Gamma Irradiation Inhibits Neointimal Hyperplasia in Rats After Arterial Injury

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Background and Purpose Restenosis complicates a significant proportion of endovascular and open vascular procedures such as carotid endarterectomy. In contrast to the primary atheroma, restenosis is characterized by intimal hyperplasia of vascular smooth muscle cells. We hypothesized that gamma radiation would reduce restenosis by limiting intimal hyperplasia after arterial injury.

Methods To demonstrate the effect of gamma radiation on smooth muscle hyperplasia in vivo, a standardized bilateral carotid balloon catheter arterial injury was produced in 37 rats. A single dose of 750, 1500, or 2250 cGy (1cGy=1 rad) gamma radiation was delivered to the right carotid artery at either 1 or 2 days after injury; the shielded contralateral carotid artery served as matched control. At 21 days after injury, vessels were perfusion-fixed in situ, and cross-sectional area of neointima was determined from axial sections using image analysis.

Results Marked reductions in neointimal cross-sectional area were demonstrated in vessels subjected to 1500- and 2250-cGy radiation at both 1 and 2 days after injury. A less prominent effect was noted for 750 cGy, reaching statistical significance only at 2 days after injury. By two-way ANOVA, radiation dose ($P=.0002$), timing of radiation delivery ($P=.003$), and an interaction between timing and dose ($P=.0278$) were significantly associated with reduction in neointimal cross-sectional area. At 1500 cGy, delivery of radiation 1 day after injury inhibited neointimal hyperplasia more prominently than the same dose 2 days after injury; a dose-response relation was evident at 1 day.

Conclusions Radiation may be an important adjunctive therapy for reducing the incidence of restenosis after angioplasty or endarterectomy. (***Stroke.* 1994;25:424-428.**)

Key Words • angioplasty • carotid endarterectomy • muscle, smooth • radiation • rats

Arterial stenosis is a common sequel to many vascular procedures. Restenosis after percutaneous transluminal coronary angioplasty complicates between 15% and 45% of cases[1-5] and remains a major obstacle to expanding the use of this procedure. Restenosis is a common cause of failure following carotid endarterectomy[6] and complicates many other vascular procedures including bypass vein grafting[7] and peripheral angioplasty.[8] In contrast to the typical primary atheromatous lesion, the histopathologic correlate of restenosis is intimal hyperplasia of vascular smooth muscle cells (SMCs) in a loose connective tissue matrix.[9-12] The causes of and pathophysiological mechanisms contributing to the development of restenosis are multifactorial but invariably involve the proliferation and migration of medial SMCs to the intima.[13]

A variety of pharmacologic means have been tested in an attempt to control SMC proliferation after vascular injury. Clinical trials of drugs including antiplatelet agents,[14,15] anticoagulants,[16] corticosteroids,[17] calcium channel blocking agents,[18] and colchicine[19] have proven unsuccessful in reducing restenosis rates. Heparin has been consistently successful in controlling SMC proliferation in experimental models, both systemically administered[20,21] and locally applied to the vessel.[22] However, excessive bleeding has precluded the routine clinical use of heparin after most open vascular procedures.[23] A single clinical study administering heparin 18 to 24 hours after coronary angioplasty did not demonstrate a decrease in the incidence of restenosis.[24]

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Gamma radiation affects self-renewing tissues by causing cell death during cell division and limiting proliferation by reducing the number of regenerating clonal progenitors.[25] Vascular SMCs are normally not actively dividing cell populations. However, vessel injury can induce a hyperplastic response of SMCs within the vessel wall characterized by SMC proliferation and migration; it follows that radiation should effectively inhibit neointimal formation in rapidly dividing SMCs. Rat carotid arteries damaged from within by balloon catheters have been commonly used as an animal model of SMC proliferation and restenosis following arterial injury.[26] To define the effect of gamma radiation on actively proliferating SMCs in vivo, we used the balloon catheter model of endovascular injury in rat carotid arteries to stimulate neointimal hyperplasia and delivered various doses of unilateral gamma radiation to injured vessels at 1 or 2 days after injury.

Materials and Methods

Thirty-seven male Sprague-Dawley rats (Simonsen, Gilroy, Calif) weighing 350 to 400 g were anesthetized with intraperitoneal ketamine 100 mg/kg, xylazine 6.25 mg/kg, and atropine 2 mg/kg. All procedures were performed in accordance with guidelines established by the Animal Care Committee at the University of Washington. As previously described,[27] both carotid bifurcations were exposed through a midline cervical incision, the external carotid arteries were cannulated with a 2F

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Fogarty catheter (American V. Mueller, Chicago, Ill), and the common carotid arteries were injured internally by three repeated passes of the catheter with the balloon inflated with 0.2 mL air.

At either 1 or 2 days after injury, rats were anesthetized as above, and the right carotid artery was exposed to a single dose of 750, 1500, or 2250 cGy (1cGy=1 rad) gamma radiation using a ^{137}Ce source (JL Shephard & Associates, San Fernando, Calif) delivering 66 cGy/min. The left (control) carotid artery, esophagus, and the rest of the rat were shielded using custom lead shields. Radiation dosages were initially estimated with thermoluminescence dosimeters in a killed rat at the carotid level. Dosimetry was confirmed with a Farmer-type ion chamber and thermoluminescence dosimeters in a custom-molded polystyrene rat phantom. Concordance of radiation dose using the two methods was within 5% at all measured levels. Radiation reaching the shielded left carotid artery was limited to 3.76% of the dose on the radiated side.

Twenty-one days after injury rats were reanesthetized and injected intravenously with Evans blue dye (62.5 mg/kg in 0.5 mL normal saline) to delineate the region of arterial injury; after 15 minutes carotid arteries were perfused with 200 mL intracardiac 4% paraformaldehyde in phosphate buffer at 100 mm Hg. Both carotid arteries were harvested, placed in 4% paraformaldehyde for 4 hours, then stored in a phosphate buffer solution. A 5-mm arterial segment from the center of the Evans blue–stained region in each vessel was dehydrated in graded ethanols, embedded in ethylmethacrylate, sectioned at 4-μm thickness at 20-μm intervals, mounted on glass slides, and stained with hematoxylin and eosin. The cross-sectional area of the neointima was calculated from video images of five arterial sections per vessel projected at a final magnification of ×207 using a Bioquant System IV image analyzer (R & M Biometrics, Nashville, Tenn).

Two-tailed matched-pair Student's *t* test was used to compare the mean cross-sectional areas of radiated and control (nonradiated) arteries at each radiation dose and administration interval. The neointimal quotient *(NQ)* was derived as the ratio of neointimal area of the radiated artery (A_r) to the nonradiated contralateral artery (A_n). The log of the neointimal quotient was derived by the following equation: $\log(NQ)=\log(A_r)-\log(A_n)$. Log transformations were used to standardize the variance of the data for statistical analysis. Two-way ANOVA was used to examine the effects of radiation dosage, timing of radiation after injury, and any interaction. Differences in radiation effect between days 1 and 2 at each dose were compared using the *t* test with separate variance. A one-way ANOVA was used to compare responses at different radiation doses for each day and generate dose-response analyses. All statistical analyses were generated on the software package DATA DESK (W.H. Freeman and Co, New York, NY).

Results

Rats tolerated the surgery and unilateral cervical radiation well without appreciable behavioral change or weight loss. The 2250-cGy dose of radiation produced a moist desquamation of the skin at the radiation site, whereas 1500 cGy produced mild depilation.

Histological sections of control (nonradiated) carotid arteries at 21 days after balloon catheter injury demonstrated typical neointimal hyperplasia characterized by accumulation of SMCs in the intima and resultant narrowing of the arterial lumen (Fig 1a). Arteries radiated with 1500 and 2250 cGy at 1 day after balloon injury, on the other hand, showed prominent reductions in neointimal hyperplasia compared with controls (Fig 1c and 1d). Intermediate reductions were observed for 750 cGy administered at 1 day after injury (Fig 1b). Arteries irradiated at 2 days after injury (not shown) showed histological reduction in intimal hyperplasia at various doses, which was comparable to that observed for radiation at 1 day after injury. No discernible qualitative differences were noted between radiated and control arteries with regard to endothelial regeneration (ie, differences in Evans blue staining). Similarly, the histological appearance of the media and adventitia of irradiated arteries was indistinguishable from that of nonirradiated controls, with similar degrees of perivascular inflammation and no evidence of tissue necrosis.

Fig 2 shows the results of morphometric analysis for vessels radiated at 1 and 2 days after injury compared with contralateral nonradiated controls. For radiation administered at 1 day after injury, significant reductions in neointimal cross-sectional area were observed for 1500 cGy (90% reduction; $P<.01$) and 2250 cGy (91% reduction; $P<.01$) but not for 750 cGy (26% reduction; $P=.128$). A less prominent effect was noted for radiation administered at 2 days after injury, although significant reductions in neointimal area were noted for 750 cGy (40% reduction; $P<.05$), 1500 cGy (65% reduction; $P<.05$), and 2250 cGy (73% reduction; $P<.01$).

There was a significant reduction in neointimal area at 1500 cGy administered at 1 day after injury compared with 2 days ($P=.035$), with a trend for a similar effect noted for 2250 cGy ($P=.149$) but not 750 cGy ($P=.690$). By one-way ANOVA, increasing radiation dose was significantly associated with reduction in neointimal area at 1 day ($P=.0024$) but not at 2 days ($P=.155$) after injury. By two-way ANOVA testing, both radiation dose ($P=.0002$) and timing of radiation delivery ($P=.003$) were associated with reduction in neointimal cross-sectional area; moreover, there was an interaction between these two variables in their effect ($P=.028$).

Discussion

Smooth muscle cell hyperplasia following arterial vessel wall injury has been studied extensively using the balloon catheter model employed in this experiment.[27] In this model, SMC proliferation begins in the media, followed by migration of cells through the internal elastic lamina into the intima and subsequent intimal SMC proliferation to generate a neointimal layer. In this process, normally nonregenerating vascular SMCs are stimulated by injury and a variety of mitogenic factors to become actively proliferating tissue. Majesky et al[28] showed that after balloon catheter arterial injury, SMC ornithine decarboxylase activity (indicating SMC entry into prereplicative G_1 phase) peaked at 6 hours with a rapid falloff by 9 hours, whereas the [^{3}H]thymidine index (S phase) was maximal at 33 hours with a rapid decline by 48 hours. Although thymidine uptake by SMCs may persist in the neointima adjacent to the luminal surface for up to 12 weeks, there is no apparent increase in SMC accumulation after 2 weeks in this model.[27] Similarly, the antiproliferative effect of intravenous heparin in the balloon injury model was most pronounced in the first 18 hours after injury.[28] These findings suggest that SMCs rapidly and synchronously enter the replicative cell cycle after the injury event. This cohort or clone of cells is presumably the progenitor of continued proliferation, which eventually results in neointimal hyperplasia.[29] Although the proliferative index of SMCs following radiation was not measured in this experiment, radiation likely inhibited SMC hyper-

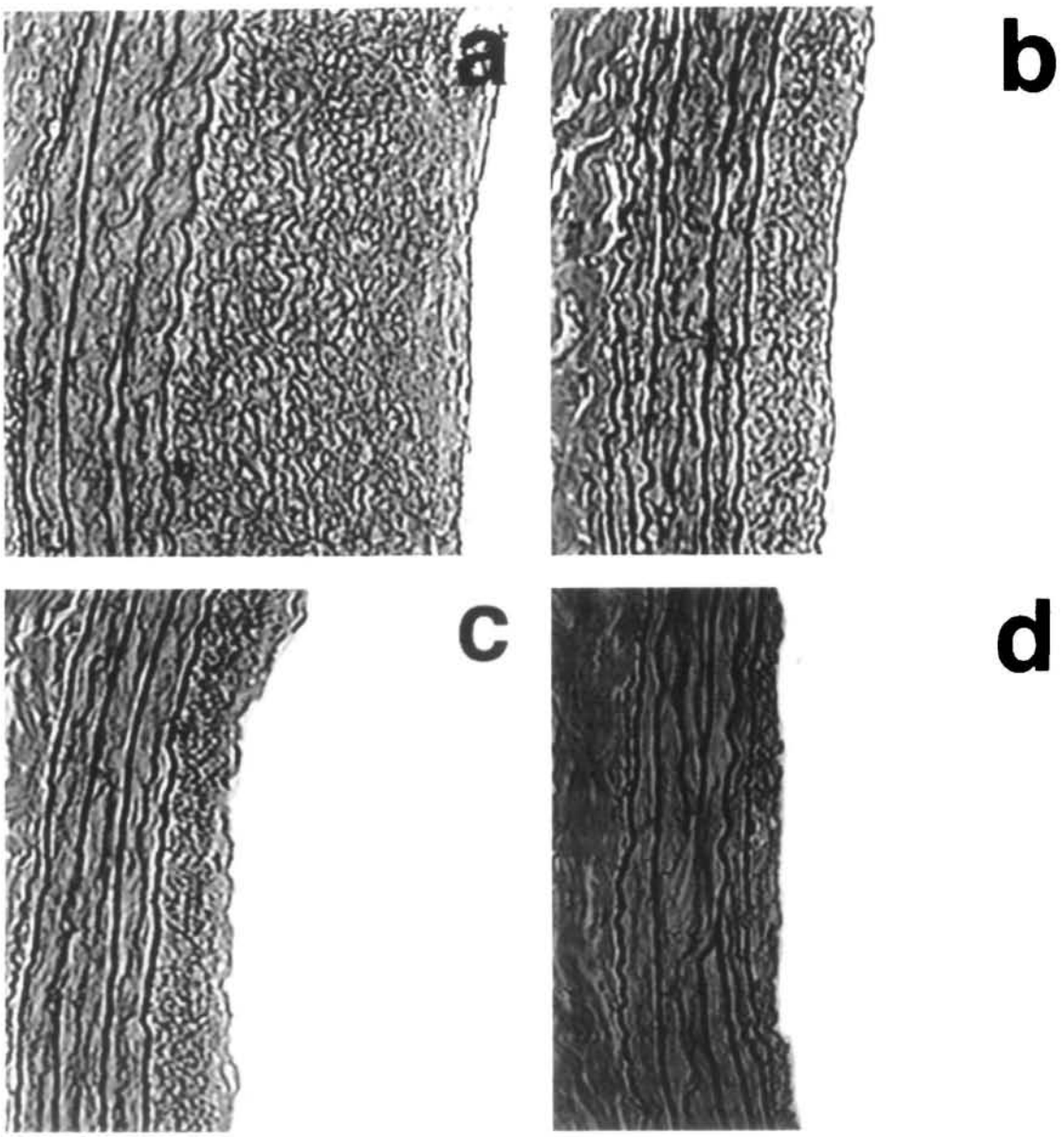

FIG 1. Photomicrographs of elastin-stained rat carotid artery in cross section at 21 days after balloon catheter arterial injury. Nonradiated control arteries (a) showed typical intimal smooth muscle cell hyperplasia medial to internal elastic laminae with luminal narrowing. Arteries treated with external gamma radiation administered at 1 day after injury demonstrated progressive inhibition of neointimal hyperplasia with increasing dose: 750 cGy (b), 1500 cGy (c), or 2250 cGy (d). Similar less prominent inhibition of intimal hyperplasia was noted in histological sections from animals radiated at 2 days after injury.

plasia by either killing progenitor cells or limiting their reproductive capacity during early cell division, thus reducing the number of clonal populations. In addition, we noted that the effect of radiation on SMC hyperplasia was more pronounced at 1 day after injury than at 2 days, suggesting that SMCs enter into the proliferative phase as a synchronous cohort of cells. Other models of radiation injury have shown that dividing cells are most susceptible to the effects of radiation during metaphase, when DNA and chromosomes undergo rearrangement injuries.[30] If SMCs enter the proliferative phase as a clone rather than sequentially, further time response studies should identify the exact window of maximal radiosensitivity and determine whether radiation inhibits intimal hyperplasia for periods longer than 21 days. This would not only lend insight into the events leading to SMC proliferation but may be valuable in defining the least amount of radiation that would be effective in suppressing the SMC response. Clinical applicability would depend in large part on such information if radiation were used to treat neointimal proliferation after vascular procedures.

Dose-response relations have been delineated for most actively dividing normal tissues with in vivo assays of clonogenic populations.[31-34] Most in vivo assays of radioresponsiveness require relatively high single-dose radiation (800 to 1600 cGy) to produce sufficient biologic damage, and the effect of smaller doses of radiation must be estimated from fractionated radiation schedules. Confluent nondividing mouse mesentery SMCs in vitro demonstrate very slow turnover rates after exposure to 2000- and 4500-cGy gamma irradiation.[35] In contrast, prolifer-

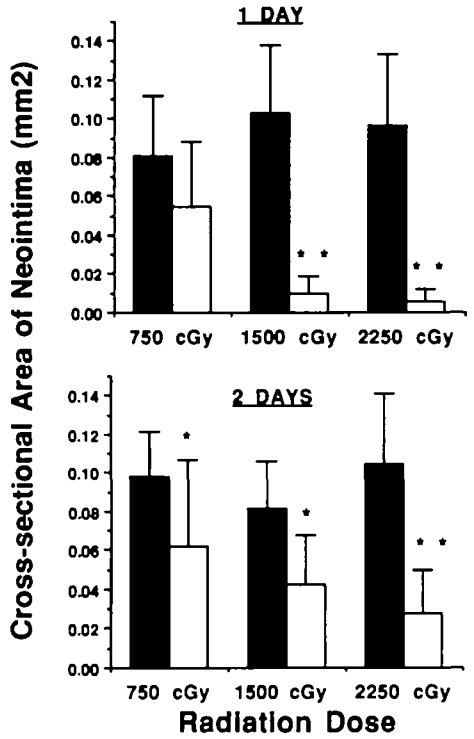

FIG 2. Bar graph shows cross-sectional area of rat carotid artery neointima at 21 days after balloon catheter injury for control (solid bar) and gamma-irradiated (open bar) vessels. At 1 day after injury (top), vessels radiated with 1500 or 2250 cGy showed marked reduction in neointimal area compared with controls, whereas 750 cGy produced less inhibition. Significant but less prominent reductions in neointimal area were noted for all doses in arteries radiated at 2 days after injury (bottom). Values are mean±SEM. *$P<.05$; **$P<.01$.

ating nonconfluent explants of primate and rabbit aortic media showed a dose-dependent reduction in [^{3}H]thymidine incorporation at doses from 100 to 3000 cGy without alterations in cell migration.[36,37] Rat aortic SMCs in exponentially growing cell cultures were moderately radiosensitive, with D_0 values of 120 to 160 cGy and extrapolation numbers of 2 to 10.[38,39]

Few studies have examined the effects of gamma radiation on SMC hyperplasia in vivo. Herbaux et al[40] found a qualitative increase in intimal hyperplasia in the region of arterial anastomosis in rats when radiation was delivered in weekly fractions to total doses of 2370 to 3080 cGy. Based on our data, it is likely that radiation in this study was administered beyond the period of maximal efficacy. Schwartz et al[41] used implanted metallic angioplasty coils to produce neointimal hyperplasia in pig coronary arteries. A small increase in neointimal cross-sectional area was noted in groups receiving 400-cGy external-beam gamma radiation at 1 day after angioplasty and divided 400 cGy fractions at 1 day and 4 days after injury. Our data suggest that the minimal effective single dose to inhibit SMC proliferation is more than 750 cGy and that fractionated doses would be most effective within the first 48 hours after injury. Single-fraction radiation doses up to 1500 cGy are generally well tolerated in humans,[42] so that radiation in the effective range for preventing intimal hyperplasia for this experiment (1500 cGy) could be clinically applied. In addition, an equivalent radiobiologic effect with less injury to normal tissues can be achieved using multifraction administration at lower radiation doses.

In the current study, single-fraction external-beam gamma radiation at doses between 750 cGy and 2250 cGy reduced neointimal hyperplasia in rat carotid arteries following balloon arterial injury. Radiation was more effective when administered at 1 day after injury compared with 2 days. The mechanism by which radiation inhibited neointimal hyperplasia in this model is indeterminate but likely involved damage to early progenitor cells during cell division, thus reducing the number of clonal populations. It is less likely that radiation reduced SMC hyperplasia by inhibiting migration from the media to the intima, since migration of SMCs in vitro was not inhibited by external radiation.[37] Nevertheless, SMCs may respond differently in vivo because of local effects of chemotactic factors.[43,44] We believe that gamma irradiation causes a reduction in neointimal proliferation by interfering with DNA synthesis and repair in actively dividing SMCs.

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Editorial Comment

Angioplasty has been used widely during the past decade to treat patients with arterial stenosis, especially in coronary arteries. Angioplasty is remarkably effective in dilating stenotic lesions, but restenosis is very common. Many approaches have been examined to prevent restenosis, but no drug or procedure has been consistently effective.

The article by Shimotakahara and Mayberg is a novel approach to restenosis, and it is a potentially important first step to treatment. Radiation to inhibit the hyperplastic response of vascular muscle after arterial injury is a clever idea. One must be cautious in extrapolation of the findings because the dose of radiation is large, sophisticated approaches will be needed to confirm the supposition that radiation inhibits neointimal proliferation, and the mechanism of the effect is obscure. Nevertheless, this new idea for treatment of arterial restenosis certainly is attractive.

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