Centered versus noncentered source for intracoronary artery radiation therapy: A model based on the Scripps Trial

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Background The Scripps Trial was a randomized study of intracoronary artery radiation therapy with iridium 192 used to treat restenotic vessels. We used the intravascular ultrasound data from the Scripps Trial to investigate whether a lumen-centered gamma or beta radiation source would reduce radiation dose heterogeneity compared with the noncentered source position used.

Methods Analysis included 28 patients with stent placement in 20 native vessels and 8 saphenous vein grafts enrolled in this trial. Radiation dosimetry for gamma radiation was calculated to deliver 800 cGy to the far field target, provided the maximum dose to the near field target did not exceed 3000 cGy. Prescribed dosimetry for beta radiation by use of yttrium 90 was 1600 cGy at 2 mm distance from the source.

Results The calculated average minimum source to target distance by use of a lumen-centered source increased by 0.18 mm from 1.70 ± 0.25 to 1.88 ± 0.36 mm, whereas the maximum distance decreased by 0.17 mm from 3.64 ± 0.60 to 3.47 ± 0.43 mm ($P < .05$). On the basis of these distances, the maximum radiation dose, as well as radiation dose heterogeneity (ratio of maximum to minimum), would have been reduced in 22 of 28 patients by use of a lumen-centered gamma or beta source ($P < .005$). The reduction in dose heterogeneity was substantially greater with a beta source compared with a gamma source (48% vs 16% reduction).

Conclusions Centering of the intracoronary artery radiation therapy delivery catheter within the vessel lumen can significantly reduce radiation dose heterogeneity when compared with a noncentered source position. This dose reduction is substantially greater for a beta compared with a gamma source. (Am Heart J 2002;143:342-8.)

Application of radiation to a stented vessel region has been shown to reduce restenosis rates compared with nonradiated vessels.[1-3] The radiation dosimetry used in these trials was chosen on the basis of experience from radiation therapy of benign hyperplasic disorders[4] and from animal data.[5,6] However, no long-term data are available regarding adverse effects of intracoronary artery radiation treatment (ICRT). Because vascular irradiation can result in a depleted cell population,[7] impaired cellular function,[8] and impaired healing after injury,[9] there may be unfavorable consequences from coronary artery radiation. Therefore it is reasonable to apply the lowest radiation dose possible to reduce the risk of toxicity.

Improving dose homogeneity may be an important factor in maximizing efficacy while minimizing toxicity.[10] The calculated ICRT dosimetry used in the Scripps Trial was based on a noncentered radiation source in the arterial lumen. Because the radiation dosimetry is calculated on the basis of minimum and maximum distances from radiation source to target, centering the source in the vessel lumen may reduce maximum radiation dose to the near field while maintaining minimum dose to the far field target. Thus the radiation dose heterogeneity (ratio of maximum to minimum dose) may be reduced. This may even be more important for beta emitters because of the greater radiation attenuation with distance. To investigate these hypotheses and to assess the value of lumen centering, we compared radiation dosimetry on the basis of the noncentered catheter position used in the Scripps Trial to a dosimetry modeled based on a lumen-centered radiation source for both gamma and beta radiation.

Methods

Patient selection criteria and study design of the Scripps Trial has previously been published.[1] In this trial, 55 patients with restenotic lesions underwent repeat angioplasty or stenting and were then randomized to receive either ICRT treatment or placebo. All target lesions not containing stents were

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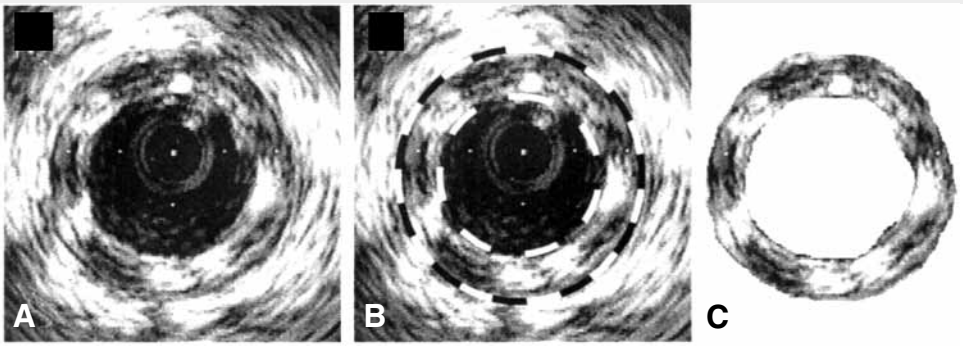
4/1/120781
doi:10.1067/mhj.2002.120781

Figure 1



A, Cross-sectional intravascular ultrasound image of stented segment. Transducer artifact is *black circle* in middle of images. **B,** Image of **A** with lumen *(inner dashed line)* and vessel borders *(outer contour)* superimposed. **C,** Plaque, *white inner region* represents vessel lumen, and *outer edge* represents vessel border.

stented. Therefore all measurements were performed on stented coronary arteries.

Patient population

For this study, we randomly selected 20 patients with native artery targets and 8 patients with saphenous vein graft (SVG) targets from the Scripps Trial population.

Radiation dosimetry

In the Scripps Trial, the radiation dose was prescribed on the basis of the assumption that 800 cGy delivered to the adventitia border farthest from the source but no more than 3000 cGy delivered to the adventitia border closest to the source would be safe and effective. To achieve this, intravascular ultrasonography was used to obtain a series of tomographic sections by motorized pullback (0.5 mm/sec) and recorded on S-VHS videotape for offline analysis. Ultrasound images were scanned, and measurements were performed along the entire length of the stent. The minimum and maximum distances between the center of the ultrasound catheter, serving as a surrogate for the ICRT delivery source, and the media-adventitia border (the target) were measured in 1-mm intervals along the stented segment of the artery. The closest and the farthest distances of all measurements obtained within one stented segment were used to calculate radiation dosimetry. The radiation oncologist and physicist combined the distance information with the specific activity of the γ emitter iridium 192 radioisotope to determine the dwell time required to deliver 800 cGy to the target farthest from the radiation source, provided no more than 3000 cGy was delivered to the target closest to the source. The 3.2F intravascular ultrasound catheter has a slightly smaller diameter than the 4.7F radiation delivery catheter (1.1 mm compared with 1.5 mm), resulting in a slightly more eccentric position within the vessel lumen. The radiation delivery catheter therefore is slightly more lumen centered than the ultrasound catheter.

The dosimetry for beta radiation was performed with the assumption of an yttrium 90 point source of 2.28 Mev maximum energy and with a prescribed dose of 1600 cGy at a distance of 2 mm from the source. The calculation involved Monte-Carlo computer simulation of the charged particle interactions that a beta particle undergoes as it traverses water-equivalent tissue.

Image selection and analysis

Recorded ultrasound images from 28 randomized patients were digitized by use of a frame grabber board interfaced to a Power PC Macintosh (Apple Computer, Cupertino, Calif) at 640×480 pixel by 8-bit image resolution. Images were acquired at 1-mm intervals (every 2 seconds at motorized pullback speed of 0.5 mm/s) along the stented artery segment. A total of 619 images were evaluated, with an average of 21 images per patient (range 15 to 46).

Definition of the center of a noncircular object is a mathematic concept. In this study we used the center of gravity within the lumen borders as the closest approximation of a lumen center (lumen center referencing). In addition, the center of gravity within the media-adventitia border was used as the closest approximation of the vessel center (vessel center referring).

Lumen border and media-adventitia borders were manually traced for each image. Plaque area including the embedded stent was extracted and determined the region of interest (Figure 1). Location of the vessel and lumen centers within the borders, respectively, was computed by use of a custom software package. The software also calculated the minimum and maximum distances from lumen and vessel center to the target, which were used for the calculation of ICRT dosimetry by use of the same algorithm as for actual administered dosimetry. The same images used for the analysis of the lumen and vessel centers were taken to trace the ultrasound transducer border together with the media-adventitia border. The software subsequently calculated the distances from the center of the probe to the target for all 619 images. The same investigator performed all tracing.

To assess lesion eccentricity, the distance between vessel and lumen center was calculated by use of the custom software. Lesion eccentricity was defined as distance between vessel center and lumen center divided by the adventitia

Table I. Maximum and minimum radiation doses and dose heterogeneity for all vessels

		Gamma source		Beta source	
Variable	**Vessel (n)**	**Noncentered**	**Centered**	**Noncentered**	**Centered**
Maximum ICRT dose (cGy)	All (28)	2016 ± 471	1689 ± 286*	2495 ± 859	2033 ± 805*
	Native (20)	2007 ± 445	1716 ± 252*	2646 ± 800	2140 ± 741*
	SVG (8)	2038 ± 565	1621 ± 370*	2117 ± 940	1766 ± 947
Minimum ICRT dose (cGy)	All (28)	797 ± 14	800 ± 0	240 ± 129	275 ± 130
	Native (20)	799 ± 3	800 ± 0	274 ± 122	288 ± 130
	SVG (8)	791 ± 25	800 ± 0	154 ± 108	243 ± 127*
Dose heterogeneity	All (28)	2.53 ± 0.63	2.11 ± 0.4*	16.38 ± 14.9	8.56 ± 4.3*
	Native (20)	2.51 ± 0.56	2.14 ± 0.3*	14.77 ± 15.2	8.40 ± 3.8
	SVG (8)	2.59 ± 0.80	2.03 ± 0.5*	20.38 ± 14.3	8.96 ± 5.8*

Given are the mean values ± the standard deviation.
*Marks statistically significant difference ($P < .05$) between centered and noncentered values.

radius (reported in percentage times 2). Lesion eccentricity was calculated for all images, and the maximum value of each data set (one patient) was used for comparison.

Statistical analysis

Statistical analysis was performed with Microsoft Excel (Microsoft Inc, Seattle, Wash) and Sigma Stat (Jandel Scientific Corp, San Rafael, Calif). Quantitative data are presented as mean ± 1 SD. Paired Student *t* test or χ^2 testing was applied for comparison of centered versus noncentered radiation source. Significant difference was defined as a *P* value <.05 by use of either a 1- or 2-tailed test. Linear regression analysis was used to investigate the relationship between lesion eccentricity and reduction in radiation dose heterogeneity, as well as between vessel size and dose heterogeneity.

Intraobserver variability

The results of 183 image analyses from 18 patients were previously presented as preliminary data. Nine of these patients were reevaluated 11 months later by the same investigator (total of 224 measurements). The exact image position of the previous selection was not known to the investigator. Mean minimum and maximum distances from lumen center to target in the initial assessment was 1.72 ± 0.20 mm and 3.19 ± 0.28 mm, compared with 1.76 ± 0.21 mm and 3.17 ± 0.22 mm ($P > .05$) as a result of the second evaluation. The mean differences between the data sets were –0.03 ± 0.26 mm and 0.02 ± 0.37 mm.

Results

In Table I the mean values and standard deviation for minimum and maximum radiation doses and dose heterogeneity (ratio of maximum to minimum dose) values are tabulated for a noncentered gamma and beta-ICRT source compared with those calculated for a lumen-centered radiation source on the basis of our modeling.

Distances from ICRT source to target

The calculated average of all minimum distances of each data set from a noncentered radiation source to the target was 1.70 ± 0.25 mm compared with 1.88 ± 0.36 mm if a lumen-centered source was used ($P < .05$). The calculated mean minimum distance in native vessels increased from 1.64 ± 0.23 mm to 1.83 ± 0.32 mm ($P < .05$), with lumen centering and in SVG from 1.83 ± 0.27 mm to 2.03 ± 0.43 mm ($P < .05$). The average of all maximum distances from each data set decreased from 3.64 ± 0.60 mm on the basis of a noncentered radiation source to 3.47 ± 0.43 mm if a lumen-centered source was used ($P < .05$). The calculated mean maximum distance by use of a noncentered source in native vessels and SVG was 3.50 ± 0.57 mm and 3.99 ± 0.56 mm, respectively, compared with 3.42 ± 0.40 mm ($P > .05$) and 3.59 ± 0.50 mm ($P < .05$) if a lumen-centered source was used.

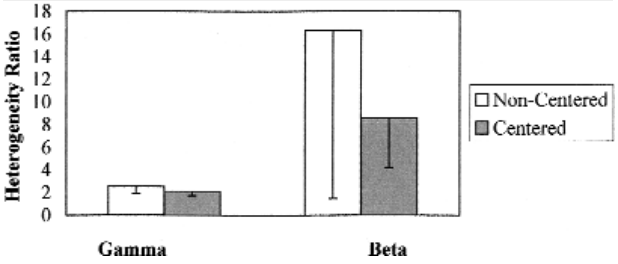
Maximum radiation dose

Use of a lumen-centered ICRT source reduced the calculated maximum radiation dose to the target compared with a noncentered source in 22 of the 28 patients for both gamma and beta source. The mean gamma dose decreased by 16% from 2016 ± 471 cGy to 1689 ± 286 cGy ($P < .001$), whereas the reduction for a beta source was 19% from 2495 ± 859 cGy to 2033 ± 805 cGy ($P < .01$). In 5 patients receiving gamma and 6 patients receiving beta ICRT, there was an increase in maximum dose with centering (1% to 42% vs 3% to 70% increase). One patient would have received exactly the same gamma dose with either a centered or a noncentered source.

Minimum radiation dose

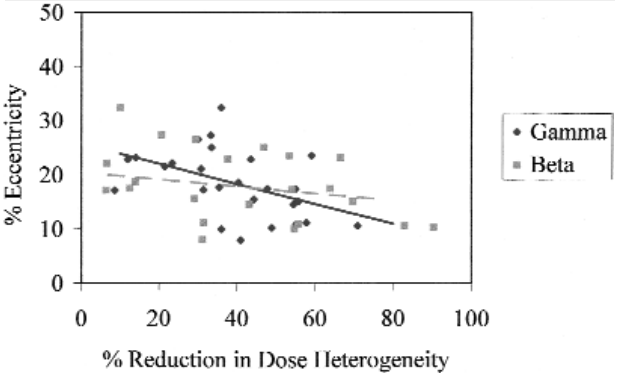
Because the minimum ICRT dose was less than 800 cGy only in those patients in whom the maximum dose would have exceeded 3000 cGy, the variability in both centered and noncentered groups was small for a gamma source. With a noncentered gamma source, the average calculated minimum radiation dose was 797 ±

Figure 2



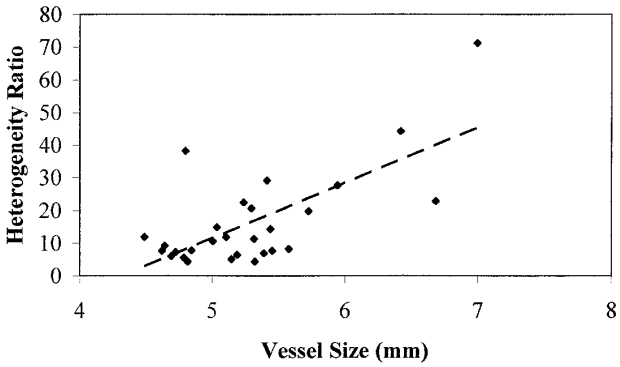
Average radiation dose heterogeneity (ratio of maximum to minimum dose) is plotted for noncentered and centered radiation source for gamma and beta irradiation (n = 28 each). *Error bars* indicate SD.

Figure 3



Relationship between lesion eccentricity and reduction in dose heterogeneity with lumen centering for gamma *(diamonds)* and beta *(squares)* radiation. Linear regression analysis revealed significant slope (–0.18 and –0.06; $P < .05$) with correlation coefficients of 0.47 and 0.41, respectively. Lumen centering more effectively reduces dose heterogeneity in lesions that have less eccentricity.

Figure 4



Relationship between dose heterogeneity and vessel size for beta radiation. Linear regression analysis revealed significant slope (17.02; $P < .001$) with correlation coefficient of 0.70. More dose heterogeneity has to be expected with larger vessels when beta source is used.

14 cGy (26 of 28 patients received 800 cGy) and increased to 800 ± 0 cGy with source centering (all 28 patients received 800 cGy vs noncentered, $P > .05$).

Use of a centered beta source would have increased the average minimum ICRT dose from 240 ± 129 cGy to 275 ± 130 cGy ($P > .05$). The average increase in minimum ICRT dose was more pronounced for SVG and reached statistical significance in spite of the small number (154 ± 108 vs 243 ± 127 [$P < .05$]). Assuming a minimum desired dose of 800 cGy to the entire target as required for gamma ICRT in the Scripps Trial, none of the 28 patients would have received the minimum dose in the beta ICRT centered or noncentered group.

Radiation dose heterogeneity

A comparison of change in dose heterogeneity with centering between a gamma and a beta source is shown in Figure 2. With a lumen-centered ICRT source, the calculated radiation dose heterogeneity would have been reduced in 22 of 28 patients for both gamma and beta ICRT. The mean heterogeneity ratio for gamma ICRT decreased by 16% from 2.53 ± 0.63 to 2.11 ± 0.36 ($P < .001$). With a beta source the reduction in mean dose heterogeneity would have been 48% from 16.38 ± 14.9 to 8.56 ± 4.3 ($P < .001$). Although there was no statistically significant difference for gamma ICRT between native vessels and SVG, there was a greater reduction (56% vs 43%, $P < .05$) for SVG versus native arteries when a beta ICRT source was used (20.38 ± 14.3 to 8.96 ± 5.8 vs 14.77 ± 15.2 to 8.40 ± 3.8). In 5 patients receiving gamma and 6 patients receiving beta ICRT, there was an increase in ICRT dose heterogeneity with centering; in 1 patient there was no change for a gamma source.

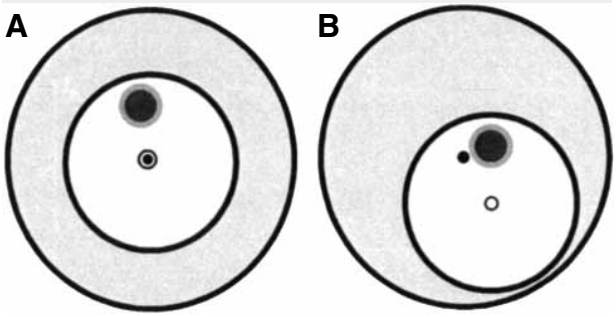
Lesion eccentricity

The average eccentricity was 18.7% ± 6.05%. Linear regression analysis between lesion eccentricity and reduction in dose heterogeneity with centering for a gamma and beta source resulted in a significant inverse relationship (Figure 3).

Vessel size

A linear regression analysis found dose heterogeneity for beta radiation was significantly correlated with vessel size (Figure 4). Regression analysis between dose heterogeneity for gamma radiation and vessel size did not reach statistical significance.

Figure 5



Effect of lesion eccentricity on dose heterogeneity. Two vessel cross-sections containing possible radiation source *(gray circle)* are schematically shown. *Outer black border* represents vessel border, and *inner black border* represents lumen border. *Shaded area* between these two borders represents plaque area. *Small solid circle (black)* represents vessel center, and *open circle* represents lumen center. **A,** Concentric lesion with radiation source *(larger gray circle)* placed eccentrically in lumen. Note that source is relatively far from vessel center, resulting in large dose heterogeneity. Lumen centering would bring source closer to vessel center and thereby reduce dose heterogeneity. **B,** Eccentric lesion with radiation source also eccentrically placed within lumen. Note that radiation source, although eccentric within lumen, is closer to vessel center than lumen center. Lumen centering in this case would lead to greater dose heterogeneity compared with noncentered source position.

Discussion

Use of the most homogenous radiation dose possible may be important for safe and effective ICRT. Currently, the therapeutic window for radiation treatment is unknown. Therefore centering the ICRT source within the target borders may be desirable.[10] Unfortunately, the space available for the radiation source positioning is determined by the lumen borders, yet the target, presumably, is within the vessel wall beyond the lumen borders. Depending on the lesion configuration, the centers within these 2 borders may be substantially different. Ideally, the ICRT source would be placed within the lumen at the vessel center. However, currently no method is available to center the radiation source with respect to the vessel wall. The second best choice is to center the radiation source within the lumen, which is possible by use of centering devices.[11] If the lesion is relatively concentric in relation to the vessel wall, lumen centering is more likely to approximate vessel centering (Figure 5, *A*).

The catheter eccentricity, that is the distance from the intravascular ultrasound (IVUS) probe to the lumen center, provides insight into how much manipulation would be required to center the catheter in the lumen. In another study from our laboratory, after an analysis of 555 IVUS probe positions during 27 interventional procedures, we found an average distance of 0.67 mm from probe to the lumen center (Arbab-Zadeh A, unpublished data, 1996). Considering the average lumen radius of 1.71 mm and probe size of 1 to 1.2 mm, the catheter was, on average, more than 50% maximum eccentric. Thus lumen centering of the catheter leads to a significant increase in minimum target distance as shown in our study.

Interestingly, in a very eccentric lesion the lumen center may be substantially distant from the vessel center. In this situation an eccentric source position in relation to the lumen center may actually be more concentric with respect to the vessel center (Figure 5, *B*). In this case, centering the radiation source within the lumen leads to an undesirable greater dose heterogeneity. Indeed, in 5 of our patients using a gamma source and in 6 patients assuming a beta source, we observed an increase in the calculated radiation dose heterogeneity with the lumen-centered system compared with a noncentered position. Therefore relative lesion concentricity may be an important requirement if dosimetry is to benefit from lumen centering. This hypothesis is supported by our finding of a significant inverse relationship between lesion eccentricity and the calculated reduction in ICRT dose heterogeneity when a lumen-centered radiation source is used (Figure 3). The lesion eccentricity observed in this study was mild, perhaps as a result of the compression and stretching effects of stenting. Hence, the calculated benefit of radiation source centering in our study may be due in part to the relatively mild lesion eccentricity found in our specific study group.

The absolute vessel size may be another important factor when considering the use of lumen-centering devices. When a small vessel (Figure 6, *A*) is compared with a large vessel (Figure 6, *B*) with the source positioned at the same minimum distance from the target, the large vessel yields greater dose heterogeneity as a result of a relatively larger maximum distance to the target. Therefore lumen centering of a radiation source in a large vessel is more beneficial than in a small vessel. This hypothesis is supported by a direct relationship between vessel size and dose heterogeneity observed in our study for beta radiation (Figure 4).

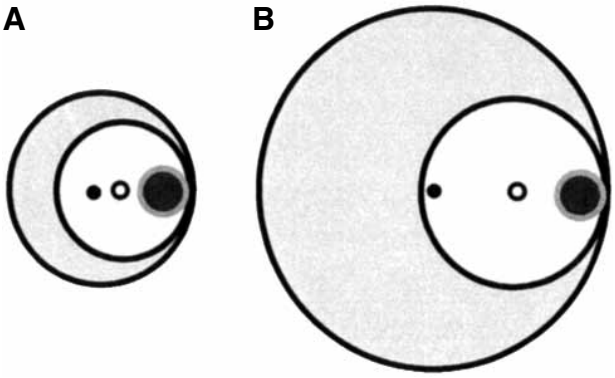
The results of this study suggest that centering of the ICRT source in the vessel lumen results in a reduction of dose heterogeneity for both a gamma and a beta source. However, the reduction was substantially greater for beta irradiation. Because the radioactive decay over distance for a beta source is by multiple factors greater compared with a gamma source, dose heterogeneity is a more crucial issue for beta emitters. Amols et al[10] modeled the dose heterogeneity for ^{192}Ir

and two beta emitters in a 5-mm diameter vessel. They determined that a deviation off center by only 1 mm resulted in an increase of dose heterogeneity from 1 to approximately 3.8 for ^{192}Ir but to more than 7 for phosphorus 32, a beta emitter. Consequently, to achieve a sufficient radiation dose exposure to the far field from an eccentric beta source, one has to administer high doses to the near field. This disadvantage becomes even more apparent if the vessel is larger than 5 mm in diameter. Our study confirmed these results by the large-dose heterogeneity detected for a beta emitter by use of a noncentered source. However, our study also revealed that ICRT, even with a perfectly lumen-centered beta source, resulted in substantial dose heterogeneity. This finding may have important clinical implications. Whereas for gamma ICRT all 28 patients in our study received the minimum prescribed dose of 800 cGy to the target with a centered source, none of 28 patients would have received this dose to the far field target if a beta source (at the modeled dose prescription) had been used. Consequently, much higher doses of beta radiation would be needed to fulfill the present prescription criteria. In view of the short penetration of beta emitters, it is not if a higher radiation dose would have any clinically untoward effects.

Study limitations

There are several limitations to this mathematical model. First, our methods assumed that the 3.2F IVUS catheter had the same dimensions as the delivery catheter and followed the same position within the vessel. The actual radiation delivery catheter used was 4.7F and thus was slightly more lumen centered than the IVUS catheter. The position of the IVUS catheter within the vessel could not be controlled and therefore is an insurmountable limitation of this study. Second, it should be noted that these calculations apply only to stented vessels, which have been optimally dilated before radiation. This results in a relatively large lumen diameter compared with the diameter of the radiation delivery catheter. Our findings therefore are not applicable to radiation delivered after balloon angioplasty either alone or before stent placement. Third, most patients studied had in-stent restenosis, so our conclusions should be limited only to this subgroup of patients. Fourth, it should be pointed out that the advantage of lumen centering may be less important if the acceptable limit of near-field radiation exposure is increased to >3000 cGy. Finally, one important question remaining is whether the demonstrated mathematically modeled advantage of lumen centering can be achieved with currently available lumen centering devices; that is, will these devices actually position the radiation source in the same location as the lumen center. The available centering systems are based on inflation of specially designed positioning balloons within the artery. Irregular and noncircular lumen borders may lead to positioning of the radiation source deviant from the geometrical center, which we used for our analysis. However, because all vessels included in this study underwent balloon angioplasty and stenting, lumen borders were observed to be rather symmetrical. Thus this effect may be negligible in our study. Furthermore, cardiac motion might influence the dose variation throughout the cardiac cycle, particularly when a noncentered radiation source is used. Current centering devices, however, use a balloon that would likely hold the ICRT catheter in position throughout the cardiac cycle.

Figure 6



Schematic display of effect of vessel size on radiation heterogeneity. Shown are two vessel cross-sections, each containing eccentric but circular lesion, and radiation source *(gray closed circle)*. Outer border represents vessel border, and inner border represents lumen border. Similar to Figure 5, *shaded area* between two borders represents plaque area. **A** and **B**, Small and large vessels, respectively. Each contains eccentric lesion with radiation source placed eccentrically in lumen. Note that source in both **A** and **B** has same minimum distance to target, but in larger vessel, maximum distance to target is much greater, resulting in more dose heterogeneity. Although source and lesion are very eccentric, source in **A** is closer to vessel center. Lumen centering in larger vessel **(B)** would result in greater reduction in heterogeneity than in smaller vessel **(A)**.

Conclusions

In this study we have documented that a radiation source centered in the vessel lumen compared with a noncentered position results in reduced radiation dose heterogeneity for both gamma and beta emitters. The amount and decrease in dose heterogeneity was substantially greater for the beta compared with the gamma source. Assuming a minimum effective dose of 800 cGy, gamma but not beta irradiation ensured adequate dose delivery to the entire target when current clinically used dosimetries are used. The degree of

lesion eccentricity and target vessel diameter influenced dose heterogeneity for both emitters. On the basis of these results, we encourage radiation source centering to reduce dose heterogeneity, particularly when a beta radiation source is used.

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