Coronary Arteries Partially Recovered Endothelium-Dependent Function Three Months After Endovascular irradiation

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Background: Radiation therapy inhibits restenosis after coronary intervention but appears to exert long-term inhibition of endothelial recovery. Also, to avoid geographic miss, normal artery adjacent to the intervention site is irradiated during brachytherapy procedures. The effect of vascular brachytherapy on normal coronaries, mimicking such segments, has not been studied. We investigated ex vivo vasomotor function at long-term follow-up after endovascular brachytherapy, and correlated functional responses to morphology and eNOS expression. Methods: Vascular responses of pig coronaries to endothelium-dependent and independent vasoactive agents 3 mo after active irradiation (RAD; n=12; 20 GY β), sham (S; n=8; catheter with inactive wire), and in native controls (C; n=8) were examined. Endothelial morphology was studied by scanning electron microscopy (SEM), and eNOS immunohistochemistry was also performed. Results: Relaxation to maximal dose A23187 (3 μM) was decreased in RAD (31.2±4.7% vs. 87.3±2.7% in S and 85.7±4.4% in C; P<0.01). Relaxation to maximal dose substance P (0.1 μM) was also less for RAD (32.0±6.6% vs. 47.3±3.1% in S and 70.2±5.1% in C; P<0.05). For RAD, contraction to PGF2α with L-NAME was similar to PGF2α alone (2.4±0.24 μM vs. 2.5±0.42 μM; NS), but was increased in S and C. Contraction to KCl was decreased in RAD. Endothelium-independent relaxation to sodium nitroprusside was increased in RAD compared to S and C. There was confluent endothelium in irradiated vessels by SEM. Immunohistochemical staining for eNOS showed similar pattern and intensity for RAD and S. Conclusions: Comparison to previous results (not shown) at 1 mo post-irradiation, endothelium-dependent relaxations were partially (~40-50%) recovered at 3 mo. Endothelial morphology and immunohistochemical staining revealed that structural recovery was complete, and no difference in eNOS expression assessed by immunostaining could be observed. These results indicate that functional endothelial recovery of irradiated normal coronaries was still incomplete at 3 mo; this may have important implications in therapeutic planning for clinical brachytherapy patients.

Long-Term Efficacy of Intracoronary Beta-Radiation for the Treatment of In-Stent Restenosis: An Angiographic and Intravascular Ultrasound Analysis of the Late Catch-Up Phenomenon

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Background: Intracoronary Beta-Radiation Therapy (BRT) has been shown to inhibit in-stent intimal hyperplasia (IH) at 6-month follow-up (FUP) in the treatment of in-stent restenosis (ISR) lesions. However, there are few data about in-stent lumen deterioration within longer FUP after BRT. Purpose: To compare the clinical, angiographic and intravascular ultrasound (IVUS) outcomes of patients (pts) with ISR treated with balloon angioplasty followed by BRT at 6 and 12-month FUP. Methods: Forty consecutive pts with ISR were treated with BRT (Novoste, Beta-Cath). Clinical, angiographic and IVUS analysis was performed in 28 pts (63%) at 6 and 12-month FUP. Results: Eighty percent (80%) of pts were free of major adverse cardiac events at 6 and 12-month FUP, respectively (p=0.3). Significant in-stent lumen loss (0.4±0.44 mm2; p=0.04) and IH growth (+1.2±0.48 mm2; p=0.03) was observed between 6 and 12-month FUP. Conclusions: Despite homogeneity between porcine & human TIMP3 mRNA, TIMP3 overexpression was evident in stented coronary tissue, transduced with TIMP3 AdV, when compared to control (data not shown), this was confirmed with TIMP3 ICC. The increased level of TIMP3 corresponded with a significantly increased rate of apoptosis, 41.0±16.6% vs. 8.9±8.1% in control (p=0.004). Crucially, the increase in apoptosis was not associated with a reduction in cell density, 32.0±1.8% vs. 33.6±4.0% in control (p=0.62). Infammation scores did not differ between the groups: TIMP3 1.5±0.6 vs. Control 1.4±0.4; p=0.69. Discussion: Apoptosis has been confirmed as a major contributor to TIMP3’s inhibitory effect on neointimal proliferation, following in-stent stent deployment. Importantly, this does not effect cell density or induce significant inflammation at 7days, thus maintaining normal vessel architecture.

CX3CR1 Gene Disruption Is Not Associated With Decreased Neointima Formation After Carotid Wire Injury in Apolipoprotein-E Deficient Mice

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Background: The fractalkine receptor (CX3CR1) is found on leukocytes and binds to endothelial cells expressing fractalkine (CX3CL1), facilitating leukocyte firm adhesion and transmigration, steps thought to be important in the development of atherosclerosis. Recently published studies have shown that CX3CR1+/apoE-/- mice have decreased spontaneous atherosclerosis when compared to apoE-/- control mice. Accordingly, we hypothesized that CX3CR1-/-apoE-/- mice would have diminished neointimal growth at 28 days after carotid wire denudation injury. Methods: CX3CR1-/-apoE-/- mice (n=13) or apoE-/- mice (n=8) were fed a Western diet for one week prior to wire denudation of the left common carotid artery, and continued on the atherogenic diet for four additional weeks. At 28 days after injury, cholesterol levels were measured, and the carotid arteries were harvested for histomorphometric analysis. Results are reported as mean ± SEM.

Results: There was no difference between the two groups in total cholesterol (1284 ± 57 mg/dL, CX3CR1+/apoE-/- vs. 1231 ± 49 mg/dL, apoE-/-; p=NS) or LDL cholesterol (1138 ± 52 mg/dL, CX3CR1+/apoE-/- vs. 1101 ± 46 mg/dL, apoE-/-; p=NS). CX3CR1+/apoE-/- mice did not have diminished neointima, and in fact there was a trend towards a larger neointima at 28 days in the CX3CR1+/apoE-/- mice versus control apoE-/- mice (77,000 ± 15,000 μm² vs. 44,000 ± 11,000 μm², p=0.14). Conclusion: CX3CR1+/apoE-/- mice do not have a decrease in neointimal growth after carotid wire denudation injury. In fact, there was a trend towards a larger neointima. The protective effect of CX3CR1 gene disruption reported in spontaneous atherosclerosis studies is not seen in this model of vascular injury on an atherogenic background.