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ABSTRACTS
XIV International Symposium on Atherosclerosis
Rome, Italy, June 18-22, 2006

We-W32 INFLAMMATION (2nd PART)

We-W32:1 ROLE OF INFLAMMATION IN ATHEROGENESIS AND IN PLAQUE INSTABILITY

F. Crea. *Catholic University, Rome, Italy*

Atherogenic stimuli cause endothelial dysfunction resulting in the expression of adhesion molecules, cytokines and chemokines, followed by adhesion and transmigration of inflammatory cells, thus triggering plaque formation. Arterial remodeling initially limits lumen reduction; further growth of the atherosclerotic plaque eventually leads to critical lumen reduction which, if not compensated for by adequate collateral development, is responsible for stable chronic angina. Treatment of stable atherosclerotic plaques is based on reduction of atherogenic stimuli burden and of platelet reactivity as well as on anti-ischemic drugs in symptomatic patients. A reduction of inflammatory cell activation might be beneficial. Notably, statins and renin-angiotensin system blockade reduce serum levels of C-reactive protein, a marker of inflammatory cell activation. Enhanced NO bioavailability, as obtained for instance, by moderate wine consumption and regular physical exercise might also be beneficial.

Patients may remain stable for years or even for decades, at one extreme of the spectrum, or may develop recurrent acute coronary syndromes at the other extreme. The transition from stable to unstable disease is not predicted by the severity of coronary stenoses nor by the extent of coronary atherosclerosis and is due to yet unknown destabilizing stimuli eventually causing occlusive or subocclusive thrombus formation. In about 2% of patients destabilizing stimuli cause hyperreactivity of smooth muscle cells responsible for coronary spasm: in these patients treatment is based on vasodilators. In about 40% of patients destabilizing stimuli cause thrombus formation in the absence of systemic evidence of inflammation: antithrombotic treatment and an invasive approach, in patients with raised troponin levels, frequently results in persistent stabilization. In the remaining 60% of patients destabilizing stimuli cause activation of inflammatory cells, and in particular of lymphocytes, which is likely to play a key role in thrombus formation. In these patients an invasive approach and a potent antithrombotic treatment result in prompt remission of symptoms, but recurrence rate of coronary instability remains high, in spite of the best currently available treatment. A better knowledge of the triggers and mechanisms of inflammation is warranted to further improve prognosis.

We-W32:2 A STANDARIZED STIMULUS AUGMENTS CRP SIMILARLY IN PATIENTS WITH A HISTORY OF STABLE OR UNSTABLE CHD

J.P. Werba[1], P.G. Massironi[1], M. Frigerio[1], C. Biancardi[1], M. Amato[1], D. Baldassarre[1,2], F. Veglia[1], E. Tremoli[1,2], M. Camera[1,2]. [1]*Centro Cardiologico Monzino, Milan, Italy;* [2]*Dept of Pharmacological Sciences, University of Milan, Milan, Italy*

Objective: To compare the CRP response to a standardized inflammatory stimulus in patients with history of stable or unstable CHD

Methods: Adjuvanted influenza sc vaccination (Inflexal V®) was given to 60 adult male patients with quiescent CHD and well-controlled CV risk factors who had presented at onset of CHD as stable CHD: silent or inducible ischemia (group 1, n=26) or acute coronary syndromes (group 2; n=34). hsCRP was determined by ELISA on plasma samples collected at baseline and 48 hours after vaccination, according to the results of a pilot time-course study performed in 5 volunteers

Results: The patients were non diabetic, non-smokers, free of inflammatory or other conditions that might presumably influence the immune response. The groups were similar in prevalence of non-coronary atherosclerosis, history of allergies, infections, CV risk factors and current use of CV drugs, including aspirin (100%) and statins (90%), as well as age, BP, BMI and mean levels of LDL-C, TG, HDL-C and median [25-75th perc] baseline hsCRP (group 1: 0.47 μg/ml [0.21-0.86] vs. group 2: 0.64 μg/ml [0.21-1.09]). Vaccination significantly augmented hsCRP in both groups (Wilcoxon test, $p<0.01$), without significant differences between groups in terms of absolute (0.12 μg/ml [0 - 0.29] vs 0.16 μg/ml [-0.02 - 0.41]) or percent (29% [0 - 81%] vs 36% [-6 - 72%] changes (Mann-Whitney tests, both NS)

Conclusion: CHD patients with history of stable or unstable disease respond similarly to a defined standardized inflammatory stimulus (influenza vaccination) in terms of CRP change.

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We-W32:3 INFUSION OF C-REACTIVE PROTEIN MEDIATES ACTIVATION OF CIRCULATING LEUKOCYTES IN HUMANS

R. Bisoendial[1], R. Birjmohun[1], F. Akdim[1], C. van 't Veer[2], C. Spek[2], D. Hartman[3], E. de Groot[4], D. Bankaitis-Davis[5], J. Kastelein[1], E. Stroes[1]. [1]*Department of Vascular Medicine, AMC Hospital, Amsterdam, the Netherlands;* [2]*Department of Experimental Internal Medicine, AMC Hospital, Amsterdam, the Netherlands;* [3]*Decode Genetics, Reykjavik, Iceland;* [4]*Department of Immunopathology, Sanguin Research, Amsterdam, the Netherlands;* [5]*Source Precision Medicine, Boulder, CO, USA*

Objective: CRP has been associated with acute clinical manifestations of atherosclerosis, independent from its severity, suggesting that CRP may have a pathophysiological role in vulnerable lesion development. Since leukocyte activation may be critical for plaque stability, we assessed gene expression profiles of peripheral leukocytes and corresponding plasma products of genes after infusion of purified recombinant human (rh)CRP in man.

Methods: Using quantitative real-time PCR analysis, whole-blood expression profiles were analyzed for 95 inflammatory markers upon infusion of 1.25 mg/kg rhCRP in

5 male volunteers. Relevant transcript levels were measured at baseline, 4 and 8 hours after rhCRP-infusion.

Results: CRP caused significant upregulation of MMP9, MCP-1, u-PA, MIP-1alpha and IkappaBalpa mRNAs in leukocytes. mRNA upregulation of MMP9 and MCP-1 was 17- and 11-fold, respectively. The increase in plasma protein levels of MMP9 (78 ± 32 to 109 ± 41 ng/mL; p=0.014) and MCP-1 (312 ± 92 to 2590 ± 898 pg/mL; p=0.007) closely mirrored mRNA findings. In whole blood culture stimulation assays, the capacity of CRP to evoke an inflammatory response was abolished by prior heat-inactivation of CRP, excluding a contributive role for contaminants within the purified CRP-preparation.

Conclusions: CRP induces activation of peripheral leukocytes, which provides a potential mechanism that links CRP to cardiovascular events beyond its role as risk indicator. This finding lends further support to the quest for CRP-lowering strategies in individuals at risk for cardiovascular disease.

We-W32:4 INFLUENZA VIRUS DIRECTLY INFECTS ATHEROSCLEROTIC PLAQUES OF NORMAL AND ATHEROSCLEROTIC MICE AND EXACERBATES INFLAMMATION IN THE ATHEROSCLEROTIC PLAQUE

M. Madjid[1,2], M. Haidari[1,2], D. Vela[1,2], S. Litovsky[1,2], P. Wyde[3], W. Casscells[1,2]. [1]*Texas Heart Institute, Houston, TX, USA;* [2]*University of Texas-Houston HSC, Houston, USA;* [3]*Baylor College of Medicine, Houston, TX, USA*

Influenza can trigger heart attacks and influenza vaccination reduces the risk of cardiovascular events. We tested if the influenza can directly infect the atherosclerotic plaques.

Methods: We infected normal and atherosclerotic apo E knockout and LDL receptor knockout mice with influenza H3/N2 virus. We also infected human coronary endothelial and smooth muscle (HCEC and HCSMC) with influenza. Respiratory syncytial virus (RSV) was used as the control virus. Culture titers are expressed in log10/50 per microliter.

Results: On day 7 after infection, we were able to culture the viable virus from lung (titer:6.8±0.9), heart (4.4±0.8), and aorta (5.9±10.8), but not from the blood (0) of the atherosclerotic mice. Plaque infection persisted despite absence of viremia. Influenza RNA was detected in the 80% of aortas and 40% of hearts removed from infected atherosclerotic mice (and not controls). We observed positive immunofluorescence for influenza virus in infected atherosclerotic plaques. Influenza infection was associated with increase in plaque macrophages. RSV detection was negative in all 3 methods. TaqMan real time PCR showed increased gene expression of chemokines (MCP-1, IL-8 and RANTES) and adhesion molecules (VCAM-1, ICAM-1 and E selectin) by several folds (i.e. 3 to 35 times) following infection of HCEC and HCSMC.

Conclusions: We have shown for the first time that influenza virus directly infects and resides in the atherosclerotic plaques. This is associated with pro-inflammatory changes in the plaque and may be considered as a preventive or therapeutic target.

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