812 New Vascular Imaging and Therapeutics

Monday, March 31, 2003, 11:00 a.m.-12:15 p.m.
McCormick Place, Room S103

11:00 a.m.

812-1 Fenofibrate Induces Plaque Regression in Hypercholesterolemic Atherosclerotic Rabbits: In Vivo Demonstration by High-Resolution Magnetic Resource Imaging

Roberto Corp, Julio J. Osende, John T. Fallon, Unnaj Zafar, Valentin Fuster, Gabor Mizsei, Hans Jned, Juan J. Badimon, Mount Sinai School of Medicine, New York, NY

Introduction: Fenofibrate has shown to reduce major cardiovascular events and slow angiographic progression of coronary atherosclerosis. Its postulated mechanism of action is through activation of peroxisomal proliferator-activated receptor-alpha, a nuclear transcrsion factor that controls a variety of cellular functions. We investigated the anti-atherogenic effects of fenofibrate on previously established experimental atherosclerotic (AT) lesions.

Method: AT-lesions were induced in NZW rabbits (n=24) by a combination of double balloon-injury and 9-month hypercholesterolemic (HC) diet. At the end of the AT-induction period all rabbits underwent MRI and 7 of them were sacrificed, processed for histology, and served as AT-control. The remaining animals were randomized into 3 groups: [1] Resuming standard chow (n=5), [2] HC-diet- placebo (n=6) and [3] HC-diet-fenofibrate (n=6).

Results: Fenofibrate had significant plaque regression (-25.3%, p=0.007 vs. baseline). The fenofibrate group had significant plaque regression (-71.4%, p=0.004) despite maintained HC-diet. Plasma lipid levels were normalized in standard chow group, whereas they remained elevated in both, the HC-diet-placebo and HC-diet-fenofibrate groups. Histomorphometry analyses, to define vascular biology or the different treatment groups, are under investigation.

Conclusion: Our data indicate that normalization of plasma lipid levels abolishes atherosclerotic progression. Fenofibrate alters plaque composition in atherogenic rabbits and there is evidence that fenofibrate has anti-inflammatory properties.

11:15 a.m.

812-2 E-Selectin and P-Selectin Are Markers of Aortic Plaque Burden as Measured by Transesophageal Magnetic Resource Imaging

William P. Warren, Sarandeep Gkam, Henrying Shen, Shenghan Lai, Subrato Chatterjee, Jose Lima, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: Cellular adhesion molecules (CAMs) play a crucial role in atherosclerotic plaque formation. This study aimed to determine whether levels of CAMs are related to the hemorrhagic nature of the plaque burden.

Method: Baseline and 6-month atherosclerotic plaque volume in the thoracic aorta was measured by combined transesophageal and surface MRI (TEMRI) in 24 patients (15 females, 9 males; mean age 52 ± 12 years) with stable angina pectoris. 48% of the plaques were >3mm, 48% of the plaques >3mm were located at the proximal, left side of the aorta. Statin treatment resulted in an average plaque regression of 3.7% (p<0.05). Overall, plaque regression was directly related to atherosclerotic plaque burden.

Conclusion: Changes in E-selectin and P-selectin were strongly correlated with the reduction in aortic plaque volume as measured by TEMRI.

11:45 a.m.

812-3 Beneficial Effects of Statin Therapy in the Atherosclerotic Human Aorta Are Related to Plaque Location

Valeria J. Vezzetti, Roberta Cotto, Zaira A. Puydas, Valerio F. Campins, Valentin Fuster, Juan J. Badimon, Mount Sinai School of Medicine, New York, NY

Background: Atherosclerotic lesions preferentially develop at low shear stress areas in the arterial system; going in parallel with areas of endothelial dysfunction. Statin therapy is known to induce clinical benefits and even plaque regression, not only attributable to its hypolipidemic effects but also to the non-hypolipidemic (pleiotropic) effects, including endothelial improvement. Because of the predilection sites of plaques and the observed anti-atherogenic effects of statins, the aim of this study was to investigate the potential of statins to operate at specific locations.

Methods and Results: MRI images of the thoracic descending aorta of 9 asymptomatic hypercholesterolemic patients (15 lesions) were acquired at baseline and 24 months after lipid-lowering therapy by simvastatin. Neutrophil counts were linearly correlated with plaque formation. In conclusion, Simvastatin therapy is promising for the treatment of atherosclerotic lesions in the descending thoracic aorta.

11:54 a.m.

812-4 Novel Photopoint Photodynamic Therapy for the Treatment of Atherosclerotic Plaques

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Background: In humans, rupture of vulnerable plaques is one of the leading causes of cardiovascular-related mortality. The current therapies for atherosclerosis focus on cholesterol lowering and reducing inflammation without affecting the proliferative cell types that cause plaque progression. Intra-vascular Photopoint Photodynamic Therapy (PDT) is a combination therapy that utilizes a photo activated drug and a light-emitting catheter to eliminate undesirable cell populations. The aim of the present study is to assess the efficacy of Photopoint as a therapy for the elimination of atherosclerotic plaque populations with a view to inducing plaque stabilization/regression.

Methods: New Zealand White rabbits (n=16) were fed a 1% cholesterol diet followed by bilateral iliac balloon endothelial denudation. At 5wk post-denudation, rabbits received rhodaminesensitive MDRH1 (10mg/kg I.V.) followed by light delivery using a Monar catheter-based clinical device with an argon laser (155mmJ) at 4, 8 and 24 hrs post-endothelial control animals received either drug or light alone. Rabbits were sacrificed at 7d post-treatment and iliac arteries harvested for histopathology and immunohistochemistry.

Results: Maximum elimination of plaque cell nuclei was achieved at 8 and 24hrs drug incubation (76% ± 3%, p=0.001). Nuclear degradation was consistent throughout entire 2cm lengths of plaque. PDT induced complete elimination of macrophage 'foam' cells and other inflammatory cells with a corresponding reduction in 'foam' cell neutral lipid. At 7days post PDT, expression of P53 correlated with cell loss. There was no evidence of inflammation, necrosis or thrombosis post Photopoint treatment.

Conclusions: Photopoint PDT may prove to be an effective therapy for the treatment of vulnerable plaque. An important component of this treatment may be the removal of macrophages by apoptotic mechanisms. Studies to investigate the chronic effects of PDT are ongoing.

Noon

812-5 Matrixin Gammadolin Decreases Vascular Inflammation in a Rabbit Model of Atherosclerosis in the Presence of Ascorbate

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Background: An increase in vascular macrophage (Macs) burden in atherosclerosis (ATH) is a characteristic of vulnerable plaque. Matrixin gamma-dolinum (MgD) is an expanded porphyrin that localizes in platelets and generates reactive oxygen species (ROS) in the presence of reducing metabolites like ascorbate (Asc). Methods and Results: To study the synergic effects of MgD and Asc on ATH, 42 rabbits were fed a 2% chow diet for 6 weeks (2 wks before and 4 wks after iliac balloon denudation), and then randomized to 6 groups: (1) Controls; (2) MgD (10mg/kg I.V.); (3) Asc (50 mg/kg I.V.); (4) Asc 4hr prior to MgD; (5) MgD + Asc simultaneously; (6) Asc 4hr after MgD. After 4 more wks on a normal diet, rabbits were sacrificed and aortic plaque surface (Sudan IV