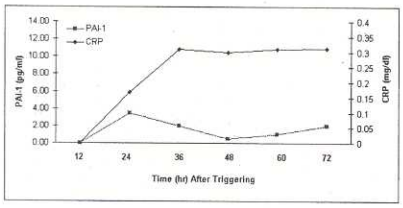
in 8 of the 9 patients from group A, while 4 of the 27 patients from group B. Statistically significant correlations between 11-d-TXB_2 and both HbA1c ($r=0.63$, $P<0.01$) and hs-CRP ($r=0.66$, $P<0.01$) were observed. ***Conclusions*** These results indicate that systemic inflammation and glycemic control is the amplifying factors for aspirin resistant thromboxane biosynthesis in patients with coronary artery disease. These results may help for tailoring therapy to control thromboxane A_2 synthesis to improve disease development and prognosis.

1486

Rising Levels of CRP and PAI-1 After Plaque Disruption Are Associated with Thrombosis

Imran S Virk, Kate Claycombe, Hongbao Ma, Ruiping Huang, Andrew Abela, Roshan Patel, George S Abela; Michigan State Univ, East Lansing, MI

Introduction: Elevated levels of C-reactive protein (CRP) and plasminogen activator inhibitor-1 (PAI-1) have been associated with an increased risk of thrombosis. This study was conducted to determine the time-dependent interaction among CRP, PAI-1 and plaque disruption leading to thrombosis. Methods: A model of plaque disruption and thrombosis was used. Atherosclerosis was induced in 16 NZW rabbits by balloon intimal injury and a high cholesterol diet for 6 months. Five normal rabbits were used as control. Serum samples were obtained from time course assays using control and atherosclerotic rabbits at 0, 12, 24, 36, 48, 60 and 72 hr after thrombus triggering with Russell viper venom and histamine and then sacrificed. Rabbit specific high sensitivity ELISA was developed to detect serum CRP and PAI-1 levels. Immunohistochemical staining for tissue factor was performed at sites of thrombosis and adjacent arterial sites. Results: Serum CRP levels increased starting at 12 hr and peaked at 36 hr (0.34 mg/dl) while serum PAI-1 levels peaked after 24 hr (3.5 pg/ml) following thrombus-triggering in atherosclerotic rabbits. CRP and PAI-1 levels did not rise in control rabbits. At postmortem, thrombi were detected only in rabbits that had higher CRP levels (0.34 ± 0.19 vs. 0.11 ± 0.07 mg/dl; $p<0.01$). Tissue factor was prominently noted at sites that had thrombus and absent from adjacent arterial sites. Conclusion: The rise in rabbit serum CRP and PAI-1 as early as 12 to 24 hr after thrombus-triggering may indicate a potential use as immediate short-term risk markers for thrombosis. The time factor in CRP and PAI-1 rise could be helpful in clinical assessment of evolving cardiovascular events.



1487

TNF-Receptor-1 Signaling in Graft-Intrinsic Cells regulates Vein Graft Neointima Formation and VCAM-1 Expression

Lisheng Zhang, Leigh Brian, Neil J Freedman, Karsten Peppel; Duke Univ Med Ctr, Durham, NC

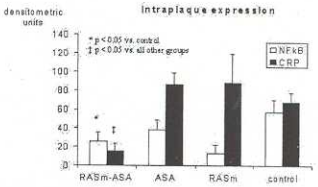
Virtually all arteriovenous bypass grafts develop a smooth muscle cell (SMC) rich neointima that predisposes to graft atherosclerosis and failure. While proinflammatory cytokines, such as TNF, are implicated in the development of atherosclerosis, their role and mechanism of action in pathophysiological vein graft remodeling has not been explored in detail. Using a murine vein graft model we previously reported that approximately 60% of neointimal cells present in vein grafts 4 weeks after implantation are derived from the graft recipient and that TNF receptor-1 (TR1) deficiency reduces vein graft neointima formation in vivo. The goal of the current study was to examine the role of TR1 signaling in the regulation of VCAM-1 expression and chemo/cytokine secretion during vein graft remodeling. We sutured inferior vena cava segments obtained from wild type C57Bl/6 (WT) or congenic TR1-deficient mice into the carotid circulation of WT or TR1(-/-) recipient mice and harvested the grafts 2 weeks later. TNF expression was undetectable in control veins but was induced in 2 week grafts, where its expression colocalized with PCNA positive cells within the developing neointima. We immunofluorescently stained cross sections of grafts for VCAM-1 expression, and averaged fluorescence intensity per unit area over the entire graft wall. TR1 (-/-) grafts placed into WT mice showed a $54\pm9\%$ reduction ($n = 3$) in VCAM-1 expression, relative to WT grafts placed into WT mice ($P<.05$). When both the graft donor and recipient were TR1 (-/-), VCAM-1 expression was reduced by over 70%. We used protein array membranes to quantitate the secretion of chemo/cytokines by primary SMCs . In response to TNF, SMCs derived from WT mice secreted RANTES (15.4 ± 7.5 fold/basal), IP-10 (14.6 ± 2.4 fold/basal) and IL-6 (4.7 ± 1.3 fold/basal)($P<.05$), while SMCs derived from TR1 (-/-) mice did not. We conclude that TNF stimulates vascular SMCs to secrete chemo/cytokines by acting through TR1. Moreover, TNF acts through TR1 to promote VCAM-1 expression in vein graft-intrinsic cells in vivo. The ability of TR1 to mediate cell adhesion molecule and chemo/cytokine expression in vascular cells may underlie the ability of vein graft TR1 to recruit graft-extrinsic cells and promote vein graft neointimal hyperplasia.

1489

Concurrent Treatment with RAS Modulators and ASA Reduces NFκB Activation and C-Reactive Protein Expression in Human Carotid Artery Plaques

Katherine J Sattler, Offer Galili, Julie E Woodrum, Monica L Olson, Saquib Samee, Fredric B Meyer, Lilach O Lerman, Amir Lerman; Mayo Clinic, Rochester, MN

Introduction: Nuclear factor κ B (NFκB) and C-reactive protein (CRP) play a role in the inflammatory process of atherosclerosis and can be induced via the local renin-angiotensin-system (RAS) or via COX-2. Thus, the current study was designed to test the hypothesis that the combination of RAS-modulators (RASm; ACE-I and/or ARB) and aspirin (ASA) reduces the expression of NFκB and CRP within atherosclerotic plaques. Methods: Samples from 68 patients undergoing carotid endarterectomy were collected. The patients were divided into groups according to treatment (RASm+ASA, ASA, RASm, control). The quantitative expression of NFκB and CRP in endarterectomy samples was analyzed using Western blots. Results: Plaques from patients taking the combination of RAS-modulators and ASA showed significantly lower expression of NFκB and of CRP than plaques of patients treated differently (figure, $p < 0.05$). Positive expression of NFκB was associated with a higher incidence of pre-procedural cerebrovascular symptoms than a negative expression (14/35 (40%) vs. 5/33 (15%), respectively, $p = 0.03$). Patients taking the combination were less often symptomatic than patients without (4/20 (20%) vs. 9/14 (64.2%), respectively, $p = 0.014$). Conclusion: The combination of RAS-modulators and ASA decreases the expression of inflammatory mediators in the atherosclerotic plaques in humans and provides a potential mechanism for the beneficial effect of this medical treatment.



1490

Inhibitory Effect of NFκB Decoy Oligodeoxynucleotides (ODN) on Neointimal Hyperplasia in the Rabbit Vein Graft Model

Takashi Miyake, Osaka Univ Grad Sch of Med, Osaka,Suita, Japan; Kazuo Tanemoto, Kawasaki Med Sch, Okayama, Kurashiki, Japan; Motokuni Aoki; Osaka Univ Grad Sch of Med, Osaka,Suita, Japan

As autologous vein remains the commonly used conduit for bypass grafts, neointimal hyperplasia is known to be one of the major disease processes in vein graft failure. We have focused on the important role of NFκB, which controls the expression of numerous genes involved in various cytokines and adhesion molecules in vascular diseases. Indeed, we already reported that the suppression of NFκB activation by NFκB decoy ODN induced apoptosis of VSMCs and protected various stress-induced endothelial cell death in in vivo. In this study, we focused on the effects of NFκB decoy ODN on inhibition of restenosis after graft implantation using vein graft of rabbit hypercholesterolemic model. Jugular vein to carotid artery interposition grafts in rabbits were treated intraoperatively with NFκB decoy ODN (40 mmol/L) by ex-vivo pressure-mediated transfection (300mmHg, 10min). At 4 weeks after vein implantation, EVG staining demonstrated that the treatment with NFκB decoy ODN significantly suppressed intimal hyperplasia as compared to scrambled decoy ODN (scrambled decoy: $3.83\pm0.50mm^2$, NFκB decoy: 1.79 ± 0.19 mm^2, $P<0.001$). Medial thickness of NFκB decoy ODN-treated grafts was significantly increased ($P<0.05$), leading to a significant reduction in intima-to-media ratio in the graft transfected with NFκB decoy ODN as compared to scrambled decoy ODN (scrambled decoy: 1.48 ± 0.27, NFκB decoy: 0.44 ± 0.06, $p<0.001$). Vascular reactivity study demonstrated that the grafts transfected with NFκB decoy ODN significantly improved the endothelium-mediated vasorelaxation as compared to scrambled decoy ODN ($P<0.05$). Immunohistochemical staining revealed that the treatment of NFκB decoy ODN significantly inhibited the macrophage recruitment followed by the suppression of inflammatory changes ($P<0.0001$) and suppressed proliferating activity as compared to scrambled decoy ODN ($p<0.05$). The TUNEL stain demonstrated that apoptotic cells were significantly increased in vessels treated with NFκB decoy ODN, as compared to scrambled decoy ODN ($P<0.0005$). Here, we demonstrated that the inhibition of NFκB activation using decoy ODN inhibited the development of neointimal hyperplasia in rabbit vein graft. Therefore, this strategy would be useful to reduce vein graft failure.

1491

Inflammatory Markers CD40L, IL-6, Neopterin, and CRP are Not Influenced by Homocysteine-Lowering Therapy in Patients with Coronary Artery Disease

Øyvind Bleie, Inst of Med, Univ of Bergen, Bergen, Norway; Anne G Semb, Inst of Med, Univ of Oslo, Oslo, Norway; Jan E Nordrehaug, Inst of Med, Univ of Bergen, Bergen, Norway; Helga Refsum, Per M Ueland, Univ of Bergen, Bergen, Norway; Heidi Grundt, Dennis W Nilsen, Central Hosp in Rogaland, Stavanger, Norway; Ottar Nygård; Inst of Med, Univ of Bergen, Bergen, Norway

Purpose: Inflammation is an important part of arteriosclerosis. Homocysteine is established as an independent risk factor in occlusive vascular disease. Futhermore, independent of plasma total homocysteine (tHcy), vitamin B6 is also associated with the risk of vascular disease. The precise underlying mechanism of these associations is, however, unknown. Several clinical trials are investigating whether lowering tHcy can prevent or halt the development of arteriosclerosis. We tested the effects of homocysteine lowering B-vitamin therapy used in the Western Norway