Radioactive 133-Xenon Gas-Filled Balloon to Prevent Restenosis

Dosimetry, Efficacy, and Safety Considerations

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Background—Ionizing radiation administered intraluminally via catheter-based systems using solid β and γ sources or liquid-filled balloons has shown reduction in the neointima formation after injury in the porcine model. We propose a novel system that uses a 133-Xenon (^{133}Xe) radioactive gas-filled balloon catheter system.

Methods and Results—Overstretch balloon injury was performed in the coronary arteries of 33 domestic pigs. A novel ^{133}Xe radioactive gas–filled balloon (3.5/45 mm) was positioned to overlap the injured segment with margins. After vacuum was obtained in the balloon catheter, ≈2.5 cc of ^{133}Xe gas was injected to fill the balloon. Doses of 0, 7.5, 15, and 30 Gy were delivered to a distance of 0.25 mm from the balloon surface. The dwell time ranged from 1.0 to 4.0 minutes, depending on the dose. Localization of ^{133}Xe in the balloon was verified by a γ camera. The average activity in a 3.5/45-mm balloon was measured at 67.7±12.1 mCi, and the total diffusion loss of the injected dose was 0.26% per minute of the injected dose. Bedside radiation exposure measured between 2 and 6 mR/h, and the shallow dose equivalent was calculated as 0.037 mrem per treatment. Histomorphometric analysis at 2 weeks showed inhibition of the intimal area (intimal area corrected for medial fracture length [IA/FL]) in the irradiated segments of 0.26±0.08 with 30 Gy, 0.07±0.24 with 15 Gy, and 0.12±0.89 with 7.5 Gy versus 0.76±0.08 with control $P<0.001$.

Conclusions—^{133}Xe gas–filled balloon is feasible and effective in the reduction of neointima formation in the porcine model and safe for use in coronary arteries. **(*Circulation*. 2002;106:725-729.)**

Key Words: restenosis ■ balloon ■ catheters

Vascular brachytherapy (VBT) using multiple types of solid β and γ sources administered intraluminally via catheter-based systems demonstrated inhibition of neointima proliferation after balloon injury in the porcine model of restenosis.[1–3] VBT used in coronary and peripheral arteries demonstrated reduction in the restenosis rate and the need for repeat revascularization in clinical trials.[4–9]

Catheter-based systems usually use solid-type sources, which were designed as wires or seeds. These sources include Iridium-192, Strontium/Yttrium-90, Yttrium-90, and Phosphorous-32. An alternative method to the solid sources are the liquid-filled balloon catheters that were tested clinically with mixtures of rhenium isotopes.[10] This method provides dilatation of the balloon catheter with a radioactive liquid, which may have advantages over wire and seeds by enabling accurate source position and uniform dose to the vessel wall. Although this technique yields desirable dose distribution, the radiological toxicity of the radioactive liquid must be considered, because there is a small risk of balloon rupture or leakage.[11] The generator and handling of the liquid isotope add logistic complexity to the procedure. To minimize the risk of contamination in the event of spillage, ultra-short half-life time isotopes were tested and showed their potential to inhibit neointima formation.[12]

We propose the use of the Xena-Cath system, an alternative, novel system using a radioactive 133-Xenon (^{133}Xe) gas that is injected into a customized balloon catheter developed to exploit the unique radiophysical, chemical, and safety attributes of ^{133}Xe gas. The purpose of this study was to determine the dosimetry, efficacy, and safety of the Xena-Cath system in the porcine model of restenosis in preparation for a human study.

Methods

Radiation Details of 133-Xenon

^{133}Xe is an inert radio-gas, which historically has been clinically used as an unsealed nuclear medicine radiopharmaceutical for ventilation function imaging (V/Q scans) and blood flow measurement studies.[13,14]

Individual dose vials have been mixed with carbon dioxide as a carrier by Dupont Inc.[15] The low-energy photons (32 and 81 kev)

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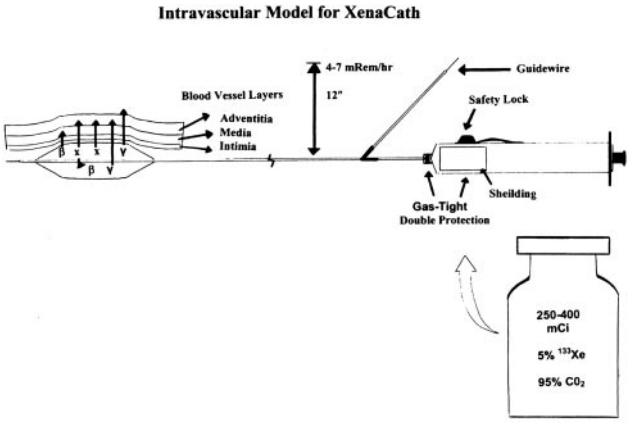

Figure 1. A diagram to illustrate the components of the Xena-Cath system.

have been used for γ camera imaging, but ^{133}Xe also emits β particles (364 kev peak), which when contained in small volumes can provide a primary brachytherapy source for short-distance tissue penetration with rapid dose fall off. ^{133}Xe has a physical half-life of 5.2 days, allowing for practical weekly based individual dose delivery as needed.[15]

In addition, Xenon is a noble gas and, therefore, whether intentionally or unintentionally released in-vivo or into the environment, remains chemically and physiologically inert. This allows for rapid removal and quick dilution from the body by exhalation, with >90% removed by first pass through the lungs.[16] As such, there is negligible organ uptake or radiation dose risk in vivo.[16,17] The gas state provides rapid dilution in air or with exhaust, whereby patient and personnel would not have the same risks of contamination and accumulation as with radioactive liquid or equivalent compounds.

Porcine Overstretch Injury and Radiation Protocol

The animal rights and radiation safety committees of the Washington Hospital Center, Washington, DC, approved the study protocol. The investigation conformed to the guidelines of the American Physiological Society for the care and use of laboratory animals. The methods of the balloon overstretch injury were previously described. In brief, juvenile pigs from Thomas D. Morris, Inc (Reisterstown, Md) underwent balloon (20 mm in length) overstretch injury in 2 coronary arteries (left anterior descending, left circumflex, or right coronary artery) for each pig by inflation with a standard angioplasty balloon having a diameter 30% larger than the reference vessel diameter. Each inflation (30 seconds) was taken to 10 atm separated by a 1-minute deflation period to restore coronary perfusion. Subsequently, a modified prototype PTCA-type balloon (2.5 to 4.0 mm in diameter and 30 to 40 mm in length) over a flexible 0.014-inch guidewire was inserted into the treated vessel and positioned to cover the injured segment, while attempting to maintain adequate proximal and distal margin length coverage as verified by fluoroscopy. Those vessels assigned radiation treatment received closed-system injection balloon inflation with predetermined quantities of inert ^{133}Xe gas prepared with CO_2 in vial form by Dupont Radiopharma, Inc. The catheter balloon diameter was selected to avoid additional overinflation injury. A diagram to illustrate the components of the Xena-Cath system is displayed in Figure 1. Based on prior in vitro phantom-based dosimetry measurements and Monte Carlo–type model calculations, dose rates were applied to quantify inflation time required to deliver an assigned dose of 0 Gy (control n=6), 7.5 Gy (n=9), 15.0 Gy (n=11), or 30 Gy (n=7) to a depth of ≈0.25 mm from the balloon surface. Contrast angiography was applied to verify the ^{133}Xe–filled balloon was fully inflated and in contact with the arterial wall. On average, treatment time ranged from 1.5 to 4.0 minutes. Total balloon-injected radioactivity was up to 300 mCi of ^{133}Xe gas within a total average volume range of 1.5 to 2.0 cc. In some animals, a γ camera was used to detect ^{133}Xe in the balloon and

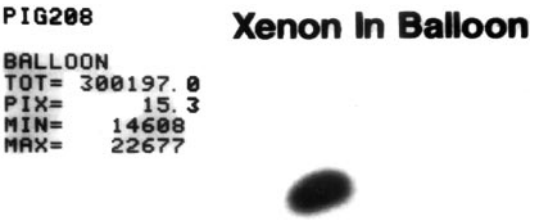

Figure 2. ^{133}Xe in the inflated balloon in the coronary artery of the pig during treatment, detected by γ camera.

compare it with the traces of the gas while the balloon was being retrieved (Figure 2). After radiation treatment was complete, the delivery catheter and guiding catheter were removed and the cut-down site was repaired. Full radiation safety protocol and monitoring was followed per radiation safety committee guidelines. Routine postoperative care was with aspirin as the sole antiplatelet therapy for 30 days.

Dosimetric Measurements

In vitro microdosimetry and safety studies were carried out. Customized solid water phantoms were fashioned such that a tangential section of the balloon was adequately exposed during inflation and on which multiple layers of 0.125- to 0.250-mm-thick GafChromic film could be placed before inflation. At least 5 cm of solid water was placed above and beyond the piece containing the catheter to compensate for scattering and absorption. Several timed xenon experiments were carried out with controlled parameters, including balloon size, amount of injected xenon activity, and exposure times. Preinjection and postinjection measurements were made of the ^{133}Xe vial contents, the gas-tight syringe (10 to 25 cc) (Hamilton Inc), and the tested catheter. Quantified estimates of any free gas loss, residual catheter containment, and syringe residuals were all recorded to confirm assumed injected radio activity amounts, as well as to assess leakage per exposure sample. After 7 days, the Gaf Chromic film layers were measured for maximal exposure point readings, as performed using a spot densitometer. Reference tissue depths were equivalent to film layer depths, and each measured optical density was correlated to an equivalent total dose with use of a dose-response curve analysis published using ^{125}I (closet γ-ray/x-ray emission energy). Results were also comparatively matched to preliminary standard Monte Carlo simulations. A calibrated survey monitor was used to measure and record exposure and reading levels at the locations of the operators as follows: 1 m above the injector, 30 cm above the injector, 30 cm from the catheter, and 30 cm from the utilized balloon. Exposure rates and cumulative levels were measured and documented at various distances from the catheter and in the room.

Tissue Analysis Protocol

Two weeks after the treatment, the animals were euthanized and the coronary arteries were perfusion fixed. Serial 2- to 3-mm transverse segments were processed and embedded in paraffin. Micro cross-sections were stained with H&E and Verhoeff van-Giesson elastin stain. An experienced observer blinded to the treatment group examined the histology. Each artery had 5 to 8 cross-sectional specimens that were evaluated for neointima formation, luminal encroachment, medial dissection, alteration of the internal and external elastic lamina, and morphological appearance of cells within the neointima, media, and adventitia.

Histomorphometric analysis was performed on each segment with evidence of medial fracture (2 to 5 for each analyzed artery). The histopathological features were measured using a computerized personal computer–compatible image analysis program (Optimas 6, Optimas, Inc).

Measured Variables

The maximal intimal thickness (MIT) is determined by a radial line drawn from the lumen to the external lamina at the point of greatest

TABLE 1. Measurements of Radiation Dose Rate at Various Tissue Depths From the Balloon Surface*

Tissue Depth From Balloon Surface, mm	Dose Rate, cGy/mCi per hour
0.125	880–920
0.250	210–240
0.375	132–150
0.500	32–50
0.750†	14–20
1.00†	10–12

*Balloon wall thickness is 80 to 100 μm. Range of gross injection activity of ^{133}Xe is ≈50 to 200 mCi. Percent balloon volume of total injected volume is 45% to 60%.

†Values for 0.75 to 1.00 mm may actually be greater but undermeasured because of minimal exposure threshold requirements for film change of 800 to 1000 cGy.

tissue growth. The arc length of the medial fracture (FL), traced through the neointima from one dissected medial end to the other, was used as a measure of the extent of injury. Area measurements were obtained by tracing the lumen perimeter (luminal area [LA], mm^2), neointima perimeter (intimal area [IA], mm^2), and external elastic lamina (vessel area [VA], mm^2). The ratio of intimal area to fracture length (IA/FL) was obtained to correct for extent of injury. Additional measurement parameters included vessel perimeter (VP) and adventitial area (AA). Measurements were cross-checked for accuracy by random repetition of 25% of stenosis and determination of percentage variability.

Statistical Analysis

Statistical comparison was performed of the IA, IA/FL, LA, MIT, AA, VP, and VA between control and variably dose-irradiated arteries using either one-way ANOVA with the Bonferroni correction for groups whose SD of the means was not statistically different (ie, $P>0.05$ by Bartlett's test) or by the Kruskal-Wallis test for groups whose SD of the means was statistically significant different ($P<0.05$ by Bartlett's test). By this analysis, statistically significant differences between treatment groups were considered to be those with $P<0.05$.

Results

Radiation was delivered successfully and safely to all arteries. There were no radiation-specific side effects or excess dose exposures observed. The personnel exposure at bedside during the treatment was calculated to be <0.17 to 0.24 mR.

The calculations of the dose rate as a function of distance from the balloon into the vessel wall are displayed in Table 1. Cumulative results of all histomorphometric measurements are shown in Table 2. A profound reduction in the neointima formation indices (IA, IA/FL, and MIT) was noted within all doses of ^{133}Xe compared with control (Figure 2). Overall the number of the occluded vessels with mural thrombosis was higher with a dose of 30 Gy, 2 of 7 compared with 1 of 11 in the 15-Gy dose and none in the 7.5-Gy and the control arm.

There was a statistically significant reduction of corrected intimal area (IA/FL) for the 7.5-Gy and 15-Gy groups compared with the control group and reduction in adventitial area in the 15-Gy group with respect to the control group. There was no excess of inflammation at the irradiated arteries compared with control. However, there was deterioration of the results in terms of increase in intimal area and reduction of luminal area with 30 Gy compared with 15 Gy (Tables 2 and 3). In addition, there was less vasavasorum at the adventitia of the 30-Gy group compared with control. Representative histology for each of the treatment arms is displayed in Figure 3. Review of multiple artery sections did not demonstrate any overt evidence of early medial or adventitial layer necrosis formation of pseudoaneurysm or excess of inflammation in the radiated vessels compared with control. However, thrombus formation was noted in a limited section, especially in the higher dose-treated group. An example of thrombus is shown in Figure 4.

Discussion

The primary finding of this study was that the ^{133}Xe delivered into porcine coronary arteries after balloon injury resulted in significant reduction of the neointima formation with a dose response. In addition, the Xena-Cath system portrays a uniquely safe radiation exposure profile.

The Xena-Cath system provides potential conformal, self-centering (with respect to the lumen), and direct interface with the exposed arterial wall. This should provide relatively simplified, predetermined high-dose rate delivery at a prescribed tissue depth from the outer balloon surface. Dose quantities of inert ^{133}Xe can easily be injected to provide short treatment times of <3 to 5 minutes, and cycles of deflation and inflation may require overcoming patient tolerance during complete vessel obstruction. The use of standard external exhaust ventilation and standard handling protocol provided simple administration of treatment without risk of excessive exposure attributable to any unexpected contamination.

In addition, ^{133}Xe can be provided on an as-needed basis for quantity, with individualized precalibrated dose units. This eliminates considerations related to radionuclide generators, long half-life storage, or wasted costly inventory.

The efficacy of ^{133}Xe using doses of 7.5 and 15 Gy demonstrated similar histologic findings to those reported with other solid sources, such as Iridium-192, Yttrium-90, and Sr-90/Y, at similar doses used in the same model of overstretch balloon injury of porcine coronary arteries.[1–3] Of

TABLE 2. Histomorphometric Analysis and Dose Response

	n	IA, mm^2	FL, mm	IA/FL	MIT, mm	VP, mm	VA, mm^2	LA, mm^2	AA, mm^2
Control	6	1.51±0.35	2.04±0.59	0.76±0.13	0.50±0.10	9.38±0.70	5.96±1.23	3.18±0.79	5.08±1.41
7.5 Gy	9	0.32±0.53	1.72±0.77	0.37±0.89	0.23±0.32	9.37±0.99	6.08±1.49	3.92±1.91	3.77±0.71
15 Gy	11	0.16±0.31	2.05±0.88	0.09±0.19	0.15±0.30	9.52±1.73	6.12±2.15	3.99±2.35	3.05±0.72
30 Gy	7	0.22±0.25	1.44±0.83	0.25±0.29	0.33±0.41	8.71±1.32	4.86±1.84	2.81±1.97	3.53±1.73

Values are mean±SD.

TABLE 3. Statistical Significance Between Treated Groups and Control

	IA	FL	IA/FL	MIT	VP	VA	LA	AA
7.5 Gy	$P<0.01$*	NS	$P<0.05$*	NS‡	NS	NS	NS	NS
15 Gy	$P<0.01$*	NS	$P<0.01$*	NS‡	NS	NS	NS	$P<0.01$†
30 Gy	$P<0.01$*	NS	NS	NS‡	NS	NS	NS	NS

*Dunnett's test for groups with SDs not statistically different (ie, $P>0.05$ by Bartlett's test).
†Kruskall-Wallis test for groups with SDs statistically different (ie, $P<0.05$ by Bartlett's test).
‡$P=0.053$ from Kruskall-Wallis test.

interest is the deterioration of the results seen with the dose of 30 Gy, which could be the result of excess of thrombosis related to this high dose. The total occlusion rate detected in 2 of 7 (28%) of the treated arteries is unusual for nonstented arteries and should be attributed to the lack of healing and delayed reendothelialization as a result of the radiation treatment. The presence of thrombus in the irradiated arteries compromised the expected increase in luminal area in the irradiated arteries. Thus, only incremental gain in the lumen area was measured with 7 and 15 Gy, and smaller lumen area was measured with 30 Gy compared with control despite nearly complete inhibition of the neointima. This can be explained by the presence of thrombus occupying the lumen of the irradiated arteries. When the totally occluded arteries were excluded from the analysis, the luminal area of the 30-Gy group was similar to the dose of 15 Gy and the intimal area was substantially less compared with control. The recent published clinical trials suggest that prolonged antiplatelet therapy (Clopidogrel) minimized the late thrombosis.[18] Thus, it is possible that administration of Clopidogrel in the present experiment could minimize the thrombosis seen with the 30-Gy dose.

Prior reports have described various radiation doses and prescription depths. However, these are varied among systems.[19–21] Furthermore, it remains unclear what exact target cells and what doses are optimal to inhibit restenosis with the use of vascular brachytherapy.[22] It is possible that deeper radial tissue doses may increase toxicity and provoke additional fibrosis and thrombosis.[23–25]

The proximity of the radioactive gas to the lumen wall and the centering features of the system within the lumen overcome the limited penetration capabilities of the β-emitter and the soft x-ray generated from ^{133}Xe.

This prospective, controlled study with the Xena-Cath system has provided additional animal data determining that specific doses of intraluminal brachytherapy show significant measured-dependent inhibition of restenosis. The observed results of the study did not demonstrate any early findings of deeper vascular or deep adventitial radiation injury, because none of the irradiated arteries presented with fibrosis or necrosis at follow-up. In this study, the prescribed dose did not extend deeper than 0.25 mm into the injured media or adventitia, yet showed excellent results. This may also be of theoretical long-term benefit in the reduction of adverse events over higher megavoltage energy β emitters or higher energy photon (γ) sources, particularly in combination with noncentered delivery systems.

Personnel who do routine Xena-Cath treatments with an injection dose of 350 mCi and an average pass-through exposure of 2 to 5 Mc per procedure would still receive only ≈4.5 mrem/year per 1000 treatments (with standard protective shielding). Standard exhaust venting and closure of the cath laboratory suite during use would provide rapid elimination and equilibrium with any expected minor routine activity loss to safe concentrations of minimal derived air concentration levels (1.0 to 4.0 μCi/mL within 9 to 11

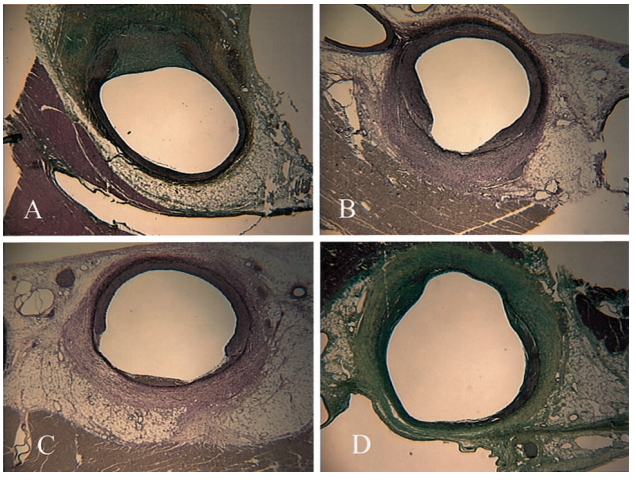

Figure 3. Representative micrographs at ×40 instrument magnification of thick sections from injured pig coronary arteries, stained with Verhoeff-van Gieson elastin. Healing responses at 2 weeks in 4 treatments are compared. Samples are shown from the control group (A), 7.5-Gy-treated group (B), 15-Gy-treated group (C), and 30-Gy-treated group (D).

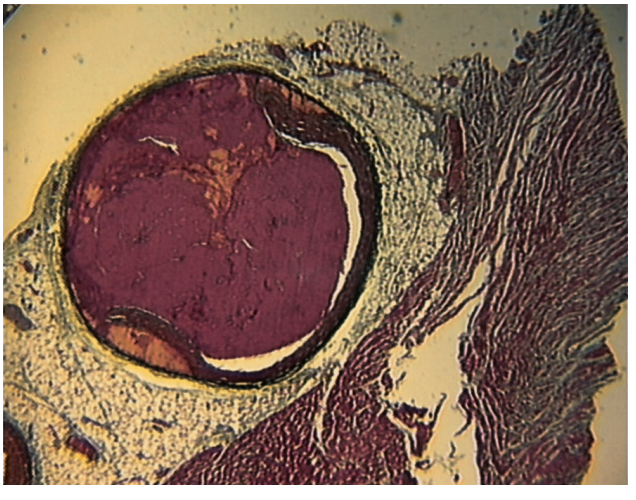

Figure 4. Histological cross-section of artery exposed to balloon injury and radiation (30 Gy). Note absence of neointima formation and intraluminal thrombus.

minutes for 350 mCi loss). Even with high activity loss, personnel exposure both with and without lead aprons is still 0.44 to 1.0 mrem and 44 to 100 mrem, respectively.

Limitations of Study

The device was evaluated within a limited dose range. Additional dose-finding studies might be useful to enhance efficacy and define safety. The use of young nonatherosclerotic porcine coronaries for this study may be limited by unknown contributing factors in an older, diseased human artery, although some reported human data have paralleled beneficial outcomes based on similar pig model studies.

The length of follow-up of 14 days reported in the porcine overstretched balloon injury model does not reflect long-term follow-up. Finally, potential of incomplete reendothelialization and absence of potent antiplatelet therapy could have contributed to the presence of thrombus at the irradiated vessels. Future studies in animals and humans of results after at least 6 months are warranted to confirm longevity of efficacy.

Conclusion

Intravascular brachytherapy administered by a custom ^{133}Xe inert gas into a balloon-type catheter is effective in markedly reducing postangioplasty neointima formation as studied in the porcine model. Morphometric results show evidence of optimal benefit at doses of 15 to 29 Gy without observed adverse radiation changes in the studied arteries.

In addition, the radiation safety profile of the Xena-Cath system and its performance and handling in the cath-laboratory during the preclinical experiments support additional clinical investigation.

Acknowledgments

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