Liquid-Filled Balloon Brachytherapy Using $^{68}$Ga Is Effective and Safe Because of the Short 68-Minute Half-Life

Results of a Feasibility Study in the Porcine Coronary Overstretch Model

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Background—Liquid-filled balloons for coronary brachytherapy provide significant advantages over solid sources in dose homogeneity but carry the risk of life-threatening radiointoxication after balloon rupture and laboratory contamination in case of a spill. We hypothesized that the positron emitter $^{68}$Ga, with a half-life of only 68 minutes, was well suited to overcome these safety obstacles while providing full therapeutic efficacy.

Methods and Results—The feasibility, efficacy, and safety of $^{68}$Ga liquid-filled balloon brachytherapy were investigated in the porcine coronary overstretch model. Four groups of 5 balloon-induced coronary lesions were irradiated with 8, 12, 16, and 24 Gy targeted to the adventitia. Ten unirradiated lesions served as controls. Segments treated with 16 or 24 Gy exhibited marked suppression of neointimal proliferation at 28-day follow-up, with quantitative parameters of intraluminal proliferation reduced to less than 20%. This beneficial effect was not compromised by untoward edge effects. Uninjured but irradiated vessels did not show histological signs of radiation damage. The $^{68}$Ga whole-body dose due to balloon rupture was estimated to be 5 rem/50 mCi treatment activity and compared favorably with that of $^{188}$Re (78 rem/50 mCi).

Conclusions—$^{68}$Ga positron radiation suppresses neointimal proliferation at doses of 16 and 24 Gy. This biological efficacy, coupled with the attractive safety profile, suggests the selection of $^{68}$Ga as an attractive isotope for liquid-filled balloon brachytherapy. (Circulation. 2001;103:1793-1798.)

Key Words: angioplasty • restenosis • radioisotopes

Coronary brachytherapy is currently seeking to establish its role as the first clinically applicable treatment to effectively overcome restenosis. After a first period of exclusive use of solid radiation sources, balloon catheters filled with liquid radioactivity were proposed as an attractive alternative and in a recent investigation demonstrated clinical efficacy. Liquid-filled balloons carry the advantage that the self-centering balloon geometry results in a precisely defined radiation dose field that improves on the lack of dose control inherent to uncentered source-wire systems. This advantage is associated with 2 significant risks: intravascular balloon rupture and spill of a radioactive fluid in the laboratory. Both risks are primarily due to the long physical half-life of the previously proposed radioisotopes, including $^{188}$Re (3.7 days) and $^{186}$Re (17 hours).

We hypothesized that the use of positron emitters with half-lives <2 hours might overcome the safety problems and performed initial phantom experiments and cell-culture studies (H.-P.S., unpublished data, 1998) to investigate the tissue penetration and antiproliferative efficacy of positron radiation emitted by $^{18}$F, $^{11}$C, $^{13}$N, $^{15}$O, and $^{68}$Ga. Generator-available $^{68}$Ga, with a half-life of only 68 minutes, appeared to be the most attractive candidate among these isotopes. Consequently, the goal of this study was to assess the antirestenotic efficacy of $^{68}$Ga in a porcine coronary model and to compare the remaining risk of this approach with that of previously suggested rhenium isotopes.

Methods

Preparation of Liquid Radioactivity

$[^{68}\text{Ga}]{\text{GaCl}}_{3}$ was “milked” from a $^{68}$Ge/$^{68}$Ga radioisotope generator (DuPont Pharma), giving a total yield of 50 mCi $^{68}$Ga in a volume of 5 mL. The activity concentration of the eluate was increased to 20 to 100 mCi/mL (target volume 0.5 to 0.8 mL) through rotary evaporation. The concentrated solution was drawn into a 2.0-mL plastic syringe and placed in a lead-shielded container for transport to the animal laboratory. The entire preparation took ~15 minutes and was...
performed by a technician of the cyclotron laboratory serving the clinical PET facility.

The concentrated generator eluate was filled into balloon catheters (ACS Lifestream RX 2.5/30 mm or RX 3.0/30 mm, Guidant Corp) that were used as intracoronary radiation sources providing a 30-mm-long dose field. The useful in-balloon volume was 0.15 to 0.22 mL, and the total filling volume, including dead space, was 0.35 to 0.44 mL. The Lifestream perfusion balloons were selected because their design allows maintenance of antegrade blood flow during radiation delivery. The balloon length of 30 mm was chosen to ensure that the treatment balloons exceeded the length of the injury (created with 20-mm-long balloons) on both sides by 5 mm.

Dosimetry

$^{68}$Ga (half-life 68 minutes) deploys a therapeutic tissue dose through positrons of a maximum energy of 2.9 MeV. Accurate dosage requires knowledge of the dose deployed per disintegration of the isotope for a given balloon geometry and a given distance from the balloon surface. These constants were determined in a preceding series of phantom measurements using radiosensitive film. On the basis of these values, a computer program was written to facilitate intraprocedural dosimetry and to free the operator’s attention for medical aspects. Once the initial in-balloon activity was entered, this program continuously calculated the remaining in-balloon activity. Before irradiation, the software informed the operator about the expected dwell time. During irradiation, the accumulated dose and remaining dwell time were displayed, and most importantly, the program called for source removal once the prescribed dose was reached.

Animal Experiments in the Porcine Model

Anesthesia

All experiments were conducted in accordance with the guidelines for animal experiments set forth by Indiana University. Seventeen juvenile farm pigs weighing 23 to 25 kg were premedicated with intramuscular atropine (0.5 mg), acepromazine (0.25 mg/kg), and ketamine (33 mg/kg), and animals were intubated and mechanically ventilated with 20% to 30% isoflurane and 40 vol% oxygen. Animals were kept in a metabolic cage equipped with a video camera and an image digitizer. Luminal circumference, luminal area, media fracture length, external elastic lamina (IEL) circumference, IEL area, adventitial circumference, and adventitial area were measured with the NIH image program. Neointimal area (IA), IA/fracture length ratio (IA/FL), and maximal intimal thickness (MIT) were used to characterize the restenotic response. The parameters characterizing each analyzed artery were calculated by averaging the data from all segmental cross sections exhibiting an intimal lesion with disruption of the internal elastic lamina (IEL).

Operator Doses

Operator dose increments due to $^{68}$Ga positron annihilation radiation were modeled assuming simplified radiation geometry. Radiation was taken to originate from a point source 5 cm deep inside the chest; complete positron absorption within the patient’s body was assumed. Similar calculations were performed for $^{188}$Re. X-ray–induced neck-collars doses reported for cardiologists performing a typical diagnostic and interventional procedures were used for comparison.

Statistics

Continuous parameters in Tables 1 and 2 are given as mean±SEM. Histomorphometric parameters for individual arteries were calculated by averaging values from all cross sections of this artery that showed signs of injury. Parameters given in Table 2 were finally calculated for each individual dose group by averaging results from individual arteries. Differences between the dose groups were analyzed by 1-way ANOVA. Differences between the histomorphometric measures were assessed by comparison of each dose group versus control by t test analysis. In case of failure of the data to meet t test premise criteria, data were compared by the Mann-Whitney
TABLE 1. Porcine Coronary Overstretch Model: Lesion Characteristics, In-Balloon Activity, and Dwell Time

<table>
<thead>
<tr>
<th>Group (Dose, Gy)</th>
<th>I (0)</th>
<th>II (8)</th>
<th>III (12)</th>
<th>IV (16)</th>
<th>V (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of arteries</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>No. of segments</td>
<td>63</td>
<td>16</td>
<td>14</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Segments/artery</td>
<td>7.0±0.15</td>
<td>3.2±0.33</td>
<td>4.7±0.41</td>
<td>5.0±0.38</td>
<td>5.4±0.42</td>
</tr>
<tr>
<td>Vessel diameter, mm*</td>
<td>2.65±0.01</td>
<td>2.75±0.13</td>
<td>2.78±0.20</td>
<td>2.53±0.31</td>
<td>2.98±0.08</td>
</tr>
<tr>
<td>Balloon/artery ratio</td>
<td>1.28±0.04</td>
<td>1.27±0.06</td>
<td>1.26±0.05</td>
<td>1.35±0.12</td>
<td>1.21±0.04</td>
</tr>
<tr>
<td>Fracture length, mm</td>
<td>1.14±0.10</td>
<td>1.09±0.11</td>
<td>1.36±0.19</td>
<td>1.29±0.13</td>
<td>1.58±0.31</td>
</tr>
<tr>
<td>Fracture length/luminal circumference‡</td>
<td>0.20±0.02</td>
<td>0.26±0.05</td>
<td>0.24±0.03</td>
<td>0.23±0.02</td>
<td>0.28±0.04</td>
</tr>
<tr>
<td>In-balloon activity, mCi</td>
<td>...</td>
<td>6.4±1.4</td>
<td>5.9±1.4</td>
<td>12.1±2.0</td>
<td>9.8±0.8</td>
</tr>
<tr>
<td>Dwell time, min</td>
<td>...</td>
<td>13.3±2.2</td>
<td>17.3±3.6</td>
<td>10.3±1.9</td>
<td>19.0±1.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Parameters of groups I to V not significantly different by 1-way ANOVA.

*Measurements taken from preoverstretch spot films.
†Balloon diameter taken from manufacturer specifications.
‡Luminal circumference=length of IEL+fracture length.

Results

Animal Groups and Baseline Vessel Parameters

Seventeen swine underwent the coronary overstretch procedure. There were 2 intra procedural deaths due to intimal dissections with complete vessel occlusion. Coronary artery irradiation was generally well tolerated. Three animals with LAD irradiation developed moderate ST-segment changes during dwell time, which were interpreted as ischemia due to diagonal branch occlusion. None of the animals died during the 28-day follow-up period. Twenty-eight coronary vessels were evaluated histologically. Of these 28 vessels, 25 exhibited coronary lesions characterized by IEL disruption, and 3 overstretched segments did not exhibit a lesion and were used to study the impact of positron radiation (8 Gy and 2×16 Gy) on native undamaged coronary arteries.

Table 1 shows radiologically measured preoverstretch vessel diameters and the selected balloon/artery ratios together with the obtained fracture lengths to characterize the created lesions. None of the input parameters exhibited a statistically significant difference between the 5 groups.

Histological Results

Representative photomicrographs characterizing the vessel segments treated with each of the different doses are given in Figure 1. Unirradiated control segments (A) were characterized by transmedial tears filled out by cellular tissue encroaching on the lumen. The EEL region surrounding the tear site occupied an expanded area and contained an increased amount of collagen, fragmented elastic fibers, and fibroblast-like cells. Segments irradiated with 8 Gy (B) exhibited additional enlargement of intraluminal proliferative tissue for any particular tear length. A significant perivascular fibrosis was expressed over the lesion site, including vasa vasorum and cardiac nerves (indicated by an arrow). Segments irradiated with 12 Gy exhibited less neointimal tissue bulk than seen in the 8-Gy group and a trend to less than in the control group. Perivascular fibrosis was similar to that found in the 8-Gy group. Segments irradiated with 16 and 24 Gy were markedly different, characterized by a nearly complete absence of intraluminal proliferation. There was neither a clear repair of transmural tears nor luminal narrowing. The perivascular fibrosis remained similar to that seen at lower doses, with similar amounts of collagen and elastic fibers (D and E). Uninjured segments (F) treated with doses of 8 and 16 Gy did

TABLE 2. Histomorphometric Results Characterizing Treated Coronary Segments

<table>
<thead>
<tr>
<th>Group (Dose, Gy)</th>
<th>No. of Arteries</th>
<th>IA, mm²</th>
<th>IA/FL, mm</th>
<th>MIT, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (0)</td>
<td>9</td>
<td>0.50±0.05</td>
<td>0.49±0.06</td>
<td>0.40±0.05</td>
</tr>
<tr>
<td>II (8)</td>
<td>5</td>
<td>0.75±0.15</td>
<td>0.68±0.10</td>
<td>0.62±0.08</td>
</tr>
<tr>
<td>III (12)</td>
<td>3</td>
<td>0.46±0.16</td>
<td>0.34±0.12</td>
<td>0.32±0.11</td>
</tr>
<tr>
<td>IV (16)</td>
<td>3</td>
<td>0.07±0.04</td>
<td>&lt;0.001*</td>
<td>0.05±0.03</td>
</tr>
<tr>
<td>V (24)</td>
<td>5</td>
<td>0.07±0.02</td>
<td>&lt;0.001*</td>
<td>0.05±0.02</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*Statistical comparison by t test vs 0-Gy control group.
†Statistical comparison by Mann-Whitney rank sum test vs 0-Gy control group.
not show any evidence of radiation damage. In particular, there was no focal necrosis, no inflammatory reaction, no augmented collagen deposition, and no increased density of elastic fibers, nor was a reduced cell count observed in the media. Taking those criteria together, the uninjured segments were morphologically equal to normal porcine coronary arteries.

One artery in the 24-Gy group showed a thin unresolved mural thrombus, and 1 artery in the 12-Gy group showed signs of an unresolved intramural hemorrhage. All irradiated segments were angiographically patent at 28 days.

**Histomorphometric Results**

Morphometric analysis of injured vessels revealed that the neointimal response was proportional to the degree of injury in the control, 8-Gy, and 12-Gy groups, as previously described. A marked and statistically significant suppression of all parameters of neointimal volume (IA, IA/FL, and MIT) down to 20% of control values was observed, however, in the 16- and 24-Gy groups (Table 2, Figure 2), such that no relationship to the degree of injury was detectable. Each vessel in these groups displayed multiple segments with complete suppression of measurable neointima formation, whereas other segments showed a small amount of neointimal tissue. No stimulated neointimal response or less effective neointima suppression on the edges of the lesions was observed in either high-dose group histologically or in the pre euthanasia angiograms. The group receiving 12 Gy showed a nonsignificant decrease in the neointimal parameters to ≈75% of control. The group receiving 8 Gy was

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**Figure 1.** Microphotographs showing typical cross sections through treated coronary artery segments. **A,** Control artery, overstretched but not irradiated (ends of IEL tear are indicated by arrows). **B,** Artery irradiated with 8 Gy showing stimulation of neointimal proliferation. **C,** Artery irradiated with 12 Gy and moderate neointima suppression. **D** and **E,** Arteries irradiated with 16 and 24 Gy, both exhibiting complete suppression of intraluminal proliferation. **F,** Irradiated native coronary artery not exhibiting any histological abnormality.

**Figure 2.** Changes in restenosis characterizing parameters IA, IA/FL, and MIT relative to control group. Control values were normalized to 1.0.
Accidental Systemic Loss of 50 mCi $^{68}$Ga

Accidental containment of the laboratory is another important concern raised against the liquid-filled balloon technique. Because of current radiation safety regulations, an area contaminated with $^{68}$Ga would need to be decontaminated, covered with plastic foil, shielded with Plexiglas, and posted as a “radiation area” once the dose rate at 30 cm distance exceeded 2 mR/h. Our estimates for a realistic spill of 5 mCi indicate that such shielding and posting needed to be maintained for only 3.5 hours to ensure that personnel would actively keep the maximal possible distance away from the spill zone. Accordingly, we consider the low patient doses after balloon rupture and the moderate radiation safety measures after a spill to be the most pronounced advantages that make $^{68}$Ga safer than any other liquid radioisotope previously proposed for brachytherapy.

Another concern has been that the 511-keV radiation associated with positron annihilation might lead to high operator exposure rates. Estimated dose values indicate, however, that fluoroscopy and cineangiography will in fact cause the vast majority of the operator radiation burden during any application of this approach.

On the basis of the enhanced safety profile of $^{68}$Ga, our study focused on ascertaining the antirestenosis efficacy of this isotope in the porcine model. Marked suppression of neointima formation at doses of 16 and 24 Gy is the major treatment effect of this approach. Thus, this study confirms that exposure of vascular tissue to positron radiation indeed yields the same favorable result already gained in earlier experimental studies with $\gamma$- and $\beta$-radiation.

The histological results seen with the 8-Gy dose highlight an important side effect of this (and other) brachytherapy approaches: the possibility of stimulation of intimal proliferations at low doses. We believe that (1) therapeutic exposures should provide $\geq 16$ Gy at 1-mm depth; (2) penetration of radiation into the depth of the adventitia may be important not only for targeting restenosis-triggering cell populations $^{3,4,6}$ but also for avoiding low doses in the immediate neighborhood of the vessel; and (3) the dose field should safely overlap both ends of the lesion in the longitudinal vessel axis to avoid the possibility that submaximal doses hit marginal portions of the lesion. On the basis of these considerations, we intentionally used irradiation balloons longer than the overstretch injury (30 versus 20 mm) and have not observed untoward edge effects. The rationale for this approach is based on another important observation of this study, which is that uninjured but irradiated vessels did not

### TABLE 3. Whole-Body Dose Estimates* to a Patient After Accidental Systemic Loss of 50 mCi $^{68}$Ga

<table>
<thead>
<tr>
<th>Organ</th>
<th>Absorbed Dose, rem/50 mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>2.6</td>
</tr>
<tr>
<td>Liver</td>
<td>5.0</td>
</tr>
<tr>
<td>Testes</td>
<td>2.4</td>
</tr>
<tr>
<td>Ovaries</td>
<td>2.8</td>
</tr>
<tr>
<td>Kidneys</td>
<td>4.8</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>8.5</td>
</tr>
<tr>
<td>Lungs</td>
<td>2.4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2.2</td>
</tr>
<tr>
<td>Uterus</td>
<td>2.8</td>
</tr>
<tr>
<td>Bladder</td>
<td>2.6</td>
</tr>
<tr>
<td>Effective whole-body dose equivalent</td>
<td>5.0</td>
</tr>
</tbody>
</table>

*Taken from ICRP publication No. 53. Data determined on the basis of organ and whole-body dose measurements performed with several gallium isotopes (including $^{68}$Ga) in humans.

associated with a trend toward increased neointimal formation.

Determination of arterial remodeling by analysis of EEL circumference at the injury sites did not reveal any significant differences between irradiated and nonirradiated arteries or between arteries that had received different radiation doses.

### Operator Exposure

Because of our model calculations, operator exposure rate increments due to brachytherapy were 0.6 mrem for $^{68}$Ga and 0.2 mrem for $^{188}$Re, assuming in-balloon activities of 50 mCi required to deploy a 24-Gy dose within 4 minutes. For comparison, doses accruing because of x-ray exposure were reported to be 5 to 16 mrem for a typical procedure, including diagnostic coronary angiography and single-vessel intervention. $^7$

The exposure rate for operator and personnel after a spill of $^{68}$Ga was estimated to be 3.0 mR · h$^{-1}$ · mCi$^{-1}$ at a distance of 30 cm from the radioactive spot once positron radiation was absorbed by appropriate shielding. Thus, an initial dose rate of 15 mR/h would result from a spill of 5 mCi. After 3.5 hours, the remaining dose rate would fall below the threshold of 2 mR/h because of the rapid isotope decay.

### Discussion

This study represents the first investigation to test the efficacy and safety of $^{68}$Ga-based brachytherapy and also to characterize the impact of positron radiation on neointimal proliferation in the porcine model. We wished to evaluate $^{68}$Ga because its half-life of only 68 minutes promised a significant risk reduction in comparison with previously proposed rhenium isotopes with half-lives of $\geq 17$ hours.

Accidental radiointoxication of the patient may occur because of a loss of liquid radioactivity into the circulation. The hazard of such an event is comparatively small with $^{68}$Ga, because resulting whole-body and organ doses are low. Table 3 specifies such doses calculated from tabulated doses per unit of activity estimated by the International Commission on Radiological Protection (ICRP, publication No. 53). These data are based on pharmacokinetic measurements in patients after systemic delivery of various gallium isotopes. $^6$ Remarkably, the effective $^{68}$Ga whole-body dose of 5.0 rem is $>15$ times lower than the life-threatening dose of 78 rem caused by a ruptured balloon loaded with the same $^{188}$Re or $^{192}$Ir activity. $^9$The low $^{68}$Ga doses also compare favorably with x-ray–induced patient doses accruing during an interventional procedure $^7$ and are far below the threshold of 50 rem, above which physiological changes due to acute radiation exposure have been described.

Accidental containment of the laboratory is another important concern raised against the liquid-filled balloon technique. Because of current radiation safety regulations, an area contaminated with $^{68}$Ga would need to be decontaminated, covered with plastic foil, shielded with Plexiglas, and posted as a “radiation area” once the dose rate at 30 cm distance exceeded 2 mR/h. Our estimates for a realistic spill of 5 mCi indicate that such shielding and posting needed to be maintained for only 3.5 hours to ensure that personnel would actively keep the maximal possible distance away from the spill zone. Accordingly, we consider the low patient doses after balloon rupture and the moderate radiation safety measures after a spill to be the most pronounced advantages that make $^{68}$Ga safer than any other liquid radioisotope previously proposed for brachytherapy.

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exhibit histological abnormalities or additional intraluminal proliferation at doses of 8 or 16 Gy after 28 days (Figure 1F).

Perivascular fibrosis is observed in irradiated vessels at 28 days (Figure 1), characterized by formation of collagen and elastic fibers. This fibrosis is consistently noted over the lesion site, and its presence would suggest a chronic constrictive effect. No such constriction was observed, however, either in these experiments or in a larger cohort of juvenile swine investigated and characterized in an earlier investigation.3

In conclusion, liquid ⁶⁸Ga contained within angioplasty balloons suppresses neointimal proliferation at doses of 16 and 24 Gy in the porcine model, and the severity of patient radiointoxication after potential intravascular balloon rupture is significantly reduced in comparison with earlier suggested β-emitters. Thus, we recommend ⁶⁸Ga as an isotope of attractive choice for further clinical investigation of liquid-filled balloon brachytherapy.

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