gender differences were analyzed in relation to the interval between symptom onset and diagnosis (T1), and between established diagnosis and surgical treatment (T2) using Pearson Chi-square test. The intervals T1 and T2 were subdivided in three time frames: A (0-4h), B (4-24h), and C (>24h).

Results: Of all AAD patients, 34% were female (p < 0.02). Overall, in-hospital mortality was 34% in female vs 25% in male patients (p < 0.02). A significant delay to diagnosis (T1) was documented in women reflected in a lower percentage of women in the early time frame A (24% vs 20%) and intermediate frame B (28% vs 36%), and a high proportion in the late frame C (48% vs 35%) (p = 0.05). With respect to T2 (time to treatment) no difference was documented in the proportion of either sex. (T2: 42% vs 46% men. 27% vs 31% men, 29% vs 23% men, ns).

Conclusions: A significant time delay to diagnosis, but not to the initiation of treatment, causes excess mortality in women. Currently, further analyses are underway to clarify if the delay is due to more atypical symptoms, or other factors that may be interacting with gender.

Clinical Outcomes of Patients Presenting With Aortic Intramural Hematoma Versus Communicating Dissection Affecting the Descending Aorta
Monika B. Schill, Michael L. Lieber, Jane M. Kasper, Richard D. White, Cleveland Clinic Foundation, Cleveland, Ohio.

Background: Aortic intramural hematoma (IH) is a variant of aortic dissection, distinguished by absence of both intimal tear and direct flow between true and false lumens, and often thought to be more stable. This study evaluated for differences between outcomes in IH compared with communicating dissection (CD) affecting the descending aorta.

Methods: Patients who underwent computed tomography (CT) or magnetic resonance imaging (MRI) for evaluation of acute aortic dissection were identified. IH was confirmed by MRI, and CD was diagnosed by either MRI or CT. Only patients with an acute presentation and involvement limited to the descending aorta were included. One-year follow-up data was obtained on each patient.

Results: Nineteen patients with IH and 37 patients with CD were identified. Demographics and traditional cardiac risk factors were compared between each group. Hypertension was present in greater than 80% of the patients in both groups. Tobacco use was significantly higher in IH compared with CD (81% vs 47%, p < 0.05). Although IH patients were generally older (67 ± 13.3 vs 61 ± 11.5), with more evidence of coronary artery disease (37% vs 13%), these characteristics were not significantly different between each group. IH often had involvement of the distal arch (53%) or to the renal arteries (46%), with none extending to the iliacs. In contrast, CD more often showed extension distal to RA (50%). A higher rate of unfavorable outcomes was seen in IH compared to CD patients, though this difference was not statistically significant (58% vs 36%, p=NS). Outcomes in IH consisted of end-organ ischemia in 5 patients (16%) and moderate to severe de-endothelialization with saccular outgrowths in the hematoma in 8 patients (42%). In CD, end-organ ischemia occurred in 6 patients (16%), rupture in 4 patients (11%), and progressive aneurysm dilation in 5 patients (14%).

Conclusions: IH and CD limited to the descending aorta represent two distinct disease entities, with differing clinical characteristics and outcomes. Importantly, IH is not a precursor to CD.