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Effect of External Beam Irradiation on Neointimal Hyperplasia After Experimental Coronary Artery Injury

ROBERT S. SCHWARTZ, MD, FACC, THOMAS M. KOVAL, PHD, WILLIAM D. EDWARDS, MD, FACC, ALLAN R. CAMRUD, RN, KENT R. BAILEY, PHD, KEVIN BROWNE, MD, FACC, RONALD E. VLIETSTRA, MB, BCH, FACC, DAVID R. HOLMES, JR., MD, FACC

Rochester, Minnesota

Human coronary artery restenosis after percutaneous revascularization is a response to mechanical injury. Smooth muscle cell proliferation is a major component of restenosis, resulting in obstructive neointimal hyperplasia. Because ionizing radiation inhibits cellular proliferation, this study tested in a porcine coronary injury model the hypothesis that the hyperplastic response to coronary artery injury would be attenuated by X-irradiation.

Deep arterial injury was produced in 37 porcine left anterior descending coronary artery segments with overexpanded, percutaneously delivered tantalum wire coils. Three groups of pigs were irradiated with 300-kV X-rays after coil injury: Group I (n = 10), 400 cGy at 1 day; Group II (n = 10), 400 cGy at 1 day and 400 cGy at 3 days and Group III (n = 9), 800 cGy at 1 day. Eight pigs in the control group underwent identical injury but received no radiation. Treatment efficacy was histologically assessed by measuring neointimal thickness and percent area stenosis.

Mean neointimal thickness in all irradiated groups was significantly higher than in the control groups and thickness was proportional to X-ray dose.

X-irradiation delivered at these doses and times did not inhibit proliferative neointima. Rather, it accentuated the neointimal response to acute arterial injury and may have potentiated that injury.

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The causes of restenosis after percutaneous transluminal coronary angioplasty are complex, but they include a hyperplastic neointima forming in response to vessel injury. Clinical trials of drugs including antiplatelet agents, anticoagulant agents, corticosteroids and calcium channel blocking agents have proved unsuccessful in reducing restenosis rates. Newer devices including laser and stents have also failed to reduce the proliferation of neointima; the incidence of restenosis remains at least 30% to 45% (1–3).

Restenotic lesions consist of an obstructive, proliferative mass of smooth muscle cells in a proteoglycan matrix. Because X-irradiation is used extensively in the treatment of proliferative neoplastic and nonneoplastic disease (4–6), this study tested the hypothesis that external X-irradiation might reduce the amount of proliferative neointima after coronary artery injury. A porcine coronary injury model that accurately mimics the amount and character of human restenotic neointima (7) was used in these studies. In this model, the amount of hyperplastic neointima is proportional to the severity of injury (8), thus providing a quantitative mechanism for direct comparison of treated and untreated animals.

Methods

Study animals. All studies were performed with the approval of the Institutional Animal Care and Use Committee. Juvenile domestic crossbred pigs (weight 25 to 35 kg) were fed a normal laboratory chow diet without lipid or cholesterol supplementation. All pigs were premedicated with oral aspirin, 650 mg, at least 24 h before coronary injury. General anesthesia consisted of intramuscular ketamine, 12 mg/kg body weight, and xylazine, 8 mg/kg, injection. The ventral neck region was infiltrated with 10 ml of 1% xylocaine for local anesthesia. Oxygen was administered by face mask. Continuous electrocardiographic (ECG) and transcutaneous hemoglobin saturation monitoring was performed. The right external carotid artery was exposed and an 8F hemostatic sheath placed for arterial access. Heparin (10,000 U) was administered as an arterial bolus injection.

Method of coronary artery injury. The method of using metallic coils to induce coronary artery injury has been described previously (7). Coil implantation was performed in

From the Divisions of Cardiovascular Diseases and Internal Medicine, Radiation Oncology and Section of Medical Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota and the Watson Clinic, Lakeland, Florida. This study was supported by grants from USCI, a Division of C. R. Bard Inc., Billerica, Massachusetts, and the J. Holden DeHaan Foundation, Indianapolis, Indiana.

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Address for reprints: Robert S. Schwartz, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905.

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the left anterior descending coronary artery of 37 pigs. This artery was specifically chosen for its proximity to the anterior body surface, minimizing the distance needed for the X-ray beam to travel.

Under fluoroscopic guidance, a commercial coronary angioplasty balloon wrapped with a tantalum metallic wire coil was placed in the left anterior descending artery so that balloon oversizing by a factor of 1.5 to 2 was obtained. Inflation of the balloon deployed the coil and severely injured the coronary artery as previously described. This balloon expansion and coil injury method results in histopathologic injury by each coil wire segment. A graded spectrum of injury occurred in a spatially localized circumferential vessel wall region, yielding a graded response of neointimal thickness at each wire site (8).

Fluoroscopy and selective contrast injection shortly after coil implantation confirmed coil location, adequate coil expansion and vessel patency. The carotid sheath was removed and the carotid artery ligated. The neck wound was closed with interrupted sutures. The coil location beneath the sternum was externally identified fluoroscopically and the skin at this site was marked with an indelible ink marker. The pigs were returned to quarters for later radiation treatment.

Radiation protocol. Before implementation of the pig radiation protocol, a pig carcass was placed in the position used for irradiation with a radiation dosimeter located on the left anterior descending coronary artery to verify that delivered doses were in agreement with calculated doses. Doses reaching the artery were also estimated by using a phantom of the pig chest. Estimated accuracy of the dose reaching the coronary artery was within ±5%.

Four groups of pigs were used: three treatment groups and one control group. These groups were chosen for a variety of radiation doses and timing after arterial injury. The schedule of radiation was chosen soon after coronary artery injury because of studies (9) showing smooth muscle cell proliferation within 48 h of arterial injury. The control group received no radiation. Group I received 400 cGy 1 day after coronary artery injury; Group II received a split radiation dose consisting of 400 cGy at 1 day and 400 cGy 4 days after injury and Group III received 800 cGy 1 day after injury.

A 300-kV General Electric Maxitron X-ray machine, operated at 300 kV and 20 mA, was used for radiation treatments. The X-ray beam was filtered by 2 mm of copper for a half value layer slightly greater than 1.8 mm Cu. X-rays were delivered to a 25-cm^2 field centered on the external skin mark for coil location, at a dose rate of approximately 100 cGy/min. Except for this 25-cm^2 field, each pig was shielded with about 3 to 4 mm of lead, and backscatter was minimized. The port size was thus kept to a minimum. The pigs were returned to quarters for recovery after irradiation. With this radiation protocol, no noticeable ill effects on the general well-being of the pigs were expected. All animals were carefully observed for signs of illness or untoward effects after radiation.

The presence of the stent during irradiation would be expected to exert minimal influence within the estimated accuracy of the delivered radiation dose. In addition, there was no reason to believe that radiation-stent interaction would alter the tissue response to radiation.

Histopathologic processing and measurements. Pigs were killed at 28 ± 1 days after coronary artery injury with use of a commercial intravenous euthanasia solution. The heart was removed immediately at death and the coronary arteries were pressure perfusion fixed for 24 h with 10% neutral buffered formalin. Coronary artery segments containing the metal coils were carefully dissected free from the epicardial surface. The vessels were sectioned at 2-mm intervals perpendicularly to the vessel long axis, and the residual metallic coil fragments were removed. Each arterial segment was embedded and stained with hematoxylin-eosin and elastic van Gieson stain. All histopathologic measurements and observations were made without knowledge of treatment group by an experienced cardiac pathologist (W.D.E.) using a calibrated microscope reticle.

Each 2-mm histologic section of a given artery was examined to determine the section showing maximal lumen narrowing. The single section with the most severe stenosis was used to make all measurements. The calibrated microscope reticle was used to measure the major and minor axes of both the original and the stenotic (residual) vessel lumen. Areas of the original and stenotic lumens were calculated assuming an elliptic cross section (Area = [pi × Major axis/2] × [Minor axis/2]). Percent area stenosis was calculated as

$$\% \text{ Stenosis} = 100 \times [1.0 - (\text{Stenotic lumen area}/\text{Original lumen area})].$$

Quantitative vessel injury severity and neointimal response were measured from the elastic van Gieson-stained sections as follows. Vessel injury at every wire site was assigned an injury score based on the anatomic structures penetrated by that coil wire. This value could vary from 0 (least injury) through 3 (most injury). Table 1 shows this numeric injury-coding method. The mean arterial injury score for a section was calculated as the mean injury caused by all wires in that section:

$$\text{Mean injury score} = \frac{\Sigma \text{ weights for each wire}}{\text{Number of coil wires present}}.$$

Neointimal thickness at each wire site was measured. The mean neointimal thickness for all wire sites in the section was used as the index of injury response. For each arterial segment in this study, there was thus a mean injury score and a mean thickness of neointimal response.

Statistical methods. Two approaches to linear modeling allowed for quantitation of results. The first modeling procedure was performed to determine (separately for the

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Table 1. Assignment of Vessel Injury Score

Description of Assigned Weight	Injury
0	Internal elastic lamina intact; endothelium typically denuded; media may be compressed but not lacerated.
1	Internal elastic lamina lacerated; media typically compressed but not lacerated.
2	Internal elastic lamina lacerated; media visibly lacerated; external elastic lamina intact but may be compressed.
3	External elastic lamina lacerated; typically large lacerations of media extending through the external elastic lamina; coil wires sometimes residing in adventitia.

untreated and the treated groups) the relation between injury and proliferative thickness. The second modeling procedure permitted comparison of the groups. In this second method, three linear models were used to relate the mean proliferative thickness (dependent variable) to the degree of injury (independent variable) to quantitatively compare the responses between treated and untreated groups. A slope and intercept for each relation (treated vs. untreated) were obtained from the models. Differences in response to treatment were thus reflected by significant differences in slopes or intercepts, or both.

Linear regression analysis for mean neointimal thickness versus mean injury score was performed by using pigs from *all groups* (irradiated and nonirradiated) except those pigs experiencing sudden death. Binary variables (value 0 or 1) denoting treatment group were added to the regression equation to evaluate the significance of the treatment.

Three such regression models were made to test differences in 1) intercept assuming equal slopes, 2) slopes assuming arbitrary intercepts, and 3) slopes assuming equal intercepts. Each was performed as follows. For the first model, which tested for differences of intercepts, the regression equation was

$$\text{Thickness} = \mu \times \text{Injury} + \alpha_1 \times \text{GI} + \alpha_2 \times \text{GII} + \alpha_3 \times \text{GIII} + \text{Constant} \quad [1]$$

For the second model, in which slopes were compared assuming an arbitrary intercept, the model used was

$$\text{Thickness} = \mu \times \text{Injury} + \alpha_1 \times \text{GI} + \alpha_2 \times \text{GII} + \alpha_3 \times \text{GIII} + (\beta_1 \times \text{GI} + \beta_2 \times \text{GII} + \beta_3 \times \text{GIII}) \times \text{Injury} + \text{Constant} \quad [2]$$

For the third model, slopes were compared assuming that the intercept was the same. The regression equation for this model was

$$\text{Thickness} = \mu \times \text{Injury} + (\alpha_1 \times \text{GI} + \alpha_2 \times \text{GII} + \alpha_3 \times \text{GIII}) \times \text{Injury} + \text{Constant}. \quad [3]$$

In all three of these equations, the respective μ, α_n and β_n were coefficients estimated by the multiple regression, and GI, GII and GIII were the binary group variables for each irradiation group. Statistical significance was established by evaluating the resulting α_n and β_n coefficients. The α_n and β_n in each model could be interpreted as differences between the respective treated group and control group intercepts and slopes.

Table 2. Demographic Data for All Groups

Group	Pigs (no.)	Spontaneous Deaths (no.)	Days to Spontaneous Death
Control	8	0	—
I (400 cGY)	10	2	5 and 9
II (400/400 cGy)	10	1	4
III (800 cGy)	9	1	15

— = no deaths.

Results

Thirty-seven pigs underwent successful coil implantation. Table 2 gives the number of pigs in each group. Not all pigs survived the expected 28 days: sudden death occurred in four pigs at various times after coronary injury.

Clinical effects and gross examination. As expected from results in humans with comparable radiation doses, no adverse clinical or behavioral effects were apparent in any irradiated animal surviving until induced death. Gross examination of the hearts after death also showed no radiation effect. Figure 1 shows representative photographs of the neointimal proliferation found on gross inspection in the control and three treatment groups. Progressively more neointima and greater stenosis are seen in this series of photographs as radiation dose increases. Figure 2 shows coronary artery photomicrographs that are similarly representative of irradiated animals.

Histopathologic examination. Microscopic examination revealed proliferative neointimal responses and lumen stenoses of varying magnitude in all groups. The characteristics of this neointima have been previously described (7). In Group III (800 cGy) there were a few giant cells, a finding associated with irradiated tissue in humans. In this highest radiation dose group, medial edema was routinely observed. There was moderate to severe myocardial and adventitial fibrosis in all three radiation groups (Fig. 3). No fibrosis was noted in any control pig. The areas of fibrosis were the hypocellular and patchy areas typically seen after radiation.

Interestingly, segments of coronary arteries that were not injured by the coil but were within the radiation field showed essentially no reaction to the radiation, and appeared entirely normal (Fig. 4).

Table 3 lists the mean arterial injury scores and percent area stenosis for each vessel in each group. Table 4 shows the results of the linear regression modeling performed for each group separately. For the 800-cGy group (Group III), a meaningful regression line could not be generated because

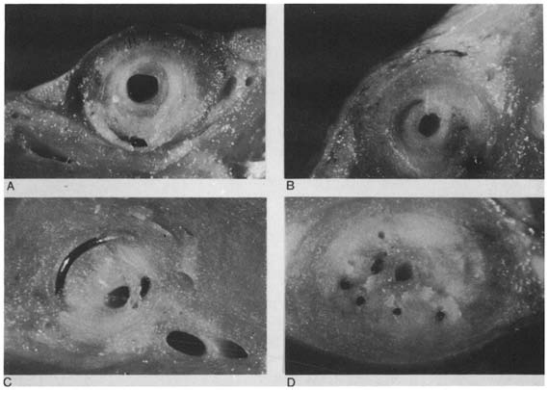


Figure 1. Photographs of representative coronary artery segments at 28 days after injury in the control group (A) and the three groups treated with X-irradiation: Group I (400 cGy at 1 day) (B), Group II (400 cGy at 1 day and 400 cGy at 4 days) (C) and Group III (800 cGy on day 1) (D). Wires from the injuring coils are shown. The degree of cellular proliferation increases in the groups receiving higher doses of radiation.

there were no low level injuries. In Figure 5, which shows the data graphically, it is evident that the regression lines for the treated groups are higher than the control lines with roughly equivalent slope but differing intercepts. Overall, these results are similar to those of prior studies in which the degree of neointimal proliferation was proportional to vessel injury.

Table 5 shows the results of the three linear regression models. These results confirm those of Table 4. In model 1, the intercepts are significantly different for the treated groups. In model 2, the slopes cannot be proved different in treated versus control groups. In model 3, the results show *that if the intercepts are constrained to be equal, the slopes* are significantly different. These results parallel the results of model 1.

Morphologic results in pigs experiencing sudden death. Sudden death occurred in four pigs, all in radiation-treated groups. Histopathologic examination of the coronary arteries in these animals showed severe stenosis consisting of organized neointima, but also with fresh thrombus at those injury sites.

Discussion

The restenosis problem remains a major limitation of percutaneous interventions for coronary artery disease. Despite pharmacologic and device-oriented research aimed at reducing neointimal hyperplasia after coronary artery injury, there has been little progress. Smooth muscle cell proliferation is thought to play a major role in the genesis of obstructive restenotic lesions. The utility of X-irradiation for the treatment of both malignant and nonmalignant proliferative conditions is well established. The hypothesis of this study was that radiation would inhibit replication of smooth muscle cells forming the obstructive neointima so that the overall acute effect would be a reduction of proliferative neointima.

External radiation and proliferation after acute arterial injury. All three irradiated groups in this study showed a statistically significant *increase* in the neointimal thickness formed as a result of coronary artery injury. The mechanisms responsible for this finding are unclear, although endothelial cells are more radiation sensitive than are medial smooth muscle cells. Thus, radiation may have enhanced the endothelial damage done by the wire coil alone. Alternatively, it may have prolonged the time required for endothelialization of the injury site, thereby causing either a more prolonged exposure of subintimal elements to flowing blood or, possibly, a larger area of damaged endothelium (10–12). Permeability of the internal elastic lamina has been shown to result from radiation damage (13), as has arterial spasm (14), both of which might also have contributed to the observed proliferative response.

The results from the 800-cGy group (Group III) were anomalous. In this group of pigs, measured injury scores were substantially higher than in all other groups. There were no mean injury scores <2.3. It is distinctly unusual for this model to have such a lack of overall variation in injury, because the amount of injury is generally difficult to standardize. The lack of lower mean injury scores might have been a coincidence or, alternatively, an indication that higher doses of radiation might enhance the mechanical damage done by the wire coils. The prevalence of higher injury scores prevented development of a meaningful regression model. Additional studies using this higher acute radi-

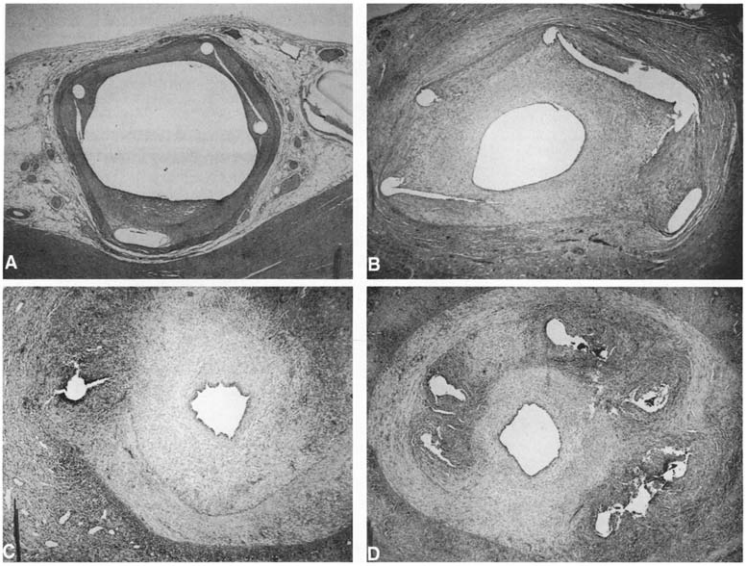


Figure 2. Composite of photomicrographs showing representative radiated coronary arteries. Severe stenoses and mechanical injury resulting from the coils are evident. **A,** Control group, no irradiation; **B,** Group I, 400 cGy on day 1; **C,** Group II, 400 cGy at 1 day and 400 cGy at 4 days; **D,** Group III, 800 cGy at 1 day. All panels, hematoxylin-eosin stain ×10, reduced by 37%.

ation dose will be required to clarify whether this finding was coincidental.

Results from previous studies. Only limited data are available on the effects of X-irradiation on arterial structure and function. Normal, uninjured coronary arteries are resistant to radiation in small and moderate doses (15). However, radiation-induced coronary artery disease from larger doses of radiation given for noncoronary neoplasia is well documented. The first report in 1967 (16) described a fatal myocardial infarction in a 15-year old boy who received 40 Gy for Hodgkin's disease. The association between arterial stenosis and irradiation for both muscular coronary arteries and larger elastic vessels has been known for >30 years (17–21). Patients who received large doses of radiation are reported to have unusable internal mammary arteries if coronary artery bypass grafting is contemplated (22).

Human coronary artery lesions resulting from radiation are substantially different from those in atheromatous coronary disease (23,24). They typically exhibit dense fibrotic reactions, and generally affect vessels in the more proximal portions (25,26). The human coronary lesions present late, typically 6 to 12 years after radiation exposure (27–30).

There are no studies of irradiated coronary arteries with fresh mechanical injury as performed here. Short-term animal studies using noncoronary vessels have shown the induction of a proliferative response. One study using hypercholesterolemic rabbits with iliac artery lesions showed strong synergism between lipids and radiation for inducing atheromatous-like lesions (31). Others (32) have found similar potentiation of radiation injury by hyperlipidemia.

Implications. The results of the current study indicate that X-ray therapy, administered at the doses and times given, is unlikely to be a viable strategy for preventing restenosis. They clearly suggest that this treatment may exacerbate the restenosis problem. Mechanical injury to coronary arteries appears to be exacerbated by subsequent irradiation. This hypothesis may be corroborated by the observation that injury scores in the 800-cGy group tended to be higher than those of the control and other treatment groups.

These results extend those of prior animal studies in that

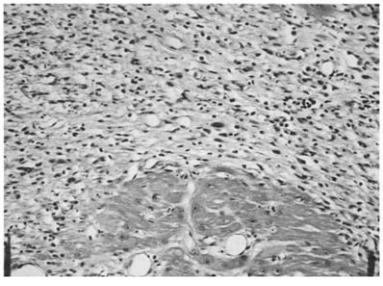


Figure 3. Patchy areas of myocardial fibrosis were found in the irradiated groups. A region of extensive myocardial fibrosis is shown in a pig that received 800 cGy of X-irradiation at 1 day after injury. A small area of residual myocardial cells is noted. Hematoxylin-eosin stain ×80, reduced by 35%.

comparatively *low dose* radiation is able to cause a measurable increase in postinjury cellular proliferation. To the extent that this model is applicable to humans, it suggests caution when radiation therapy is given to patients with recent coronary angioplasty if the site of arterial injury is within the radiation field. The results of this study suggest that it would probably be prudent to avoid radiation therapy to an area encompassing arterial injury in the immediate period after coronary angioplasty.

Limitations of the study. *The model.* The issue of how well this model reflects the human restenosis problem is quite important, as is true for all animal models of human

Figure 4. Cross section of a coronary artery that was within the radiation field but not in a segment injured by the coils. This pig received X-irradiation at a dose of 800 cGy. The artery is essentially normal in appearance. Hematoxylin-eosin stain ×10, reduced by 37%.

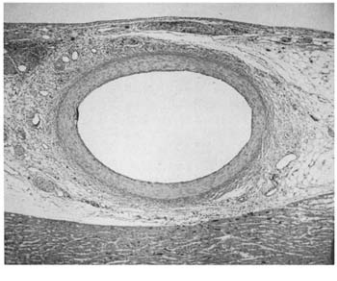


Table 3. Injury, Neointimal Thickness and Percent Stenosis

Pig No.	Mean Injury Score	Mean Neointimal Thickness	% Stenosis
Control group			
1	0.8	0.33	25
2	2.5	1.08	81
3	2	0.53	43
4	2.5	0.57	55
5	1.5	0.55	62
6	1.4	0.61	83
7	2.4	0.75	43
8	3	0.87	71
Mean	2	0.66	58
SD	0.7	0.23	20
Group I (400 cGy)*			
1	1.	0.44	8
2	2.8	0.76	93
3	1.8	0.66	70
4	2.2	0.79	76
5	2.3	1.05	88
6	2.5	1.16	96
7	1.6	0.83	69
8	1	0.58	36
Mean	1.9	0.79	67
SD	0.7	0.23	31
Group II (400/400 cGy)†			
1	1	0.42	55
2	1.8	0.96	82
3	2.4	1.01	76
4	2.7	0.98	91
5	3	1.19	97
6	1.5	0.83	73
7	1.8	0.85	78
8	2.9	1.09	99
9	2.5	1.12	80
Mean	2.2	0.90	81
SD	0.7	0.22	11
Group III (800 cGy)‡			
1	2.7	1.15	92
2	2.6	1.18	97
3	3	1.02	99
4	2.3	1.15	95
5	2.7	0.94	94
6	2.8	0.73	71
7	2.3	0.88	94
8	2.6	0.85	85
Mean	2.6	0.99	91
SD	0.2	0.17	9

*Not including two pigs that died suddenly. †Not including one pig that died suddenly. ‡Not including one pig that died suddenly.

pathologic processes. In this model, the coronary arteries are used because they are *muscular* vessels, as in humans. Other animal models use carotid or iliac arteries, which are *elastic* in nature. When comparing the results of this model with the human response, the inciting event is identical—severe mechanical vascular injury. In both cases, this injury is followed by an aggressive neointimal response frequently associated with lumen compromise. The histopathologic

Table 4. Individual Linear Regression Results: Mean Neointimal Thickness Versus Mean Arterial Injury Score*

	Slope	p Value	Intercept	p Value	r Value
Control group	0.21	0.03	0.25	NS	0.73
Group I (400 cGy)	0.26	0.04	0.30	NS	0.73
Group II (400/400 cGy)	0.25	0.005	0.37	0.03	0.84

*For Group III, there were no low level injuries; thus a meaningful regression line could not be derived.

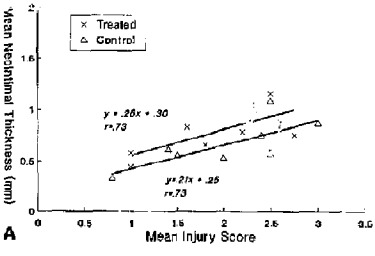
features of the neointima are identical to those of human restenotic neointima. Thus, both macroscopic features of this model (luminally obstructing neointima) and the microscopic appearance seem to mimic those of humans quite well. The limitations of this model remain unknown, as is true with all other animal models. Specifically, the time course of cellular events from arterial injury to obstructive lesion is unknown in humans because sufficient human pathologic specimens are not available for study during key stages of development.

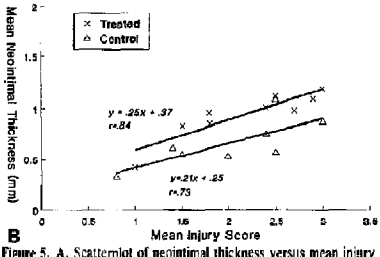
Radiation dose and timing. The timing and doses of radiation given in this study represented a "best guess" estimate because there were no previous data to guide these variables. It is possible that lower doses would have been efficacious in reducing the cellular proliferation. Prior studies suggest that higher doses might have caused an increase in the proliferative response. Because radiation clearly

Table 5. Linear Regression Results

Variable	Value	SE	p Value
Model 1*			
Constant	0.19	0.11	NS
μ	0.24	0.05	0.008§
α_1	0.15	0.08	NS
α_2	0.21	0.08	0.018
α_3	0.18	0.08	0.048
Model 2†			
Constant	0.17	0.18	NS
μ	0.26	0.08	0.008§
α_1	0.12	0.25	NS
α_2	0.20	0.26	NS
α_3	1.10	0.69	NS
β_1	0.01	0.12	NS
β_2	0.02	0.12	NS
β_3	−0.35	0.27	NS
Model 3‡			
Constant	0.30	0.05	0.007§
μ	0.19	0.10	0.002§
α_1	0.07	0.04	NS
α_2	0.09	0.04	0.028
α_3	0.07	0.04	0.048

*Thickness = $\mu \times$ Injury + $\alpha_1 \times$ GI − $\alpha_2 \times$ GII + $\alpha_3 \times$ GIII + Constant.
†Thickness = $\mu \times$ Injury + $\alpha_1 \times$ GI + $\alpha_2 \times$ GII + $\alpha_3 \times$ GIII + ($\beta_1 \times$ GI − $\beta_2 \times$ GII + $\beta_3 \times$ GIII) × Injury + Constant. ‡Thickness = $\mu \times$ Injury + ($\alpha_1 \times$ GI + $\alpha_2 \times$ GII + $\alpha_3 \times$ GIII) × Injury + Constant. §Statistically significant.





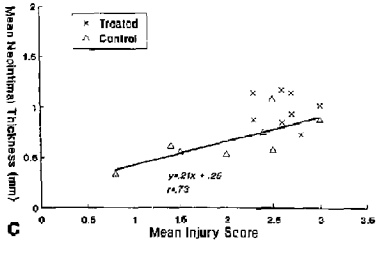


Figure 5. A, Scatterplot of neointimal thickness versus mean injury score in control versus Group I pigs (400 cGy at 1 day) and respective regression lines. Mean neointimal thickness in mm is the dependent variable, plotted as a function of mean arterial injury score. Pigs in the treated groups had significantly more neointimal thickness than did control animals. The slopes of the regression lines are not significantly different, but the y intercepts differ significantly. The regression line expressions and Pearson correlation coefficients are shown for each group. **B,** Neointimal thickness versus mean injury score in control versus Group II pigs (400 cGy at 1 day and 400 cGy at 4 days after coronary injury). The difference in intercepts is again statistically significant, while that of the slope is not. **C,** Mean neointimal thickness versus mean injury score is plotted for Group III pigs (800 cGy at 1 day after coronary artery injury). There were not enough data points with low values of injury score to make a meaningful linear regression model. The lack of low injury values may be a coincidence or an indication that the higher dose of radiation exacerbated the mechanical injury from the metal coil.

inhibits cellular proliferation, it is possible that alternative doses or timing, or both, might have yielded better results.

Conclusions. Empirically based clinical trials aimed at reducing or eliminating restenosis after coronary intervention have largely failed. Few of these trials have been performed first in animal models to test their potential efficacy. This trial was performed in a proliferative coronary artery model in the pig. The results suggest that a trial in humans using comparable doses and times after coronary artery intervention would not be prudent without further study.

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