Pulmonary vein isolation by radiosurgery: implications for non-invasive treatment of atrial fibrillation

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Aims

Electrical isolation of the pulmonary veins (PVs) has been established in clinical routine as a curative treatment for atrial fibrillation (AF). While catheter ablation carries procedural risks, radiosurgery might be able to non-invasively induce lesions at the PV ostia to block veno-atrial electrical conduction. This porcine feasibility and dose escalation study determined the effect of radiosurgery on electrophysiologic properties of the left atrial–PV junction.

Methods and results

Eight adult Goettingen mini-pigs underwent electrophysiological voltage mapping in the left atrium and the upper right PV. Radiation was delivered with a conventional linear accelerator. A single homogeneous dose ranging from 22.5 to 40 Gy was applied circumferentially to the target vein antrum. Six months after radiosurgery, electrophysiological mapping was repeated and a histological examination performed. Voltage mapping consistently showed electrical potentials in the upper right PV at baseline. Pacing the target vein prompted atrial excitation, thus proving veno-atrial electrical conduction. After 6 months, radiation had reduced PV electrogram amplitudes. This was dose dependent with a mean interaction effect of $-5.8\%$/Gy. Complete block of atrio-venous electrical conduction occurred after 40 Gy dose application. Histology revealed transmural scarring of the targeted PV musculature with doses $>30$ Gy. After 40 Gy, it spanned the entire circumference in accordance with pulmonary vein isolation.

Conclusion

Pulmonary vein isolation to treat AF can be achieved by radiosurgery with a conventional linear accelerator. Yet, it requires a high radiation dose which might limit clinical applicability.

Keywords

Atrial fibrillation • Ablation • Pulmonary vein isolation • Radiation • Radiosurgery

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in humans. The prevalence increases with age.1 Drugs often fail to accomplish sufficient rhythm control and many patients remain symptomatic even after achievement of pharmacological rate control.2 The most severe complication of AF is stroke due to left atrial clot formation and consecutive cerebral embolism.

Atrial fibrillation most commonly originates from the pulmonary veins (PVs). Ectopic electrical activity in the muscle sleeves around the veins can initiate AF while re-entrant conduction within the sleeves helps to sustain AF.1,4 Isolating the PVs at the ostia from the left atrium (LA) has provided cure from AF in a considerable share of patients undergoing transcatheter or surgical ablation. Pulmonary vein isolation (PVI) has now been established in clinical routine as a curative treatment for AF and may even be considered...
What’s new?

- This is the first study (i) to show that radiosurgery can induce complete pulmonary vein isolation (PVI), (ii) that performed voltage mapping of the target vein before and after radiosurgery, and (iii) that quantified the electrophysiological effect of radiation during dose escalation. A single-fraction dose of 40 Gy applied with a conventional linear accelerator was found to induce complete PVI which corresponded to circumferential transmural fibrosis of the target vein. Non-invasive PVI to treat atrial fibrillation required a high-radiation dose.

as a first-line therapy in selected patients.\(^5\) Circumferential lesions around the PV ostia have been created by a variety of energy sources such as radiofrequency, cryotherapy, high-intensity focused ultrasound, and laser. Energy delivery requires transcatheter, transseptal access from the right to the LV, or operative access to the heart by thoracotomy. Each method carries considerable procedural risks.\(^6\) Skilled operators are needed with each modality. Currently, the potential patient population outnumbers invasive treatment capacities.

Radiosurgery might provide a non-invasive approach to treat AF. Typically used for oncology applications, radiosurgery has been deployed to treat metastatic tumours of the heart.\(^7\) Opposed to conventional radiation therapy, stereotactic application of radiation can deliver a high-energy dose to a very circumscribed target area. Only recently, it has been attempted to radioablate myocardium in order to influence a potentially arrhythmogenic substrate. In pigs, atrio-ventricular (AV) nodal conduction was abolished and the cavo-tricuspid isthmus, which is responsible for maintenance of typical atrio-ventricular (AV) nodal conduction, was blocked using stereotactic robotic radiosurgery.\(^8\) The effect of radiosurgery on the PV antrum and the ability to ablative veno-atrial conduction has not been consistently studied. Preliminary attempts to target the PV ostia with stereotactic radiosurgery have been reported, indicating a histological effect in the target area, i.e. fibrosis, but did not provide comparative information on the electrophysiological capabilities of the veno-atrial junction before and after treatment. Moreover, a dose–response relationship has not been established. A previous study in a porcine model suggested that a dose of 25 Gy was needed to produce electrophysiologic effects in the heart.\(^9\) This study investigated the feasibility of lesion formation to achieve sustained alterations of electrical conduction at the PV ostia by radiosurgery. Dose-ranging was performed in a mini-pig model. The potential to produce complete electrical isolation was assessed by PV pacing before and after treatment. Reduction of local electrogram amplitude indicating loss of viable myocardium was investigated by voltage mapping of the target vein.

Methods

Porcine model

A porcine model was chosen since it had been used successfully in previous studies both to investigate cardiac electrophysiology during left atrial catheter ablation\(^9\) and to evaluate the effect of cardiac radiosurgery.\(^8,10\) Eight female adult Goettingen mini-pigs (Ellegard, Denmark) weighing 40–60 kg were studied according to German Federal Regulation for animal research after approval of the institutional ethics committee. Animals underwent general anaesthesia initiated by ketamine (Ketavet, Pfizer, New York, NY, USA) and xylazine (Rompun, Bayer, Leverkusen, Germany) im and continued by propofol 2% (Disopropian, AstraZeneca, Wedel, Germany) iv. After intubation, they were maintained on a respirator (Oxylog, Draeger, Luebeck, Germany) and were fixated in a tight vacuum bag. Vital signs, electrocardiogram (ECG), and oxymetry were continuously monitored.

Imaging

A contrast-enhanced cardiac computed tomography (CT) scan was performed on a 64 slice scanner (Somatom Definition 64, Siemens, Erlangen, Germany) with ECG trigger. This CT scan was used for left atrial image integration into the electroanatomic mapping system and for radiation treatment planning. Acquisition was performed during end-expiration and -inspiration to assess respiratory motion. Thus, maximal respiratory and cardiac displacements of the PV area could be incorporated in the treatment plan. The right upper PV was chosen as a target for radiation due to sufficient size and an anatomic location that permitted catheter insertion.

Electrophysiologic study

The femoral vein was punctured under ultrasound guidance and a steerable sheath was advanced into the right atrium. After transseptal puncture, 5000 units of heparin were administered. A 6F National Institute of Health (NIH) catheter was inserted into the right upper PV. To visualize the individual anatomy, contrast agent was applied during biplane fluoroscopic imaging. The NIH catheter was then exchanged for a quadrupolar 5F electrode catheter. Using the NavX Ensite Classic cardiac mapping system (St Jude Medical, St. Paul, MN, USA), the LA and the target vein were reconstructed and registered with a segmented image of the CT scan. By roving of the catheter tip, local electrical amplitudes were determined in the right upper PV antrum, the proximal vein and the distal vein, and an electroanatomic voltage map was created. Voltage amplitudes >2 mV indicated viable tissue. Voltages <0.3 mV were defined to represent scar tissue. The proximal vein represented the target area for radiation. The target vein was paced at different proximal and distal locations of its circumference with a 10 V impulse of 2 ms duration observing the atrial activity (P wave) in the surface ECG. Upon completion of the electrophysiologic study, the femoral sheath was removed.

Radiation treatment

Animals were treated with single-fraction radiosurgery. Homogeneous gamma radiation doses ranging from 22.5 to 40 Gy were applied using increments of 2.5 Gy (Gy = absorbed dose in Joule per kilogram). These doses can be considered relatively high. For example, the doses of single-fraction radiosurgery for brain metastases usually range between 18 and 25 Gy. The individual dose was randomly assigned. Radiation targeted the circumference of the proximal upper right PV. Based on the CT scan, a treatment plan was designed that contoured the clinical target volume and adjacent critical structures to be protected from radiation. Radiation
direction, field, and intensity were determined and the randomized dose prescribed (Eclipse Planning system version 10.0, Varian Inc., Palo Alto, CA, USA). Location and shape of the target and beam path distance were similar in mini-pigs as compared with adult humans. A safety margin around the target volume for compensation of cardiac (2–3 mm) and respiratory motion (10–15 mm) was implemented from 4D CT data. The volume including the target volume plus safety margins is called the internal target volume. The dose drop-off outside the target area was 6%/mm [anterior/posterior (AP)], 10%/mm [superior/inferior (SI)], and 2.5%/mm [left/right (LR)], respectively. The drop-off values were obtained from the corresponding treatment plans of the animals treated in this trial. A stereotactic frame that had been used during CT facilitated positioning in the isocentre of the linear accelerator. A cone beam CT was used for registration during treatment delivery. Radiation was delivered with a conventional linear accelerator (Clinac DHX 2000, Varian Inc.). Afterwards, anaesthesia was stopped followed by extubation upon return of spontaneous respiration.

Radiation doses at a distance of 1.5 cm from the intended target volume were calculated incorporating dose drop-offs and safety margins accounting for organ motion. One has to be aware that the biological effect of radiotherapy depends not only on the total dose but also on the dose per fraction. The biological effect of radiotherapy increases with the dose per fraction. Radiation regimens including different doses per fraction can be compared by calculating the so-called equivalent dose in 2 Gy fractions (EQD2), which considers both the total dose and the dose per fraction. The EQD2 is calculated with the equation $\text{EQD}_2 = D \times (d + \alpha/\beta)/2 \text{Gy} + (\alpha/\beta)$, as derived from the linear-quadratic model ($D = \text{total dose}, d = \text{dose per fraction}, \alpha = \text{linear (first-order dose dependent) component of cell killing}, \beta = \text{quadratic (second-order dose dependent) component of cell killing}$, and $\alpha/\beta = \text{dose at which both components of cell killing are equal}$). The most commonly used $\alpha/\beta$ ratio for late radiation morbidity in normal tissues is 3 Gy, which has also been assumed in this study.

Follow-up

Six months post-radiosurgery, the electrophysiologic study was repeated and results were compared with pre-treatment findings. Electrophysiologic voltage mapping was performed using the NavX Ensite Velocity cardiac mapping system (St Jude Medical). Corresponding to baseline measurements, the reconstructed target vein was registered with a Newly segmented image of the CT scan. Pacing the target vein was assess conduction to the atrium was performed in analogy to baseline measurements.

Animals were sacrificed and a histological examination was performed to assess radiation-related lesions at the target vein.

Statistics

Potential amplitudes measured before and after treatment were analysed by mixed analysis of covariance (ANCOVA), as this was considered most robust with respect to the varying number of recordings in different animals and different PV locations during different times. Amplitudes were explained by time (before or after radiation), dose, location (LA, antrum, proximal, and distal vein), two- and three-way interactions, and individual (random effect). Distributional assumptions and the need for a transformation were checked by plotting the residuals against predicted values. Results are presented as F-tests and 95% confidence intervals (CIs) without adjustment for multiplicity. Statistical modelling and estimation was performed using SAS software JMP 9.0.2 (SAS Institute Inc., Cary, NC, USA, 2010).

Results

Electrophysiologic properties of the target vein

At baseline, voltage mapping consistently showed electrical potentials in the upper right PV (Figure 1). On average, 38 potentials were recorded from different locations within and around each vein. Maximal amplitudes in the target vein varied between subjects, confirming the need to assess individual baseline electrophysiologic properties in order to quantify amplitude changes after radiotherapy. Pacing the target vein prompted atrial excitation in each pig, proving veno-atrial electrical conduction in this model (Figure 1).

Follow-up was scheduled 6 months after radiation. One pig had to undergo premature examination due to a bronchial-mediastinal fistula with pneumonia and sepsis 1 month after radiation (37.5 Gy) and was not included in the evaluation. In another pig (25 Gy), femoral access could not be achieved during follow-up. Thus, electrophysiologic repeat measurements after 6 months were available in six pigs.

A decrease of potential amplitude in the targeted proximal vein, the adjacent antrum, and the distal vein was noted at doses above 30 Gy (Figure 2 and Table 1). Radiation with 40 Gy reduced potential amplitudes in the target vein to $<0.3 \text{ mV}$, indicative of electrically inactive scar tissue. Amplitudes in the LA were not affected. Analysis of covariance of logarithms of amplitudes showed that radiation reduced amplitudes in the target area by 77% (CI 70–83%) at 33.8 Gy. This was dose dependent with a mean interaction effect of $-5.8/\text{Gy} \text{ (CI} -4.1 \text{ to } 7.5/\text{Gy})$. The effect of radiation and its dose dependency differed between left atrial, antral, proximal and distal PV locations ($P = 0.048$ for three-way interaction). Expected ratios of amplitudes had a total random coefficient of variation of 3.0; they are shown for all doses and locations in Figure 3.

Pacing the target vein 6 months after radiotherapy resulted in atrial excitation after treatment with doses up to 35 Gy. Thus, veno-atrial conduction was preserved. After radiation with 40 Gy, pacing from within the target vein prompted no atrial excitation. Non-excitability and entrance block indicated complete PVI. The highest dose also caused collateral damage to the AV node evidenced by complete AV block in the individual that had undergone radiotherapy with 40 Gy (see Supplementary material online, Figure 5A).

For the animal receiving the highest dose of 40 Gy, which showed complete atrio-venous block after treatment, the dose drop-offs were 2.4 Gy/mm in AP direction, 4.0 Gy in SI direction, and 1.0 Gy/mm in LR direction, respectively. The safety margins accounting for organ motion were 6.0 mm (AP), 12.5 mm (SI), and 5.0 mm (LR), respectively. Taking into account both dose drop-offs and safety margins, the doses at a distance of 1.5 cm from the intended target volume were 18.4 Gy (AP), 30.0 Gy (SI), and 30.0 Gy (LR), respectively. Given the limitations of the $\alpha/\beta$ model for very high doses per fraction, the EQD2 at a distance of 1.5 cm from the intended target volume were calculated to be 79 Gy3 (AP), 198 Gy3 (SI), and 198 Gy3 (LR), respectively.
Pathology

Histology revealed a significant dose–response relationship in the targeted area with fat tissue necrosis at doses >20 Gy and partial transmural scar formation in the PV musculature at doses >30 Gy, as previously described.13 Complete circumferential fibrosis of the PV musculature occurred after 40 Gy (see Supplementary material online, Figure S8). Radiation-induced damages of adjacent structures were found after 37.5 Gy (bronchial-mediastinal fistula leading to pneumonia, sepsis, and premature death) and after 40 Gy (AV node fibrosis). Pulmonary veins showed no stenosis.

Discussion

This study quantified for the first time the dose-dependent effect of radiosurgery on the electrical capabilities of the left atrial–PV junction. Our study confirmed active electrical properties of the PVs in the pig species used and proved the appropriateness of the model to study radiation-induced effects. High doses >30 Gy were required to induce amplitude reduction of antral and proximal PV potentials associated with scarring of the PV musculature. Radiation was capable of inducing complete PVI after 40 Gy dose application.

Pulmonary vein electrophysiology

In humans, myocardial muscle fibres extend from the LA into the PVs at a length of 1–3 cm; muscular sleeves are thickest at the proximal end of the veins (1–1.5 mm) and gradually taper distally.14 Electrophysiological properties of these sleeves have been extensively studied. During sinus rhythm electrical conduction into the PV occurs. Under pathologic conditions, impulses generated in the PV by an ectopic trigger or by highly frequent circulatory movement propagate from the PV to the LA and drive the arrhythmia.15 The endpoint of invasive ablation targeting the PV is complete isolation which can be proven by entrance block and/or exit block. Clinically, entrance block can be detected by abolishment of PV potentials following atrial activity. Exit block can be evaluated by an effective electrical stimulus applied within the vein lacking impulse conduction to the atrium. Baseline PV mapping proved electrical activity in each target vein. Therefore, our model was appropriate to investigate electrophysiologic changes of the left atrial–PV junction after radiotherapy. Previously, Sharma et al.8 found no electrical potentials in the PV of their porcine model (Hanford mini swine), thus no atrio-venous conduction could be established and no creation of atrio-venous block could be investigated. Consequently, radiation effects were examined in the LA next to the PV orifices. Signal amplitude reduction following 25 Gy was used as an indicator of conduction block. Our study showed amplitude reduction and partial formation of scar in the PV target area with higher doses from 30 to 35 Gy, which was not yet associated with complete entrance or exit block of the PV. Therefore, electrical isolation should not be deduced from attenuation of local voltage amplitude. In our study, application of 40 Gy was required to achieve isolation of a targeted vein as evidenced by electrical amplitudes <0.3 mV throughout the venous target area and high-output pacing without atrial response. This
also corresponded to circumferential transmural scarring upon histology.

Non-invasiveness

Sharma et al.\(^8\) employed the CyberHeart System to create cardiac lesions by radiosurgery. This required surgically or catheter implanted fiducials next to the target site for real-time intra-treatment image guidance. Radiosurgery therefore necessitated a preceding invasive procedure and implied potential peri-procedural complications. In contrast, our study represents the first genuinely non-invasive approach to alter electrophysiologic properties of heart tissue.

**Figure 2** Voltage maps of the right upper PV before (right) and 6 months after radiation (left) with 22.5 Gy (A), 32.5 Gy (B), and 40 Gy (C). Purple colour indicates voltage amplitudes above 2 mV in viable tissue. Grey colour indicates voltages <0.3 mV defining scar tissue. Radiation with 22.5 Gy left local voltages unchanged. Partial scarring was found after radiation with 32.5 Gy. Radiation with 40 Gy induced complete scarring of the PV.

**Table 1** Potential amplitudes in the PV target area before and after radiation

<table>
<thead>
<tr>
<th>Radiation dose (Gy)</th>
<th>Baseline Maximum amplitude (mV)</th>
<th>Baseline Minimum amplitude (mV)</th>
<th>Baseline Mean amplitude (mV)</th>
<th>After radiation Maximum amplitude (mV)</th>
<th>After radiation Minimum amplitude (mV)</th>
<th>After radiation Mean amplitude (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.5</td>
<td>3.71</td>
<td>0.67</td>
<td>2.48 ± 1.12</td>
<td>3.43</td>
<td>0.56</td>
<td>2.41 ± 1.38</td>
</tr>
<tr>
<td>25</td>
<td>5.16</td>
<td>3.72</td>
<td>3.17 ± 2.16</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>27.5</td>
<td>1.65</td>
<td>0.12</td>
<td>0.7 ± 0.53</td>
<td>1.42</td>
<td>0.12</td>
<td>0.63 ± 0.5</td>
</tr>
<tr>
<td>30</td>
<td>5.05</td>
<td>2.67</td>
<td>4.27 ± 1.12</td>
<td>5.82</td>
<td>0.51</td>
<td>1.75 ± 1.63</td>
</tr>
<tr>
<td>32.5</td>
<td>8.01</td>
<td>2.21</td>
<td>4.15 ± 2.19</td>
<td>1.76</td>
<td>0.06</td>
<td>0.48 ± 0.43</td>
</tr>
<tr>
<td>35</td>
<td>1.93</td>
<td>0.47</td>
<td>0.97 ± 0.42</td>
<td>0.55</td>
<td>0.22</td>
<td>0.36 ± 0.12</td>
</tr>
<tr>
<td>37.5</td>
<td>6.54</td>
<td>0.1</td>
<td>1.67 ± 1.66</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>40</td>
<td>10.2</td>
<td>0.36</td>
<td>2.49 ± 1.97</td>
<td>0.17</td>
<td>0.00</td>
<td>0.05 ± 0.04</td>
</tr>
</tbody>
</table>

Note that baseline amplitudes differed between individual pigs.
Non-arrhythmia model

This study was conducted in a non-arrhythmia model. Therefore, it could not measure the definite antiarrhythmic effect of radiosurgery targeting the LA–PV junction. Instead, this dose escalation study focused on the feasibility of tissue ablation at the PV antrum which has been shown to be the crucial site for clinically effective ablation with other energy sources. Conventional PVI techniques create circular ablation lines around the PV ostia adapted to the individual anatomy. This makes it feasible to determine a desired ablation site from CT imaging and to use radiation in an anatomy-based approach. In our study, registration of gated cardiac CT images obtained prior to the procedure was used to define the anatomic target. In humans, PVI can be performed during sinus rhythm and the presence of AF is not required during the procedure. Likewise, acute interventional success is not defined by arrhythmia suppression. Therefore, it seemed feasible to investigate the effect of radiosurgery in the absence of AF. Current invasive techniques use complete electrical isolation of the PV as an endpoint. This is done by transcatheter mapping and/or pacing of the PV antrum. While electrical isolation is also the goal of radiotherapy, proving electrical block after radiation would require catheter intervention and render this approach invasive. Therefore, radiotherapy has to be performed with optimized setup and radiation parameters that will assure a sufficient ablation effect. Our study provides initial evidence on the radiation dose (40 Gy) that might be required to achieve PVI.

Time-dependent effect

To determine the effect of radiation on veno-atrial conduction for study purposes, we performed mapping in the chronic phase after radiosurgery. PV mapping would have not been appropriate immediately after exposure due to a time-dependent effect of lesion formation. Time-dependent generation of electrophysiological effects has been described previously in a porcine model by Sharma et al. After radiosurgical intervention (70 Gy) targeting the AV node, progressive AV conduction delay occurred with second degree AV block developing after 35 days and third degree AV block after 49 days. Thirty-three days after exposure (38 Gy), the left atrial appendage showed no local electrograms while only minimal effects were seen after 16 days. After radiation therapy in man, cardiac side effects of thoracic radiation have been reported to occur within 3–6 months. Therefore, post-treatment evaluation was performed after 6 months in our model to assure formation of permanent changes. Time-dependent generation of PVI after radiosurgery implies that a patient would not experience immediate relief from symptomatic AF after radiosurgery. This is a considerable disadvantage as compared with catheter ablation.

Completeness of pulmonary vein isolation

Even current ablation techniques fail to achieve lasting PVI with a single procedure in a considerable number of patients. While immediate intraprocedural mapping of the PV could prove electrical isolation in all treated veins, post-procedural mapping after a healing period regularly found electrical reconnection of some PVs, independent of energy source. Thus, sustained transmural lesion formation of the PV is technically challenging even by invasive methods with direct energy application. Different ablation energy requirements in different locations around the PV antrum circumference might explain the difficulty of achieving sustained electrical block not only by transcatheter ablation but also by radiation with doses <40 Gy, which created no circumferential transmural scarring.

Whether incomplete isolation with doses <40 Gy might already be clinically beneficial to suppress AF is speculative. In humans, ablation might be clinically effective despite the presence of gaps, which could be found even in asymptomatic patients undergoing repeat EP study after an ablation procedure. Therefore, the application of radiosurgery in an animal model of AF would be certainly of much interest to assess the true antiarrhythmic effect. Yet, the most established endpoint of catheter ablation, which is complete PVI, should be achieved by radiotherapy in order to secure maximal procedural efficacy. In view of high-radiation doses required to produce complete PVI but causing collateral damage, radiotherapy might share a dilemma of catheter ablation, where potential side effects also limit the use of higher energies to assure the creation of permanent veno-atrial block.

Radiation-related normal tissue damage

Taking into account the chest circumference of the mini-pigs used in our study, the external beam path lengths will be similar as compared with humans. In our animal receiving 40 Gy, the EQD2 at a distance of 1.5 cm from the intended target volume ranged between 79 GY3 in AP direction and 198 GY3 in SI and LR directions, respectively. These doses are beyond the tolerance doses TD50S, which represent the doses associated with up to 50% severe complications within 5 years. Tolerance doses derive from radiotherapy for mediastinal and pulmonary tumours. The TD50S are 65 Gy for the lungs (pneumonitis and lung fibrosis), 70 Gy for the heart (pericarditis and pancarditis), 70–100 Gy for blood vessels (sclerosis and stenosis), and 72 Gy for the oesophagus (stricture, stenosis, ulcers, and perforation). The TD50S (up to 5% of severe complications within 5 years) are 45 Gy for the lungs, 60 Gy for the heart, 50–60 Gy for the blood vessels, and 60 Gy for the oesophagus, respectively. In our animal

Figure 3 Ratios of geometric mean amplitudes (before/after radiation) in the LA (green diamonds), the PV antrum (turquoise circles), the proximal vein (lilac crosses), and the distal vein (red plus signs), computed from an ANCOVA of 461 measurements in six pigs with total random coefficient of variation of 1.46. Error bars of matching colours were computed from ± SE of logarithms. A yellow reference line marks ratio 1 (no effect).
receiving 32.5 Gy (the minimum dose showing a histological scarring effect),\textsuperscript{13} the EQD2 was beyond 100 Gy\textsubscript{3} in SL direction and in LR direction. Therefore, greatest caution is required when considering the use of the technique presented here in humans, particularly when targeting all PVs. It may be administered only to patients with a short-life expectancy who are suffering from significant symptoms that are refractory to other treatments and who opt for completely non-invasive therapy. Apart from potential adverse long-term effects of radiosurgery, the development of a bronchial-mediastinal fistula after 37.5 Gy application and of AV block after 40 Gy application raises concerns even about short-term complications. Moreover, since the risk of developing radiation-related late sequelae remains lifelong, there may be other long-term side effects not observed in this trial. The precision of the delivery of radiosurgery for AF requires improvement including significantly smaller safety margins. This may be achieved with the use of real-time tracking (MRI or ultrasound based) and steeper dose drop-offs by using rotational beam delivery techniques. Before using radiosurgery for AF in humans, further animal studies are required in order to investigate the potential benefits of real-time tracking and steeper dose drop-offs.

**Conclusion**

Completely non-invasive PVI by radiosurgery to treat AF appears to be feasible. In this porcine dose escalation study, using a conventional linear accelerator high-radiation doses above 30 Gy had to be applied to create scarring in the antral PV with a subsequent reduction in electrophysiological signals. The desired electrical conduction block at the PV antrum could be achieved at 40 Gy. Radiation damage to collateral structures limits the applicability of such high doses for human use. Real-time target tracking might enhance the precision of radiation delivery to provide PVI at reduced risk.

**Conflict of interest:** none declared.

**References**


