Dosimetric Measurements in Isolated Human Coronary Arteries

Comparison of Commercially Available Iridium$^{192}$ With Strontium/Yttrium$^{90}$ Emitters

Christoph Hanefeld, MD; Schgofa Amirie, MS; Dieter Borchardt, BSc; Peter Grewe, MD; K.-M. Müller, MD; Maria Kissler, MD; Andreas Mügge, MD

Background—Intravascular brachytherapy is being applied more and more in patients with coronary artery disease for the prevention of restenosis subsequent to balloon angioplasty, in particular after stent implantation. Several radiation sources (β- and γ-emitters) are available in clinical routine. It was the purpose of this study to compare the radiation doses at the level of the adventitia in diseased and stented human coronary arteries for $^{192}$Ir and $^{90}$Sr/Y emitters in routine use. In contrast to previously published work, we performed dosimetry instead of calculating depth-dose distribution by use of the Monte Carlo system.

Methods and Results—Postmortem calcified human coronary artery segments were stented and placed in an organ bath. Commercially available γ-emitters ($^{192}$Ir; Cordis Checkmate) and β-emitters ($^{89}$Sr/Y; Novoste Beta-Cath) were used. Relative dose distributions along the adventitia were measured by a specially designed scintillation detector system. Whereas dose perturbations caused by stents and calcified plaque were negligible for the $^{192}$Ir source, radiation from the beta source was significantly impaired (as much as 40%) at the level of the adventitia (3.0-mm vessel diameter). Dose perturbation was clearly dependent on the extent and severity of calcification, less affected by stent material.

Conclusions—Dose perturbation caused by calcified plaque and metallic stents is significant for β-sources. This dosimetric difference between β- and γ-emitters in diseased coronary arteries should be considered when calculating doses in intravascular brachytherapy. (Circulation. 2002;105:2493-2496.)

Key Words: angioplasty ■ restenosis ■ stenosis ■ stents ■ coronary disease

The mechanisms of restenosis after coronary angioplasty can be divided into two components: (1) a mechanical component as the result of elastic recoil, shrinking, and remodeling, and (2) neointima formation caused by proliferative response to injury.¹ Intracoronary stent placement reduced the problem of restenosis by virtually eliminating recoil and remodeling. However, stents do not decrease; in fact, they increase the proliferative component of restenosis.²,³ During the past decade, intracoronary ionizing radiation after interventions has been successfully used to reduce this proliferative process in de novo lesions and, in particular, in stented lesions.⁴⁻⁹

Various photon- or electron-emitting radioactive isotopes have been used or suggested for use in brachytherapy. The most frequently used γ-emitters are iridium$^{192}$ isotopes ($^{192}$Ir) and the most frequently used β-emitters are strontium/ yttrium$^{90}$ sources ($^{89}$Sr/Y). Many theoretical questions have been raised regarding the effectiveness of both types of emitters in delivering the required dose of 14 to 20 Gy along the vessel wall (in particular the adventitia), such as the importance of accurate source centering¹⁰ and the dose perturbation caused by calcified plaque and/or metallic stents.¹¹ In animal studies, 14 Gy radiation from a noncentred $^{89}$Sr/Y source was successful in preventing neointima formation only when radiation was performed before rather than after stenting. The authors strongly suggest that this effect is related to perturbation of the dose field by the metallic stent.¹² Despite such theoretical considerations, the clinical studies suggest that both types, γ-emitters as well as β-emitters, are effective in reducing restenosis. However, these studies have not directly compared the efficiency of γ- and β-emitters. Thus, the question remains open whether one emitter offers more advantages than the other under specific clinical conditions, such as the presence of stent and/or calcification,¹³ long and complex lesions, or large vessel size. Accordingly, recent studies for β-emitters point out that only a dose of at least 18 Gy (tissue depth 1 mm) appears to be effective for reducing restenosis in nonstented arteries and that the presence of stents may inhibit this beneficial effect.¹⁴

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From the Cardiology Clinic (C.H., S.A., A.M.) and Radiation Oncology (D.B., M.K.) at St Josef Hospital, Ruhr University, Bochum, Germany, and the Department of Pathology (P.G., K.M.M.) at Bergmannsheil-Kliniken, Ruhr-University, Bochum, Germany.

Correspondence to Dr Andreas Mügge, Cardiology Clinic, St Josef Hospital, Ruhr University, Gudrunstrasse 56, 44791 Bochum, Germany. E-mail andreas.muegge@ruhr-uni-bochum.de

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2493
This study is intended to compare dose homogeneity between routinely used $^{192}$Ir and $^{90}$Sr/Y emitters in isolated human coronary arteries in the presence of calcified plaques and metallic stents. Since it is well accepted from previous work that metallic stents do perturb the dose of $\beta$-emitters and low-energy photon emitters,15,16 we focus on the relative dose distribution along the adventitial surface under conditions similar to clinical circumstances. In contrast to previous work on a similar topic,11 direct measurements were performed instead of using a calculated Monte Carlo system.

**Methods**

Segments (2 to 3 cm long) of the mid part of the right coronary artery were obtained during autopsy. Arteries free of adjacent fat and tissue were carefully removed. Segments were placed in ice-cold saline for transportation. The coronary segments were taken from 6 patients (mean age, 64.3±8.3 years; 6 men) who died as the result of neoplasm (n=4), congestive heart failure (n=1), or stroke (n=1). At autopsy, all patients had coronary artery disease. The artery segments were stented with different types of premounted stents (in 10 of 18 arterial segments Palmaz Schatz stainless steel stents with a wire thickness of 0.064 mm, in 5 segments a Cross-Flex steel stent with 0.12-mm strut thickness, and in 3 segments a Mini Crown steel stent with 0.064-mm strut thickness, all stents from Cordis Co) having a diameter of 3.0 mm. Since we did not notice a significant difference in dose perturbation between the different stents (<5% variation in the relative dose perturbation at the level of the adventitia; data not shown), we combined the data and did not further differentiate between the various stent types used. Stent placement was done under identical conditions with noncompliant balloons (3.0 mm) at an inflation pressure of 8 to 10 bar (inflation time, 1 minute). Stented segments were mounted in a special organ bath filled with 0.9% saline solution. The organ bath was made from plastic and was completely metal-free to minimize Bremsstrahlung secondary to the metallic stents. Segments were mounted in a special organ bath filled with 0.9% saline solution. The organ bath was surrounded by a 5 cm lead shielding. In some segments, the diameter of the stented artery was quantified by intravascular ultrasound (30-MHz transducer, IVUS, Boston Scientific), confirming the luminal diameter of 3.0±0.1 mm (n=5).

For dosimetry, an Optidos scintillation system was used (PTW). The scintillator tip (1.0×1.0 mm) was placed directly on the surface (adventitia) of the vessel wall so that it could be moved stepwise (1.0-mm steps) along the entire longitudinal axis of the coronary segment by an automated micrometer device. In a typical experiment, the scintillator tip was located 1.2 to 1.6 mm above the 5F and 3.7F delivery catheters, respectively; once a distance was chosen, this distance was kept constant during a set of experiments (dosimetry for the $\gamma$- and $\beta$-sources). The Optidos System is designed for quality assurance measurements in vascular brachytherapy and fulfills the requirements recommended in the report of the American Association of Physicists in Medicine (AAPM) Task Group No. 60. This system determines, in catheter systems, the source strength in terms of absorbed dose rate to water at a distance of 2 mm from the catheter axis, as per AAPM report, or at different distances, as per supplier’s instructions. In addition, dose distribution, depth-dose curve, and the longitudinal and rotational homogeneity of line sources can be assessed. During radiation, the scintillation light is guided by fiberoptic cable and converted into current by a microphotomultiplier. The dosimeter signal, being directly proportional to the absorbed dose, is integrated by the Optidos system for variable time intervals. Sensitivity is as low as 400 $\mu$Gy/s, with <1% deviation. Usually, the time of radiation exposure was adjusted to 30 seconds at each point of measurement.

The US national standard laboratory NIST has calibrated the Optidos system for sources that emit electrons. The process of calibrating the detector for $\gamma$-emitters is ongoing, and calibration factors are not available yet. Thus, an absolute dose rate was only calculated for the $\beta$-source but not for the $\gamma$-source. At the level of the adventitia in noncalcified segments, an absolute dose rate of on average 782±96 mGy/30 s was measured for the Novoste Beta Cath System, corresponding to a dose rate of 0.095 Gy/s at a depth of 2 mm from the center of the source train.

The ionizing radiation delivering systems used were the Novoste Beta-Cath System (40-mm length) and the Cordis Checkmate System (39-mm length). Source activities were 9.62 to 11.87 GBq and 1.92 GBq for the $^{192}$Ir and $^{90}$Sr/Y sources, respectively. The delivery catheters for Beta-Cath and Checkmate systems had an outer diameter of 5F and 3.7F, respectively.

After completing measurement, a small needle was used to pinpoint the beginning and end of the evaluated area along the vessel wall. The arterial segments were placed in 5% formalin. Radiography (with a Faxitron 8050 table-model x-ray unit from Rode & Schwarz) of the segments documented stent expansion and localized calcified plaque/deposits, in particular those related to the area analyzed for radiation perturbation. After radiography, each segment was dehydrated (ethanol was increased from 50% to 96% vol/vol), defatted, and embedded in methacrylate plastic (Technovit 9100 from Hereus Kulzer GmbH). Cross-sections (1 mm) of the stented coronary artery segments were cut with a rotary cutter microtome (Accutom-5 from Struers). Cross sections were ground and polished (Phoenix 4000 from Jeant Wirtz) to a thickness <8 $\mu$m and stained with a modified Elastic-an van Gieson for light microscopic analysis, which provides clear delineation of calcified plaque. Artery segments were divided into three parts (≈5 to 6 mm length each), and the extent of calcification was graded semiquantitatively into three classes: no calcification, minor calcification (thickness ≤0.4 mm), and moderate/severe calcification (thickness >0.4 mm).

Care was taken to consider only such calcifications as were located between the scintillation detector and the radiation source. Morphometry revealed the following diameters: lumen, 3.1±0.1 mm; intima, 0.45±0.29 mm; and media, 0.13±0.07 mm. The thickness of calcified plaques/deposits was in the range 0.14 to 1.02 mm (median, 0.41 mm).

**Statistics**

Individual data from representative experiments are the mean of three individual measurements; otherwise, data are given as mean±SD. (Absolute dose rate is given in mGy/30 s.) If indicated,
The adventitia from the stents and calcifications irrespective of the thickness of the 18 mm length) nor calcified deposits significantly perturbed (Figure 2, A and B). Neither stent material (Palmaz-Schatz, calcifications were documented by radiography and histology severely calcified and stented coronary artery segment. Calcitative surface (Figure 2C). By contrast, absence and presence of the artery segment along the adventitial surface (1 mm stepwise). Radiation dose was measured for 30 seconds at each point. Maximal radiation dose in the absence of the stented vessel was normalized to 100%; percent changes in radiation dose are given.

Results
Delivery catheters for the radioactive sources were mounted first in the organ bath in the absence of coronary artery segments. The tip of the scintillation system was moved from 1.0 mm toward 2.0 mm above the delivery catheter. Increasing the radial distance by 1.0 mm reduced the relative dose on average by 74.5±28.0% (n = 4) and 29.4±2.9% (n = 4) for the β- and γ-source, respectively. As shown previously, the decrease of radial dose is high for β-sources and lower for γ-sources.

Figure 2 shows a representative set of measurements in a severely calcified and stented human coronary artery segment. Calcifications were documented by radiography and histology (Figure 2, A and B). Neither stent material (Palmaz-Schatz, 18 mm length) nor calcified deposits significantly perturbed the γ-radiation; almost identical doses were measured in the absence and presence of the artery segment along the adventitial surface (Figure 2C). By contrast, β-radiation showed significant dose inhomogeneity along the adventitial surface; dose perturbation up to 40±4% (n = 3 measurements; as compared with the condition in the absence of the vessel) was noted in this particular coronary segment (Figure 2D).

The Table summarizes the measurements for all vessels. As expected, the γ-radiation was not significantly affected by stents and calcifications irrespective of the thickness of calcified plaque/deposits. The radiation dose at the level of the adventitia from the β-emitter was reduced by between 11±8% (no calcification, only stented vessel wall) and 32±18% (stent with moderate/severe calcification).

Discussion
At present, intracoronary brachytherapy appears to be the only commercially available effective technique for preventing in-stent restenosis in patients after balloon angioplasty. However, many problems remain unresolved, including the precise target of radiation (adventitia) and the optimal dose (10 to 18 Gy) required to sufficiently suppress proliferative processes without inducing cell death within the entire vessel wall. Currently, several types of emitters and radiation sources are on the market or under clinical investigation. The most widely used emitters are 192Ir for γ-radiation and 90Sr/Y for β-radiation.

On the basis of physical principles and theoretical calculation models (eg, the EGS4 Monte Carlo system), γ-emitters may combine some advantages, in particular better penetration and no need for source centering in coronary arteries. In contrast, β-sources offer advantages in terms of radiation protection and dose rate (which determines time of radiation exposure). Since most patients treated with brachytherapy have been stented in severely diseased coronary arteries, we were interested in finding out how stents, in combination with various degrees of calcified plaque, affect dosimetry at the level of the adventitia, that is, the most likely target of brachytherapy, for commercially available γ- and β-sources. This topic has been previously addressed by several investigators; however, most of them used Monte Carlo simulation techniques or measured the effect of metallic stents only.
Our main findings are (1) dose perturbations caused by stent and calcified plaque were negligible for the 192Ir source; (2) stent material in combination with calcifications significantly impaired radial dose distribution for the 90Sr/Y source. This dose reduction was on average 11% in noncalcified stented vessels and mounted up to 40% in severely calcified, stented arteries. It appears that the degree of calcification has a greater impact on radial dose distribution for β-particles than metallic stents themselves. Calculated (stenotic) plaques could influence dose homogeneity at the level of the adventitia, mainly by two mechanisms: First, by shielding effects of the plaque itself; and second, de-centering of the delivery catheter within the vessel lumen. Both systems used in the present study were not centered. Our experimental setup plus other limitations of the measurements (limited control of distance between radiation source and vessel surface/tip of the scintillation system, limited precision of the dosimetry) do not allow us to differentiate between the two causes of dose homogeneity, shielding, and de-centering effects.

Our measurements are in accordance with previous calculated results, that is, that dose perturbations caused by the presence of metallic stents were found to be far more significant for the 90Sr/Y source than those for the 192Ir source.11 Amols and coworkers reported an average dose reduction of β-emitters between 4% and 14% in the presence of various stents, for example, ≈11% at 0.125 mm radial distance from steel stents. This range of dose reduction is comparable to that observed in the present study in stented but noncalcified human artery segments. More importantly, we observed a major dose perturbation for β-particles in severely calcified human arteries (dose reduction on average, 31.8%). Thus, we believe that the dosimetric differences between β- and γ-sources in diseased human coronary arteries should be considered for dose prescription in intravascular brachytherapy, for example, by increasing the dose for β-sources in calcified stented arteries. Whether the considerations are clinically important is, however, still questionable. In at least one pilot study at a 6-month follow-up after β-radiation therapy,20 delivered dose as well as tissue composition have been shown to fundamentally influence volumetric outcome. Furthermore, it has been observed in a recent dose-finding study that β-radiation therapy prevents restenosis in a dose-dependent manner and that only a dose as high as 18 Gy both reduced restenosis and induced luminal enlargement.14 These observations underline the importance of precise dose prescription.

In controlled and open clinical studies, both β- and γ-emitters were effective to prevent restenosis in patients with in-stent stenosis.21 It is interesting to note that the dose prescribed in these studies that used β-emitters was up to 30% to 40% higher (≈18 to 24 Gy at a depth of 2 mm) as compared with those that used γ-emitters (≈14 to 15 Gy).21 It is speculated that this difference in dose prescription between β- and γ-sources may account for the similarity in the clinical outcome to prevent or treat in-stent restenosis.

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References

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