Biology Contribution

Dose-Escalation Study for Cardiac Radiosurgery in a Porcine Model

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Received Dec 5, 2013, and in revised form Feb 21, 2014. Accepted for publication Feb 24, 2014.

Summary

The authors performed a proof-of-principle cardiac radiosurgery dose-escalation study to mimic catheter ablation for atrial fibrillation noninvasively. Nine mini-pigs were treated with a single-fraction dose of 0 and 17.5-35 Gy. Transmural scarring of cardiac muscle tissue was noted with doses ≥32.5 Gy. The dose-response relationship was significant, with ED50 for intense fibrosis of 31.3 Gy. Short-term side effects were not noted. Long-term effects were not noted. Long-term effect

Purpose: To perform a proof-of-principle dose-escalation study to radiosurgically induce scarring in cardiac muscle tissue to block veno-atrial electrical connections at the pulmonary vein antrum, similar to catheter ablation.

Methods and Materials: Nine mini-pigs underwent pretreatment magnetic resonance imaging (MRI) evaluation of heart function and electrophysiology assessment by catheter measurements in the right superior pulmonary vein (RSPV). Immediately after examination, radiosurgery with randomized single-fraction doses of 0 and 17.5-35 Gy in 2.5-Gy steps were delivered to the RSPV antrum (target volume 5-8 cm³). MRI and electrophysiology were repeated 6 months after therapy, followed by histopathologic examination.

Results: Transmural scarring of cardiac muscle tissue was noted with doses ≥32.5 Gy. However, complete circumferential scarring of the RSPV was not achieved. Logistic regressions showed that extent and intensity of fibrosis significantly increased with dose. The 50% effective dose for intense fibrosis was 31.3 Gy (odds ratio 2.47/Gy, \( P < 0.01 \)). Heart function was not affected, as verified by MRI and electrocardiogram evaluation. Adjacent critical structures were not damaged, as verified by pathology, demonstrating the short-term safety of small-volume cardiac radiosurgery with doses up to 35 Gy.

Conclusions: Radiosurgery with doses >32.5 Gy in the healthy pig heart can induce circumscribed scars at the RSPV antrum noninvasively, mimicking the effect of catheter ablation. In our study we established a significant dose-response relationship for cardiac...
Introduction

Stereotactic radiosurgery (SRS) has found its way into routine practice for cancer treatment, but it is also used for noncancerous disease. A potentially new indication for SRS is the noninvasive treatment of cardiac arrhythmias (1), which has recently been under investigation in animals (2, 3) and in a single human patient (4). Atrial fibrillation (AF) is the most common arrhythmia (5); the source of AF often originates in the pulmonary veins (PVs) (6). For the treatment of AF, electrical PV isolation by catheter ablation has been established in clinical practice and may be considered as a first-line option for paroxysmal AF (5-7). However, catheter ablation is complex to perform; in addition, it is not always available and carries significant risks (eg, stroke), especially for older patients (8, 9). Such patients might benefit from noninvasive treatments, and radiosurgery may be an optional modality.

A shortcoming of previous investigations of cardiac SRS (CSRS) (2, 3) was the necessity of using gold markers (fiducials) for target tracking, which were sutured onto the heart via open surgery, but even minimally invasive fiducial implantation would invalidate the noninvasive treatment approach for AF. These studies also did not establish a meaningful dose-response relationship in the heart. We therefore investigated the effects of CSRS in the PV antrum in a dose-escalation study using a completely noninvasive treatment method without fiducials. The primary endpoint of this study was the induction of fibrotic lesions at the PV antrum, which might be able to subsequently block the veno-atrial electrical connections. We also investigated potential side effects in adjacent critical structures.

Methods and Materials

Ten female adult Göttingen mini-pigs (Ellegaard, Dalmose, Denmark) were intended for CSRS treatment according to German regulations for animal welfare, after approval of the responsible animal care committee. The animal model has similar heart dimensions, electrical conductivity, and cell arrangements as compared with humans (10), and results would be comparable to previous studies (2, 3). The anatomy of the mini-pig shows a small left atrium with a small left superior and 2 large inferior PVs with common ostia and a large right superior pulmonary vein (RSPV) (11). The RSPV was chosen for treatment in this study because of catheter accessibility.

One animal was destined for baseline evaluation without CSRS and 9 animals for treatment with single-fraction CSRS. Dose schedules were planned from 15 Gy to 35 Gy in 2.5-Gy steps for a balanced distribution around the previously estimated lowest effective dose of 25 Gy (2, 3). All animals were randomized to a sequence of prescribed doses to minimize the correlation of dose with animal age, weight, and follow-up time.

The animals were kept in 2 groups on a maintenance diet (Altromin Spezialfutter, Lage, Germany) to keep a constant weight before and after treatment. The study was independently monitored by a veterinarian for compliance with regulations. Pretreatment diagnostics and CSRS were performed on a single day. Follow-up was performed 6 months after treatment, on the basis of findings from previous studies (2, 3, 12, 13). All clinicians participating in the study were blinded as to dose schedules until the final evaluation, to obtain unbiased results.

Animal preparation

All animals underwent general anesthesia using a mixture of 10 mL ketamine (Ketavet; Pfizer, New York, NY) and 6 mL xylazine (Rompun; Bayer, Leverkusen, Germany), with continuous sedation throughout the procedure (6-8 hours) using 20 mL/h intravenous propofol (Disoprivan; Astra Zeneca, Wedel, Germany) injection. An endotracheal tube was inserted for normocapnic ventilation (Fabius; Draeger, Lübeck, Germany). For transport, diagnostics, and treatment, mobile respirators (Oxylog; Draeger, Lübeck, Germany) were used. Vital functions, electrocardiogram (ECG), and CO₂ were constantly monitored. A vacuum bag (BlueBag; Elekta, Stockholm, Sweden) was tightly formed around each animal to ensure stable positioning during transport and treatment.

Pretreatment imaging

For treatment planning, contrast-enhanced cardiac CT (Somatom DefinitionAS+ 64-Slice; Siemens Healthcare, Eschborn, Germany) at end-inspiration and endexpiration was obtained using chest electrodes for ECG gating. Before scanning, the vacuum bag was affixed to a stereotactic frame (BodyFix Localizer; Elekta) for reference during CSRS. Computed tomography reconstruction was performed with 1 mm slice thickness at end-systole and end-diastole during both inspiration and expiration. For pretreatment diagnostics we performed ECG-gated cardiac MRI (Achieva 1.5T; Philips, Amsterdam, The Netherlands) at end-expiration. Steady-state free precession cine MRI sequences were used to determine basic cardiac function, including left ventricular ejection fraction. T2-weighted sequences were included for structural analysis of atrial myocardium, and T1-weighted inversion-recovery radiosurgery. The long-term effects and toxicity of such high radiation doses need further investigation in the pursuit of cardiac radiosurgery for noninvasive treatment of atrial fibrillation. © 2014 Elsevier Inc.
delayed-enhancement studies after contrast injection (14) were performed to detect differences in myocardial scarring before and after treatment.

**Electrophysiological measurements**

For cardiac access the femoral vein was punctured using ultrasound guidance. A steerable sheath (St. Jude Medical, St. Paul, MN) was introduced by the Seldinger technique and advanced into the right atrium (RA). After transseptal puncture, an NIH catheter (Cordis, Bridgewater, NJ) was introduced into the RSPV. The vein anatomy was visualized by application of contrast media and documented during biplane fluoroscopy. A mapping catheter was inserted into the RSPV to measure electrical signals. Pacing with a stimulus of 5 V at 2 ms was performed with a conventional stimulator (UHS20; Biotronik, Berlin, Germany) at the distal, medial, and proximal aspects of the vein. A 6-lead surface ECG was continuously registered on electrophysiology recording systems (Cardiolab; GE Healthcare, Little Chalfont, UK) to evaluate veno-atrial conduction block.

**Cardiac stereotactic radiosurgery**

Treatment planning was performed with Eclipse software (Varian Medical Systems, Palo Alto, CA). The clinical target volume encompassed 8-10 mm muscle tissue along the RSPV, beginning at the antrum level and extending 3-5 mm into the veno-atrial wall. We included the blood pool in the vein, creating a disk-like target structure. An internal target volume was generated from the planning CTs at end-inspiration, end-expiration, end-systole, and end-diastole to account for untracked respiratory (10-15 mm) and cardiac (1-3 mm) motion during treatment. For the planning target volume (PTV), we extended the internal target volume by 5 mm to account for radiation delivery inaccuracies.

For CSRS, we generated a 3-dimensional conformal treatment plan with 7 static multileaf collimator fields. The dose was calculated using the analytical anisotropic algorithm with compensation for contrast enhancement. The designated dose covering at least 95% of the PTV was prescribed in a single fraction with maximum doses of 107% (< 0.2). This homogeneous dose distribution is characteristic for radiosurgery but ensured that maximum doses were < 2.5 Gy (dose-escalation step) above the prescription dose. Doses to critical structures were minimized without compromising PTV coverage or homogeneity (Table 1).

Cardiac SRS was delivered using a Clinac DHX linear accelerator (Varian Medical Systems), the stereotactic frame for general positioning, and cone beam CT for fine alignment using the RSPV as surrogate.

**Treatment evaluation**

Magnetic resonance imaging and electrophysiology measurements were repeated 6 months after treatment and compared with pretreatment findings. Histopathologic analysis was performed after euthanasia under general anesthesia. Autopsy was done on the same day to exclude autolytic artifacts. Thoracic organs (pleura, pericardium, esophagus, trachea, and lungs) were grossly evaluated for treatment-related side effects and concomitant diseases.

After formalin fixation the RSPV with adjacent structures was cross-cut in serial sections of 3 mm from the distal vein to the RA. Structures of interest, such as atria, pulmonary arteries, aortic and atroventricular valves, bronchus, trachea, and esophagus, were cut into segments by predefined schemes, color marked for further examination, and photographed for later correlation to pretreatment measurements. Additional biopsies were taken from all macroscopic lesions.

All sections were embedded in paraffin for microscopic evaluation. The slides were cut with a rotary microtome (Leica Biosystems, Wetzlar, Germany) with section thicknesses of 3 μm and stained with hematoxylin and eosin, Elastica-van-Giesson, and Masson Trichrome. A semi-quantitative analysis by light microscopy of the respective layers was performed. Radiation damage, inflammation, bleeding, clots, necrosis, cell regeneration, healing, and cellular atypia were assessed using a predefined scale (Table 2) determined by previous experiments (2, 3) and in-house experience. The treatment effects were scored by a single pathologist blinded to the radiation dose.

**Statistical analysis**

Data are expressed as mean and range unless indicated otherwise. Maximum likelihood estimation (using JMP software, version 9; SAS Institute, Cary, NC) of ordinal and nonlinear logistic regressions on dose was used to compute 95% confidence intervals (95% CIs) for odds ratio per Gy and 50% effective dose (ED50). The nonlinear model was parameterized as an Emax model with Hill exponent. Approximate standard errors and t-quantiles were used for CIs when the likelihood ratio method did not converge.

**Results**

Animal age at treatment was 627 (416-723) days, and weight increased from 49 (34-60) kg to 62 (55-69) kg after 197 (182-230) days of follow-up. As designed, these variables did not correlate with dose (Spearman’s rank correlation coefficients $r_S<0.2$).

**Procedural course**

Because of lack of femoral vein access, baseline electrophysiology was not performed in 2 animals (17.5/20 Gy). Baseline MRI was not performed for 1 animal (25 Gy), and 1 animal (27.5 Gy) was not set up with cone beam CT and was therefore treated with stereotactic frame reference only. One animal had a major complication and died of pericardial
effusion during the baseline electrophysiology procedure, so that 15 Gy was omitted. All other animals were integrated back into their groups 1 to 2 days after treatment.

**Electrophysiology**

After catheterization of the RSPV, pacing this target vein during baseline prompted atrial excitation, thus proving veno-atrial electrical conduction in this animal model. Six months after CSRS veno-atrial conduction was reassessed, and pacing the vein prompted again atrial excitation in each animal. No complete veno-atrial electrical block could be demonstrated after treatment.

**Histopathology**

All animals that underwent electrophysiology measurements showed a fossa-ovalis defect due to transseptal puncture. The animal treated with 17.5 Gy demonstrated no significant fibrosis at the RSPV but mild fatty tissue necrosis (FTN) with foamy macrophages of 1.5 cm diameter around the target vein. The animal treated with 20 Gy showed only mild fibrosis 0.5 cm along the RSPV in one-quarter of its circumference, with surrounding moderate FTN of 2 cm diameter. The animal treated with 22.5 Gy showed moderate fibrosis at 2 cm along the RSPV in three-quarters of its circumference. Adjacent fulminant FTN of 2.5 cm diameter was also noted.

After 25 Gy and 27.5 Gy only mild fibrosis was noted 1 cm and 0.5 cm along the RSPV in both one-quarter of its circumference, with mild FTN of 0.6 cm diameter and no FTN, respectively. With a dose of 30 Gy a moderate partly transmural, partly patchy fibrosis in 2 cm along the RSPV in half of its circumference and only mild FTN of 1.5 cm diameter was observed. The animal treated with 32.5 Gy showed intense but not complete transmural fibrosis 1.5 cm along the target vein and in three-quarter of its circumference.

**Fig. 1.** Treatment plan example (27.5 Gy). Upper left: Three-dimensional dose projection onto the pulmonary vein antrum. Lower left: Dose-volume histogram of the treatment plan. Right: Two-dimensional dose projection in axial (top), coronal (middle), and sagittal (bottom) planes. CS = coronary sinus; CTV = clinical target volume; IVC = inferior vena cava; LA = left atrium; PTV = planning target volume; RA = right atrium.
The RA myocardia. Findings are summarized in Table 3. Showed scattered foamy macrophages and focal fibrosis of were found. The surrounding FTN of 1.5 cm diameter portion of the vein, small areas of remaining muscle layers fibrosis was focal and mostly transmural. At the cranial damage, with radiation-induced fibrosis 2 cm along the RSPV and around most of the vein circumference. The animal treated with 35 Gy showed the most extensive circumference, with moderate FTN of 2 cm diameter. The animal treated with 35 Gy showed the most extensive damage, with radiation-induced fibrosis 2 cm along the RSPV and around most of the vein circumference. The fibrosis was focal and mostly transmural. At the cranial portion of the vein, small areas of remaining muscle layers were found. The surrounding FTN of 1.5 cm diameter showed scattered foamy macrophages and focal fibrosis of the RA myocardia. Findings are summarized in Table 3. Examples are presented in Figure 2.

The extension and intensity of fibrosis correlated significantly and monotonously with increasing dose, given \( r_S = 0.7524 \) (longitudinal extent, \( P = 0.0193 \)), \( r_S = 0.7849 \) (circumferential extent, \( P = 0.0122 \)), and \( r_S = 0.9319 \) (intensity, \( P = 0.0003 \)). The \( E_D_{1cm} \) for longitudinal extent was estimated at 23.8 Gy (95% CI 17-30 Gy given \( E_{max} = 2 \)). The residual standard deviation was 0.6 cm where the measurements of longitudinal extent were given as multiples of 0.5 cm. The \( E_D_{50} \) for circumferential extent was estimated at 28.0 Gy (95% CI 20.1-41.9 Gy; Hill exponent \(-1.735\)). Ordinal logistic regression resulted in an odds ratio of 2.47/Gy (95% CI 1.36-9.72) and an \( E_D{50} \) of 31.3 Gy for intense fibrosis. The \( E_D{50} \) for at least moderate fibrosis as a dichotomy was 23.7 Gy (95% CI 18.4-29 Gy) 

(Fig. 3). The fat tissue necrosis was not dose dependent (\( r_S = 0.18 \), 95% CI \(-0.55\), to +0.75). The fat tissue necrosis was not dose dependent (\( r_S = 0.18 \), 95% CI \(-0.55\), to +0.75).

### Treatment side effects

Superficial radiation damage or reactions like coughing or weight loss were not noted in any animal during follow-up. At baseline all animals had normal heart function as assessed by MRI, with no gross damage at follow-up. We found normal kinesis of the valves and no relevant changes in ejection fraction compared with baseline. Close critical structures (bronchial tree, pulmonary artery) showed no evidence of radiation damage.

### Discussion

The smooth-muscle layers of the PVs are electrophysiologically active and connected to the left atrial musculature, and they are a major source of AF (5-7). The therapeutic principle of catheter ablation is the electrophysiologic isolation of the PVs by inducing scars that inhibit electrical conduction. Scarring might also be achieved by other ablative procedures. The hypothesis of our study was that radiosurgery might be able to induce tissue scarring comparable to catheter ablation but with the advantage of a completely noninvasive approach.

Our animal study was planned as a proof-of-principle study to investigate the feasibility of CSRS, with the objective to achieve circumscribed fibrosis in the PVs with subsequent electrophysiologic blocking. We demonstrated, for the first time, the general feasibility of completely noninvasive CSRS in an animal model using a widely available linear accelerator. Furthermore, we were able to demonstrate that high external beam radiation to focal areas of the PVs can indeed induce tissue scarring, and we observed a significant dose-response relationship for the induction of fibrosis but with a gentler slope than for other organs, like spinal cord or esophagus (15, 16). The radiation-induced fibrosis was also not as homogeneously distributed as compared with other energies used for catheter ablation (17, 18). Contrary to previous studies (2, 3),

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Treatment parameters of the dose-escalation study</th>
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</thead>
<tbody>
<tr>
<td>Dose (Gy)</td>
<td>PTV coverage (%)</td>
</tr>
<tr>
<td>17.5</td>
<td>97</td>
</tr>
<tr>
<td>20.0</td>
<td>98.5</td>
</tr>
<tr>
<td>22.5</td>
<td>97</td>
</tr>
<tr>
<td>25.0</td>
<td>95</td>
</tr>
<tr>
<td>27.5</td>
<td>95</td>
</tr>
<tr>
<td>30.0</td>
<td>98</td>
</tr>
<tr>
<td>32.5</td>
<td>96</td>
</tr>
<tr>
<td>35.0</td>
<td>97</td>
</tr>
</tbody>
</table>

**Abbreviations:** CTV = clinical target volume; max = maximum; PTV = planning target volume.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Fibrosis intensity grading score for the pulmonary vein target area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Description</td>
</tr>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Minimal</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Intense</td>
</tr>
<tr>
<td>5</td>
<td>Complete</td>
</tr>
<tr>
<td></td>
<td>No evidence of fibrosis</td>
</tr>
<tr>
<td></td>
<td>Increased intercellular substance and disorganized architecture compared with control</td>
</tr>
<tr>
<td></td>
<td>Some scattered smooth-muscle cells are replaced by fibrocytes</td>
</tr>
<tr>
<td></td>
<td>Up to 50% of smooth-muscle cells are replaced by fibrocytes and collagen fibers</td>
</tr>
<tr>
<td></td>
<td>More than 50% of smooth-muscle cells are replaced by fibrocytes and collagen fibers</td>
</tr>
<tr>
<td></td>
<td>100% of smooth-muscle cells are replaced by fibrocytes and collagen fibers</td>
</tr>
</tbody>
</table>
our results translate into the need to apply at least 32.5 Gy for CSRS treatment effect.

Complete electrical block was not achieved because the areas of dense fibrosis, noted at single doses above 32.5 Gy, were not completely circumferential. Although the hypothesis has been proven that PV muscular scarring can be induced by radiosurgery, the results of this study have raised a number of radiobiological and technical questions also warranting further dose escalation.

We are aware of significant limitations of our study. This study explored a wide dose range, and more animals would need to be treated within the narrow therapeutic window we framed. Additionally, it remains unclear whether the observed results, especially the dose-response relationship in young healthy pigs can be translated to human AF patients. Radiation effects in a young population may be different from the effects in older individuals, and aging might impact radiation effects. Cardiac remodeling has been observed in patients with a long-lasting history of AF (19), and the impact of this remodeling on radiation sensitivity is also unclear. Furthermore, patients with AF often have a history of medical interventions and other comorbidities that might impact radiation effects.

Catheter ablation is an invasive, although minimally invasive, procedure, whereas radiosurgery offers the advantage of a noninvasive approach. However, catheter ablation offers at least 2 major advantages over radiosurgery, namely the immediate electrophysiologic effect and the possibility of real-time monitoring of the efficacy during the procedure. By the lack of electrophysiology measurements a noninvasive method misses an important endpoint for catheter ablation, which is the proof of PV isolation. This will not be measurable after CSRS, because a major goal of radiosurgery should be to avoid an invasive catheter intervention. The endpoint of CSRS will therefore be the freedom from AF, and a large patient series might be needed to prove the effectiveness of this treatment method.

Time to effect plays a significant role in CSRS. Whereas catheter ablation is intended to deliver immediate relief or freedom from AF, it seems to take 70-100 days for the major effect of radiation to be realized (12, 13). It also remains unclear whether tissue reactions from CSRS are homogeneously distributed throughout the treated area, which may be the cause of failed PV isolation in our study. Longer follow-up times may also lead to further tissue scarring, leading to PV isolation at a later time, which has not been investigated.

Technical considerations of CSRS delivery in non-sedated humans also need further investigation. Lack of PV isolation in our study might be caused by dose smearing due to target motion because we did not use motion compensation (20). However, with the designed homogeneous dose distribution this was not relevant for our dose-finding study, because most of the target area received the prescribed dose. For treatment of human AF patients, on the other hand, motion compensation will be necessary to ensure efficacy and to minimize side effects risks, especially with high single-fraction doses. The majority of modern linear accelerators are capable of treating small moving targets in the whole body by means of gating or motion compensation (21, 22) and in vivo animal studies have already proven accurate radiation delivery to the heart (23). Yet the challenge for CSRS remains fiducial-free target tracking so as to not invalidate the noninvasiveness of the procedure. Ultrasound or MRI tracking could further provide accurate noninvasive imaging for CSRS, and these are currently under investigation (24, 25). Other energy forms, such as heavy ions, could result in steeper dose gradients and higher biological effectiveness and are also under investigation (26).

Cardiac SRS has been proven safe in our study with doses up to 35 Gy and follow-up times of 6 months. Surrounding critical structures like the bronchial tree can potentially tolerate higher maximum doses different from previous reports (27). These findings could also be relevant for dose limitations during radiosurgery of central lung tumors. Yet doses above 30 Gy may already induce significant side effects, such as myocarditis and cardiovascular disease (28), and may increase the risk of radiation pneumonitis (29). Additionally, the human PVs are often close to the esophagus (30), which is known to be radiosensitive (31). Long-term toxicity needs further investigation because side effects to the heart may occur years after treatment (30), with potential increase in risk

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Fibrosis extent (cm along PV)</th>
<th>Circumference fibrosis (part of PV)</th>
<th>Fibrosis intensity (scale 0-5)</th>
<th>Fat tissue necrosis (cm around the vein)</th>
<th>Fat tissue necrosis (scale 0-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>None = 0</td>
<td>0.0</td>
<td>None = 0</td>
</tr>
<tr>
<td>17.5</td>
<td>0.0</td>
<td>0</td>
<td>Minimal = 1</td>
<td>1.5</td>
<td>Mild = 2</td>
</tr>
<tr>
<td>20.0</td>
<td>0.5</td>
<td>1/4</td>
<td>Mild = 2</td>
<td>2.0</td>
<td>Moderate = 3</td>
</tr>
<tr>
<td>22.5</td>
<td>2.0</td>
<td>3/4</td>
<td>Moderate = 3</td>
<td>2.0</td>
<td>Moderate = 3</td>
</tr>
<tr>
<td>25.0</td>
<td>1.0</td>
<td>1/4</td>
<td>Mild = 2</td>
<td>0.6</td>
<td>Minimal = 1</td>
</tr>
<tr>
<td>27.5</td>
<td>0.5</td>
<td>1/8</td>
<td>Moderate = 3</td>
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<td>None = 0</td>
</tr>
<tr>
<td>30.0</td>
<td>2.0</td>
<td>1/2</td>
<td>Moderate = 3</td>
<td>1.5</td>
<td>Mild = 2</td>
</tr>
<tr>
<td>32.5</td>
<td>1.5</td>
<td>3/4</td>
<td>Intense = 4</td>
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<tr>
<td>35.0</td>
<td>2.0</td>
<td>1</td>
<td>Intense = 4</td>
<td>1.5</td>
<td>Mild = 2</td>
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Abbreviation: PV = pulmonary vein.
of radiation-induced coronary events as demonstrated in fractionated breast cancer radiotherapy (28, 32-35). Also in our study only a single PV was treated, whereas in human AF all PVs, generally 4, would require isolation. This may further increase the risk of side effects as compared with our animal results, requiring smart treatment planning and potentially sequential treatment. For arrhythmia patients at advanced age, on the other hand, long-term cardiac toxicity might play a minor role, not outweighing the benefit of noninvasive arrhythmia treatment. Still, close critical structures like the esophagus will be a major limiting factor for CSRS, and careful consideration is necessitated before moving into human clinical trials for radiosurgery treatment of AF.

Conclusion

This proof-of-principle dose-escalation study demonstrates for the first time that radiosurgery with a conventional linear accelerator can noninvasively induce focal lesions in anatomically defined areas of the PVs, with the subsequent
creation of scar tissue. In this study we established a significant dose-response relationship for cardiac radiosurgery. The results indicate that in normal pig hearts doses above 32.5 Gy are necessary to achieve scar formation to potentially induce an atrial-venous electrical conduction block required for the treatment of paroxysmal AF. Further dose escalation and evaluation of long-term effects associated with high radiation doses need to be established in the pursuit of cardiac radiosurgery for noninvasive treatment of AF.

**Fig. 3.** Fibrosis intensity, extent, and circumference by dose for 9 pigs (●), with logistic curves (solid lines) and 95% confidence intervals (arrows) for 50% effective doses (dashed reference lines).

**References**


