773 Low Dose Irradiation for Prevention of Restenosis

Wednesday, March 22, 1995, 8:30 a.m.–10:00 a.m.
Ernest N. Morial Convention Center, Room 26

8:30

773-1 Endovascular Radiation Prior to Stent Implantation Inhibits Neointimal Proliferation in Porcine Coronary Arteries

Ron Waksman, Keith A. Robinson, Ian R. Crocker, Michael B. Gravanis, Spencer J. Palmer, Gustavo D. Cipolla, Spencer B. King III. *Emory University School of Medicine Atlanta Georgia, GA*

Stent implantation has been shown to reduce restenosis by establishing a larger lumen not by reducing neointima formation. We have previously shown that ionizing radiation reduced neointima formation in a swine model of restenosis. The purpose of this study was to determine whether endovascular radiation of the coronary artery prior to stent implantation would affect neointima formation. Five normolipemic pigs underwent coronary angiography; segments of the LAD or the CX were chosen as targets for stenting. A high energy ^{192}Iridium source was used to deliver 1400 cGy by random assignment to one of the vessels, then 3.5 mm tantalum stents were implanted in both arteries. All animals received aspirin 325 mg daily. They were killed at 30 days, and the coronary vasculature perfusion fixed with 10% formalin. The arteries were embedded in methyl methacrylate, and sectioned with the stents in place using a low-speed saw. Serial sections spanning the injury site were ground to 30 μm, stained with toluidine blue, then evaluated by histopathologic and morphometric techniques. The maximal intimal thickness (MIT), intimal area (IA), and vessel perimeter (VP) were measured from each section. Student's paired t-test was used for comparison of groups. Stent artery ratio was similar in the radiated artery 1.52 ± 0.55 versus control 1.50 ± 0.33.

	MIT, mm	IA, mm^2	VP, mm
Control	0.9 ± 0.47	3.64 ± 1.52	10.6 ± 1.54
Irradiated	0.63 ± 0.28	2.34 ± 1.48	10.5 ± 0.62
P value	0.03	0.007	0.8

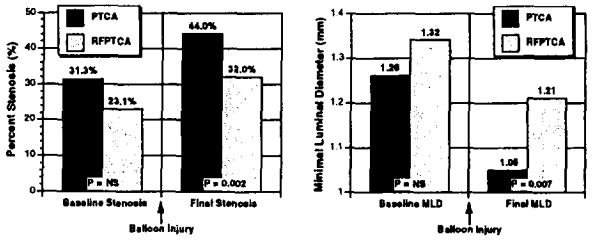
Conclusion: Endovascular radiation prior to coronary stenting reduces neointima formation and may reduce further the restenosis rate after stent implantation.

8:45

773-2 Can Low-Temperature, High-Frequency Radio Energy PTCA Influence Restenosis?

Jeffrey B. Gitlin, Joseph M. Sutton, Luis A. Guzman, Milind S. Shah, William NG, Stephen G. Ellis, Eric J. Topol *Cleveland Cinic Foundation, Cleveland, Ohio*

Radio frequency (RF) PTCA has previously been used with relatively low RF energy (0.25 MHz) producing primarily heat to facilitate lesion dilitation. At this low frequency (F), the RF energy does not penetrate beyond the balloon material and therefore is converted to heat within the confines of the balloon. A new device with a high-F source (13.56 MHz) not only affects balloon temp(T), but also directs electromechanical radiation to susceptible cellular components. 16 rabbits underwent bilateral focal femoral artery injury by air desiccation, followed by an atherogenic diet (1% cholesterol, 6% peanut oil) for 28 days. Femoral artery PTCA was performed with a 2.5 mm balloon catheter, following a protocol (3 inflations, 6 atmospheres, 60 sec.) on one femoral artery, while the opposite femoral artery underwent 3 successive RF PTCA's at 13.56 MHz, restricting T to 55 C. Angiograms were performed pre-PTCA, following PTCA, and approx. 3 weeks later at the time of sacrifice. Analysis of vessel dimensions, and percent stenosis were done by independent, blinded, quantitative measurement (QCA).



Conclusion: There were no significant differences seen in either group with regard to normal reference vessel size, lesion MLD, or diameter stenosis. Importantly, subsequent angiographic lesion progression was significantly limited in the RF PTCA group (8% MLD reduction) vs. the PTCA group (23% MLD reduction). Preliminary results in this restenosis model are encouraging and warrant further investigation.

9:00

773-3 Inhibition of Neointimal Proliferation with a Beta Particle Emitting Stent

John R. Laird, Andrew J. Carter, William M. Kufs, Timothy G. Hoopes, Andrew Farb, Sepideh Nott, Robert E. Fischell, David R. Fischell, Renu Virmani, Timothy A. Fischell *Walter Reed Army Medical Center and Armed Forces Institute of Pathology, Washington, DC; Vanderbilt University, Nashville, TN*

Neointimal proliferation in response to arterial injury is an important contributor to restenosis. Ionizing radiation inhibits cellular proliferation and may reduce neointimal formation following balloon angioplasty. Using a novel method to deliver a local endovascular radiation dose, we studied the effect of beta irradiation on the intimal proliferative response to placement of titanium stents in porcine iliac arteries.

Fourteen titanium stents containing a true beta particle emitting radioisotope, ^{32}P, were expanded in the iliac arteries of nine NIH miniature swine. Seven control stents, (no ^{32}P), and seven treatment stents with an activity of 0.14 μCi, were deployed. Treatment effect was assessed by angiography and histomorphologic examination of the stented iliac segments at day 28. The cell proliferation index (%PCNA positive cells/HPF) and cell density (number of cells/HPF) were measured.

Stent Type	Intimal Area (mm^2)	Lumen Area (mm^2)	Percent Area Stenosis
Control (n = 7)	2.47 ± 1.00	4.72 ± 0.67	33.5 ± 9.2%
Treatment (n = 7)	1.77 ± 0.44*	5.38 ± 0.81*	24.6 ± 4.4%†

*p ≤ 0.012 vs. control, †p = 0.0004 vs. control

Mean neointimal thickness at each wire site for the treatment stents was significantly less than for the control stents, (0.26 ± 0.05 mm vs. 0.34 ± 0.10 mm, p = 0.0037). The mean cell proliferation index (2.15 ± 0.91% vs. 3.95 ± 4.21% p = 0.44) and cell density (362 ± 42 vs. 349 ± 45 p = 0.46) were similar between treatment and control stents.

Conclusions: Low dose endovascular irradiation by a beta particle emitting stent reduces neointimal proliferation after experimental stent placement. This novel technique offers potential for the prevention of restenosis.

9:15

773-4 Long Term Efficacy and Safety of Endovascular Low Dose Irradiation in a Swine Model of Restenosis After Angioplasty

Ron Waksman, Keith A. Robinson, Ian R. Crocker, Michael B. Gravanis, Gustavo D. Cipolla, Spencer B. King III *Emory University School of Medicine Atlanta Georgia*

Restenosis after balloon angioplasty is characterized by neointima formation. We have previously shown that ionizing radiation reduce neointima formation two weeks after angioplasty in a swine model of restenosis. To determine the durability of this effect and the long term safety after endovascular irradiation twenty one miniswine coronary arteries underwent overstretch balloon injury with a 3.5 mm angioplasty balloon in the LAD, LCX and RCA. High energy ^{192}Iridium source was introduced immediately by random assignment to deliver 700 or 1400 cGy in 14 injured coronary arteries (LAD and CX). Six months later an angiogram was performed, the animals were killed and the coronary arteries were perfusion fixed. Serial sections were stained with H&E, VVG, MT, then evaluated by histopathologic and morphometric techniques. Intimal area (IA) and area of intimal thickness corrected for the extent of injury (IA/FL) was measured in the irradiated and control arteries and compared with pigs that underwent the same treatment but were followed for 2 weeks only.

Results: All treated arteries were patent with normal angiographic appearance. Lumen diameters at baseline and follow-up were similar. There was no difference in fibrosis at the adventitia, media, perivascular space or adjacent segments of myocardium of the irradiated arteries compared with control.

	Control	700 cGy	1400 cGy
IA/FL 2 Weeks	0.59 ± 0.23	0.42 ± 0.15**	0.17 ± 0.16****
IA/FL 6 Months	0.50 ± 0.2	0.35 ± 0.18*	0.31 ± 0.16**
IA 6 Months (mm)	1.25 ± 0.25	0.85 ± 0.47***	0.62 ± 0.45**

P values: control versus treatment group: *P = 0.009, **P < 0.001, ***P = 0.05, ****P < 0.0001

Conclusions: Endovascular low dose irradiation in this model is safe and the inhibitory effect of localized radiation on neointimal thickening (restenosis like) response to angioplasty is maintained at six months.

WEDNESDAY AM