

Cardiac Radiosurgery (CyberHeart™) for Treatment of Arrhythmia: Physiologic and Histopathologic Correlation in the Porcine Model

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Abstract

Objectives: This porcine pre-clinical investigation sought to demonstrate a new and novel application for radiosurgery, the ablation of cardiac arrhythmias. Pre-clinical studies in the porcine animal model were used to investigate the accuracy with which the pathological region in the heart that is routinely treated for atrial fibrillation could be targeted with radiosurgery. Pathologic and electrophysiologic (EP) changes resulting from radiosurgical ablation were used as primary study endpoints.

Methods: Two Hanford mini-swine (approximately 35 kg) were studied. A cardiac-gated CT study was performed. Isocentric treatments were delivered with the CyberKnife® (Accuray Inc, Sunnyvale, CA) in a single fraction at prescribed doses of 25 Gy (N=1) and 35 Gy (N=1). The treatment volume was selected to create electrical isolation of two pulmonary veins (the source of atrial aberrant tachycardias, such as atrial fibrillation) from the body (antrum) of the left atrium, as has been proven successful with thermal catheter ablation procedures. Animals were followed for six months, and then underwent electrophysiologic (EP) testing in the cardiac catheterization lab to test for electrical isolation of the pulmonary veins. Trans esophageal echocardiography was carried out to examine cardiac function post-radiosurgery. Finally, the hearts of the treated animals were submitted for pathologic analysis.

Results: Long-term follow-up after left atrial radiosurgery demonstrated transmural, circumferential fibrosis that correlated to electrical isolation, similar to that found in catheter ablation. The EP study documented intended pulmonary vein isolation (electrical block), using a decapolar Lasso catheter (Biosense Webster, Diamond Bar, CA). Histologic analysis showed transmural fibrosis and contiguity (desired) of the ablation scar within the target. Echocardiographic monitoring of atrial and ventricular function six months post radiosurgery demonstrated normal cardiac function. Both animals met the survival endpoint with no adverse events.

Conclusions: Cardiac radiosurgery for the treatment of atrial fibrillation can be safely performed in the porcine animal model using appropriate treatment planning, taking into account cardiac anatomy, motion and targeting concerns. Electrophysiologic and pathologic assessment correlated radiation-induced tissue effect to the target tissue. Proof of concept is therefore confirmed. This technique has the potential to provide a significant advancement in the treatment of atrial fibrillation and other cardiac arrhythmias, especially for those patients

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who have failed drug therapy and are not candidates for intra-cardiac catheter ablation. Clinical studies are needed to prove safety and efficacy.

Categories: Cardiac/Thoracic/Vascular Surgery, Pathology, Radiation Oncology

Keywords: cyberknife, pathology, electrophysiology, arrhythmia, atrial fibrillation, cardiac radiosurgery

Introduction

Stereotactic radiosurgery has evolved over the last decade as an important advance in the minimally invasive surgical alternative for both malignant and benign disease and new applications are emerging, potentially including treatment of cardiac arrhythmias. Radiosurgery has demonstrated applicability to treat moving targets such as lung tumors with accuracy and to successfully ablate lesions in anatomically 'in-hospitable' locations [1, 2]. The concept of using radiosurgery to treat tumors within the cardiac wall or chambers has recently been demonstrated [3, 4]. The potential exists to expand cardiac radiosurgical applications to include treatment of cardiac arrhythmias. Porcine studies have been conducted to determine feasibility of treatment of atrial fibrillation.

Historically, the treatment of Hodgkin's disease using mantle radiation often included incidental exposure of large volumes of the heart with high doses of radiation (>30 Gy). Because of long-term cardiac complications associated with these now outdated treatments there has been a reluctance to use radiation in the heart [5]. New radiosurgery systems, however, are proven to accurately deliver discrete ablative doses while sparing surrounding normal tissue. With the knowledge and recent experience gained in the use of platforms such as the CyberKnife® (Accuray Inc, Sunnyvale, CA, Figure 1) which dynamically tracks targets during treatment, cardiac radiosurgery is challenging this perception from past decades.



FIGURE 1: The CyberKnife Radiosurgery System

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Atrial fibrillation represents an enormous worldwide health care burden affecting more than 3-5 million people in the United States (US) and over 6 million people in Europe, and its prevalence is expected to double over the next 50 years as the population ages [6]. Outcomes from therapies such as drugs and thermal ablation have improved over the past twenty years but

remain unsatisfactory. Although intracardiac catheter ablation with thermal energy (radiofrequency, cryotherapy) has demonstrated a 60-70% success rate over the first year after ablation, long term success is disappointing. New data from one of the groups that pioneered the catheter ablation approach recently reported arrhythmia free survival rates of 29% after five years after a single catheter ablation procedure [7]. Furthermore the complications associated with catheter therapy, though reported to be approximately 4.5-5%, can range from vascular complication to stroke, cardiac perforation, and tamponade [8, 9].

Given the clinical need for improved treatment options for atrial fibrillation, advances in radiosurgical technology radiation energy represent a novel alternative for treatment of atrial fibrillation. Stereotactic radiosurgery has the capacity to create specific and accurate ablation lesions. Combined with the fact that it can properly compensate for motion in real time, the potential to create therapeutic ablation lesions in the heart is present. Unfortunately, there is minimal, if any experience using radiosurgery as a cardiac therapy. In addition, literature with regard to the heart and radiation has documented the association of radiation (as in mediastinal mantle radiation for Hodgkin's disease) with long term complications when large volumes of the heart were incidentally irradiated (>30GY).

Prior pre-clinical animal studies were performed to develop a clinical methodology and to determine the feasibility for radiosurgical treatment of atrial fibrillation [10]. These two porcine studies confirm the potential of this new application. Histologic and electrophysiologic evidence was obtained to correlate electrophysiologic and histopathologic results with pre-treatment radiosurgical plans.

Materials And Methods

Two Hanford miniswine were used for this study. Animals were maintained and cared for under the supervision of the research staff at the Sutter Institute for Medical Research in Sacramento, CA. The trial was conducted in accordance with AALAC Guidelines and under the Guidelines established by the USDA for the ethical care and treatment of Laboratory animals.

Surgical placement of fiducials

To exactly identify the pulmonary-vein left atrial target, a small right lateral thoracotomy was performed under endotracheal general anesthesia with Isoflurane. Gold fiducials (Civco Medical Solutions, Kalona, IA.) were surgically attached to the intersection of the pulmonary veins and the left atrium. The animals were allowed to recover for 3-4 weeks prior to the next pre-ablation studies.

Cardiac gated CT scan and baseline electrophysiology and echocardiographic study

Under a second anesthesia, a cardiac gated CT scan (GE Lightspeed CT Scanner, Waukesha, WI) was obtained using Isovue contrast to adequately identify the heart anatomy. A slice thickness of 1.25 mm was used and images were acquired from 3 cm inferior to 3 cm superior of the heart. Following this, the animal was brought to the cardiac catheterization laboratory where baseline electrophysiologic testing was performed under fluoroscopic guidance. The CARTO voltage mapping system (Biosense Webster, Diamond Bar, CA) documented normal tissue voltage in all measurements. Finally, under heparinization, a Lasso decapolar circular electrophysiologic mapping catheter was placed from the right femoral vein into the heart, across the interatrial septum, and lodged into the right superior pulmonary vein. Normal signal conduction following a 10 mA electrical pulse was confirmed across all electrodes from the pulmonary veins into the left atrium. The positioning of the Lasso catheter was documented, so as to reliably reproduce the same monitoring site for the post EP study. In addition, the location of the

surgically placed fiducials on or near the pulmonary veins was observed, as shown in Figure 2. Standard Echocardiographic views and velocity were recorded.

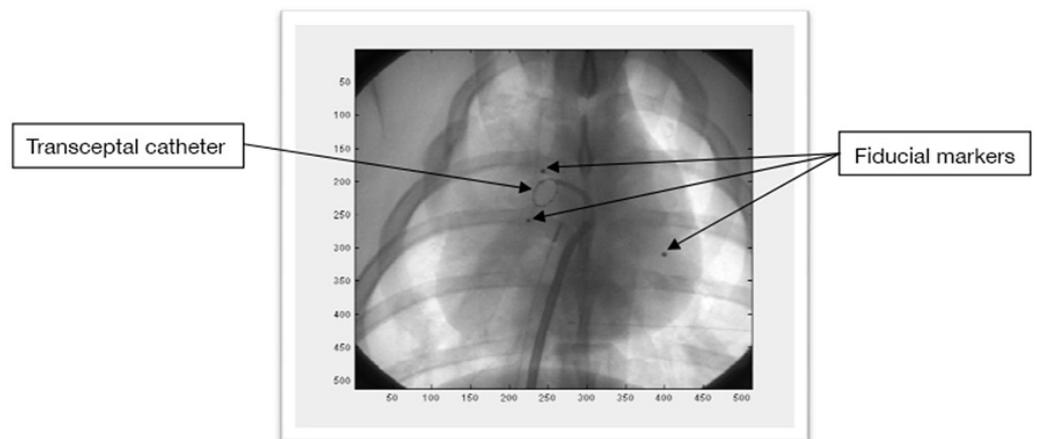


FIGURE 2: Antero-posterior fluoroscopic view of the heart with transeptal recording catheter in the right superior pulmonary vein and fiducials in place.

Prior to the termination of anesthesia, a transesophageal ultrasound probe was placed in the esophagus (just behind the heart) to monitor and record cardiac function prior to radiosurgical ablation.

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Treatment planning & delivery

CT images were transported to the MultiPlan 2.1 (Accuray Inc., Sunnyvale CA) treatment planning system, and contouring and treatment planning were performed. Two separate plans were delivered sequentially to each animal. All plans delivered dose to a single isocenter located in a pulmonary vein. In each animal, the right superior and left superior pulmonary veins were targeted. The collimator size was selected to deliver the prescription dose to a complete disk of pulmonary vein wall surrounding the isocenter. Parameters from the treatment plans are shown in Table 1.

Animal	Pig 1		Pig 2	
	RPV Plan	LVP Plan	RPV Plan	LPV Plan
Plan				
Prescription dose (Gy)	25	25	35	35
Collimator size (mm)	20	15	20	15
Beams	23	23	21	21
MU	6356	6597	9429	9810
Treatment volume (ml)	4.568	1.698	4.164	1.462
Maximum dose - combined plans (Gy)	32.98		44.42	

TABLE 1: Treatment Plan Parameters

The dose distribution for pig #1 is shown in Figures 3 and 4. The isocentric treatment resulted in a high dose gradient with doses on the left atrial wall between the two treated pulmonary veins falling below 10 Gy. The 3D surface rendering shown in Figure 4 clearly shows that the prescription dose forms a contiguous band surrounding the treated pulmonary veins.

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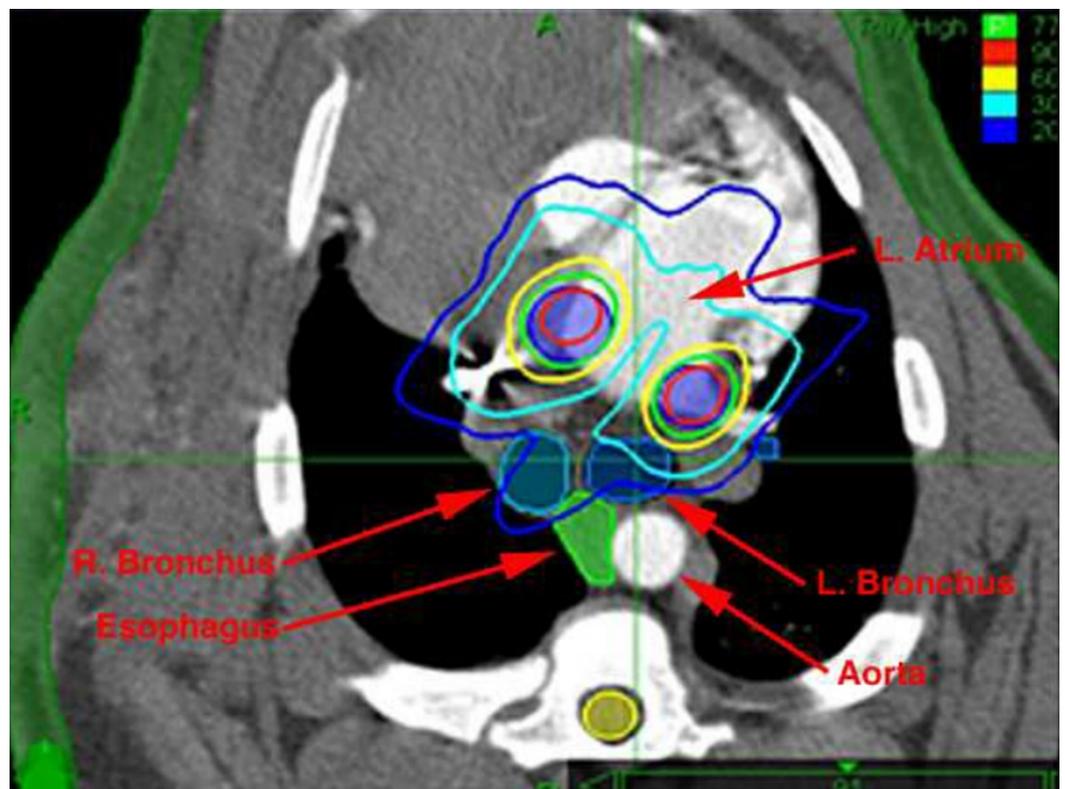


FIGURE 3: A MultiPlan Image showing the plan used to treat

Pig #1 with 25Gy.

The isodose contours show the regions receiving more than 6.5 Gy (dark blue), more than 9.7 Gy (light blue), more than 19.5 Gy (yellow), more than 25 Gy (green) and more than 29.2 Gy (red). The dark blue shaded regions indicate the isocentric targets.

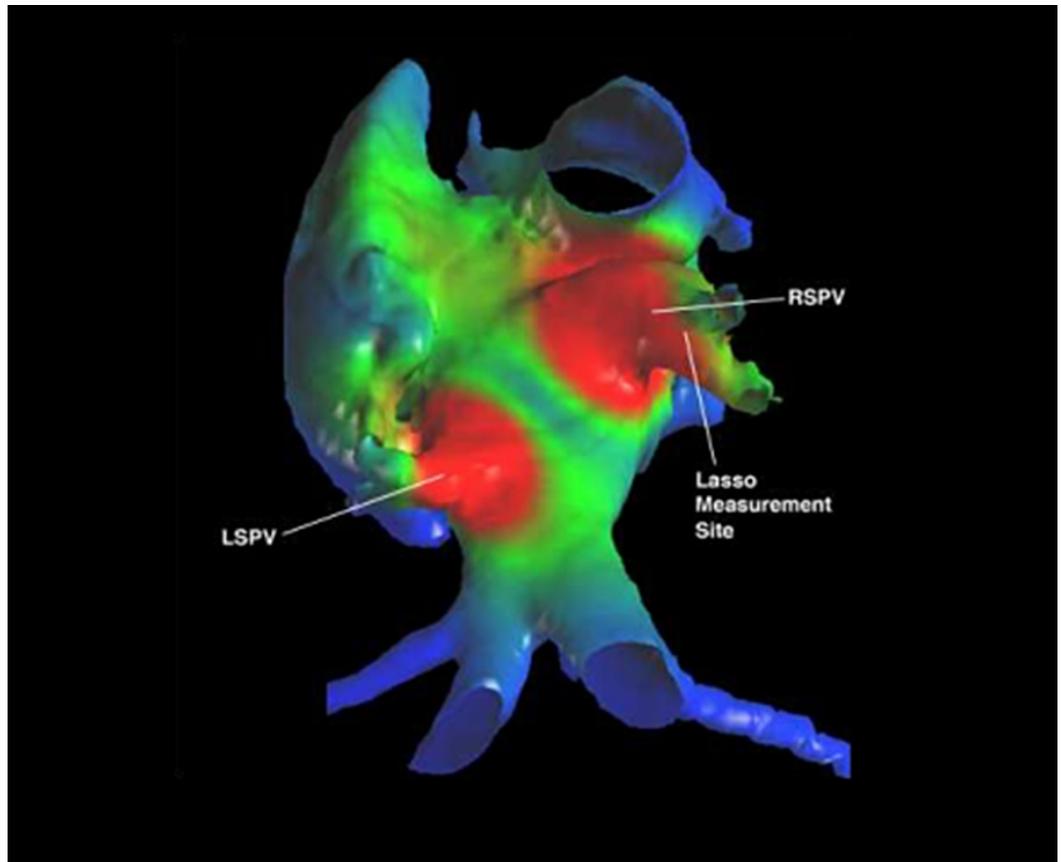


FIGURE 4: CardioPlan image of 25 Gy dose distribution on the LA surface. The surface is coded based on the dose it receives \pm 25 Gy in Red, 12.5 to 25 Gy in green, less than 12.5 Gy in blue.

The animals were irradiated with a CyberKnife system (version 7.3.1, Accuray Inc., Sunnyvale CA) equipped with an 800 MU/min linear accelerator. Target motion consisted of two components, the larger respiratory component and the lesser cardiac cycle component. Synchrony® was used to track the respiratory component of the heart motion during treatment while the lesser cardiac component was not tracked. The animal was recovered from the procedure and maintained under the care of the veterinary staff for the prescribed follow-up time.

Post-treatment electrophysiologic evaluation

At the completion of the follow-up period (6 months), the animals were anesthetized and brought to the cardiac catheterization lab. A six month follow-up was chosen to allow the heart tissue to respond to the radiation. A left heart catheterization was performed. The Lasso

catheter (10mm) was placed in the main Right upper pulmonary vein branch and a recording was taken in both animals. This was a similar position to the previous baseline study (documented by comparing pre and post ablation fluoroscopic images). Pacing was performed from all Lasso poles.

An electroanatomical map of the left atrium and pulmonary veins was performed using the CARTO® XP Mapping System and the "C" curve catheter (BioSense Webster, Diamond Bar, CA). In one pig 216 electroanatomical (EA) points were taken to record voltage potential and 227 EA points were taken in the second pig. The catheter was then withdrawn to the right atrium and a detailed map was performed, taking 98 EA points in the first animal and 87 EA points in the second.

Lastly, another transesophageal echocardiogram was performed to assess cardiac function post ablation. The animal was then euthanized.

Histopathology

Mediastinal organs were harvested, and the heart and lungs were pressure perfused with formalin prior to tissue processing by CV Path Institute. The entire heart was examined for gross abnormalities, especially the area of the pulmonary vein- left atrial junction where the ablation lesion was targeted. Each pulmonary vein ostium was opened longitudinally at the superior aspect on either side of the flow divider and gross photos were taken. "Flow divider" is defined as the central region of the left atrium separating the right and left pulmonary veins. For histology evaluation, both treatment regions were circumferentially and longitudinally (parallel to the blood flow) sectioned and entirely submitted. As shown in Figures 5, 6 each treatment site was labeled sequentially in a clockwise fashion from the superior most aspect of either the ostium of the pulmonary veins (right superior and middle pulmonary vein ostia (RSO), or common right inferior and left pulmonary vein ostia (CRILO), or the common flow divider between the two ostia (RSO-CRILO) to accomplish identification of the junction of the left atrium with the pulmonary vein orifices (the prescribed treatment region).

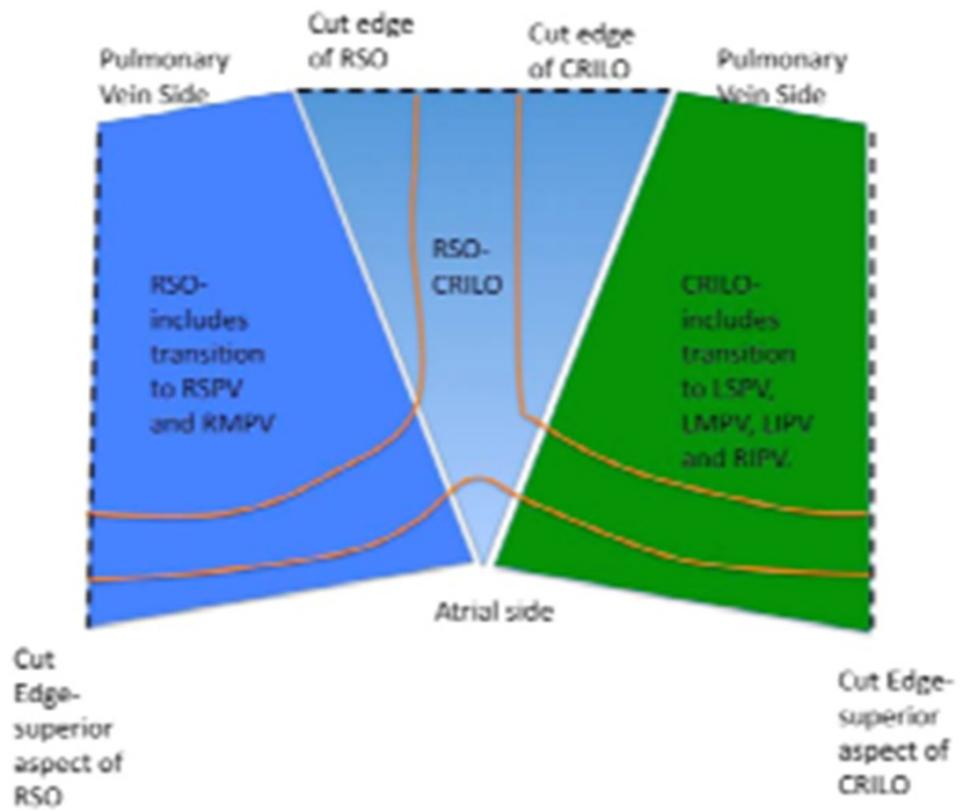


FIGURE 5: Histologic sectioning diagram of the left atrium.

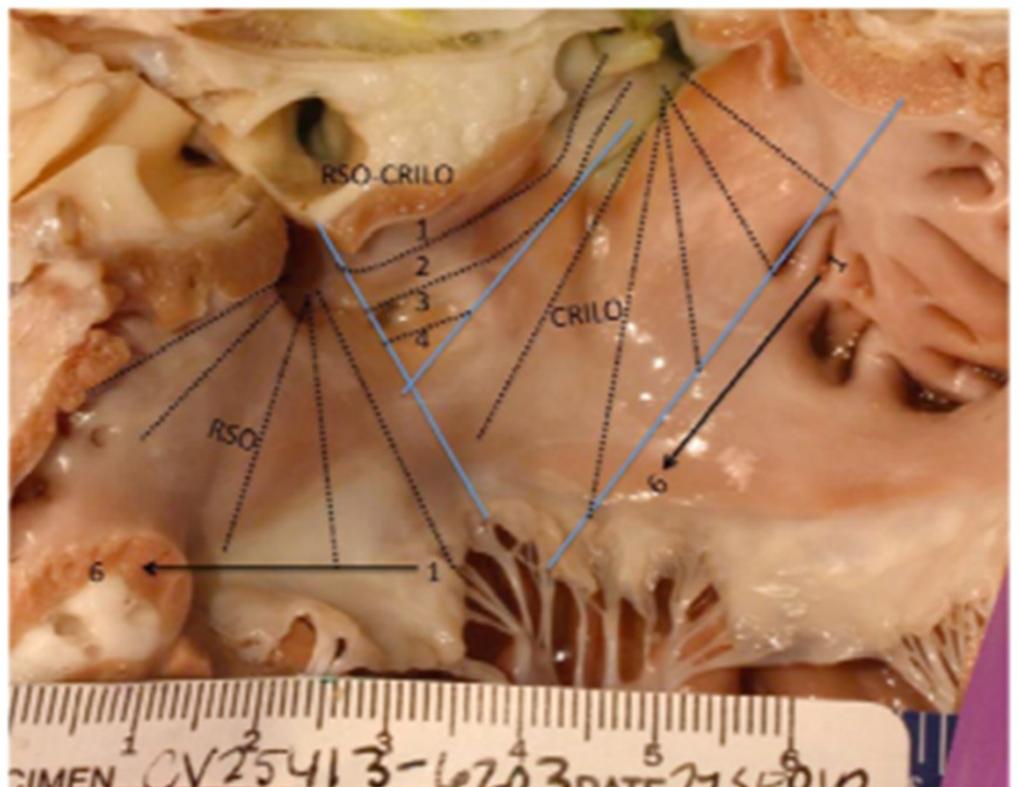


FIGURE 6: Gross image of sections evaluated in left atrium.

The blocks were submitted for paraffin processing. The paraffin blocks were cut on a rotary microtome at 4-5 microns, mounted on charged slides and stained with hematoxylin-eosin (H&E), Movat pentachrome, and Masson's trichrome stains. The slides of the pulmonary vein ostia were examined by light microscopy (Olympia BX41) and evaluated for radiation-induced injury, inflammation, hemorrhage, thrombus, fibrosis, and necrosis.

The esophagus and each lobe of lung were removed from the heart to be examined at a later date.

Results

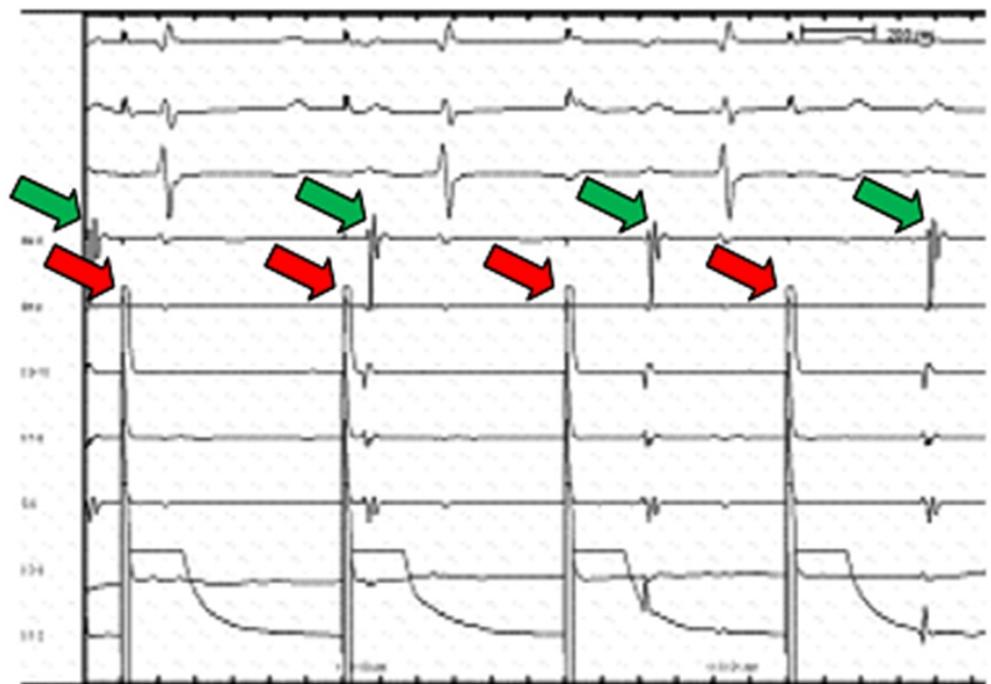
General health and echocardiographic findings

The animals survived all procedures and anesthetics without an adverse event and lived to the endpoint, 6 months post CyberKnife treatment.

Echocardiographic findings in both particular animal documented normal left and right ventricular contractility with no wall motion abnormalities. Trace mitral valve regurgitation was noticed on Doppler flow velocity examination on one animal.

Electrophysiologic results

In both pigs electrophysiologic assessment from all poles of the Lasso catheter demonstrated no electrical conduction from the right upper pulmonary veins into the antrum of the left atria (exit block). See Figure 7.

**FIGURE 7: The decapolar electrode recordings documents**

dissociation (block) of conduction in the ablation zone.

The CARTO voltage mapping system, as shown in Figure 8, documented low voltage (<1 mV) within the targeted ablation zone in the left atrium consistent with electrical block. Presence of exit block is consistent with pathology (scar), and thus mimicked the result achieved with catheter ablation (radiofrequency or other energy).

No procedural complications were observed.

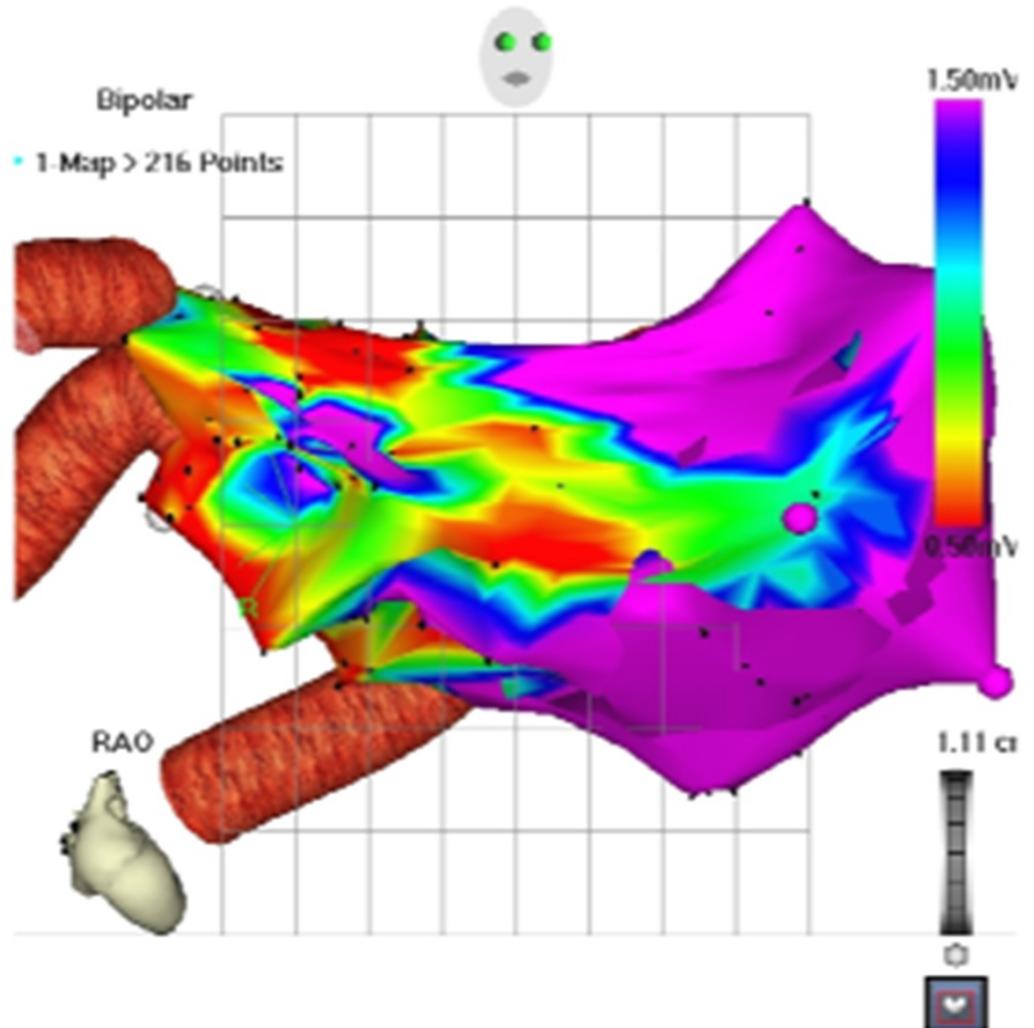


FIGURE 8: CARTO voltage map demonstrates area of low voltage corresponding to the focal ablation zone.

Histopathologic results

The histopathologic study evaluated the gross and histopathologic changes observed at 6 months following irradiation of two swine at 25 Gy or 35 Gy with the CyberKnife Radiosurgery System. Both hearts showed transmural myocardial scars consistent with radiation induced

injury in the left atrium near the right and left pulmonary vein ostia, as shown in Figure 9.



FIGURE 9: Movat pentachrome stain shows transmural myocardial lesion of the right pulmonary vein ostium.

In both animals, the sections around the right pulmonary vein ostia (RSO) showed transmural injury. The scarring showed a delicate interlacing pattern intermingled with varying degrees of persistent myocyte necrosis and vacuolar degeneration with pyknotic nuclei. There was mild persistent chronic inflammation and minimal hemorrhage within the lesions.

The higher dose animal (35 Gy) showed more extensive persistent myocyte necrosis and vacuolar degeneration compared to the lower dose animal. In addition a greater number in intramyocardial vessels demonstrated severe vasculitis with medial destruction, fibrinoid necrosis and luminal thrombi compared to the low dose animal.

Discussion

Atrial fibrillation, with its associated sequelae of stroke and cardiac failure, has reached epidemic proportions, particularly affecting the growing population of patients 60 years of age and older. Treatment modalities of drugs, surgery, and thermal ablation procedures have significant limitations. Therefore the potential use and benefits of a non-invasive radiosurgical procedure were investigated in these animal studies.

Despite the incidence of >2.6 million patients diagnosed with atrial fibrillation in the US annually [11], thermal catheter ablation is being offered to a small subset of patients. Data from catheter ablation clinical studies confirms ablation is best reserved for those patients early in their arrhythmia course, with only "paroxysms" of fibrillation episodes (paroxysmal atrial fibrillation). This figure represents >1 million patients per year in the US. The most recent

worldwide survey showed that catheter ablation has been proven to cure atrial fibrillation in variable proportions of populations. All centers in the survey performed ablation of paroxysmal atrial fibrillation, while fewer centers treated patients with advanced disease. 53.4 % of centers treated persistent AF, and 20% treated long- lasting AF. In this survey success without anti-arrhythmic drug therapy was based upon a median 1.3 procedures per patient over 18 months follow up. The complication rate was 4.5%.

Most patients receiving AF ablation procedures are young (<65 years), healthy, symptomatic, and have "healthy" hearts. The magnitude of the current ablation procedure (general anesthesia, atrial trans-septal catheterization, anticoagulation) eliminates many patients from catheter ablation procedure consideration. Patients with significant enlargement in atrial size, other complicating structural heart problems, atrial thrombus, and other co-morbidities are not candidates. There are no effective ablation strategies that can be offered to this population. In addition, limited success has been reported for catheter ablation procedures for patients with persistent or long standing AF. For these reasons the relative non-invasive use of radiosurgery may provide physicians another modality as part of a combination of drug and device therapy to address this growing need.

This study documents the creation of transmural and circumferential fibrosis correlated with electrical block following radiosurgery of cardiac tissue typically targeted in the catheter based treatment of atrial fibrillation. The study also confirmed the treatment was deliverable and safe for surrounding critical structures. Since fibrosis is considered the pre-clinical endpoint for treatment of arrhythmias with thermal based ablation procedures it may be construed that clinically radiosurgery may offer an alternative energy modality to "cure" atrial fibrillation.

The cardiac radiation effect of blocking electrical conduction had been shown experimentally in porcine and canine models by Guerra et al [12] and Perez-Castellano [13] using beta radiation seeds in a catheter directly applied to cardiac tissue. There is no report of such cardiac therapy using external beam for treatment of arrhythmias.

Over the past twenty-five years the gold standard for catheter ablation energy sources such as radio frequency and cryotherapy of atrial fibrillation has evolved to treat anatomic targets in the left atrium. Earlier in the development of ablation strategies, ablations had been performed based upon electrophysiologic mapping data. Given knowledge about the capabilities and accuracy of radiosurgery in treating moving targets the current use of anatomic targeting to treat AF, it appeared logical to attempt to use radiation as an alternative energy source to create specific lesions in the heart that mimic catheter ablation lesions. This technique has the potential to be used in a minimally invasive fashion without the use of general anesthesia and catheter manipulation inside the left chambers of the heart.

Radiosurgery has the potential to expand treatment options to patients with atrial fibrillation. Initially the treatment may be offered to patients with paroxysmal AF, older patients, patients for whom catheter ablation is not indicated, or those individuals who refuse a left heart catheter procedure. Radiosurgery may also prove successful beyond paroxysmal AF with patients experiencing persistent or long standing AF. Catheter ablation techniques have been less successful in these patient populations. Clinical data is needed and will likely alter the initial patient selection criteria.

It has been recognized that the heart may be damaged by substantial doses of radiation (>30 Gy) such as used to occur during mantle radiotherapy for Hodgkin's lymphoma in which a large volume of the heart was incidentally irradiated. [14] No pre-clinical or clinical radiosurgical studies data are available in which small volumes of cardiac tissue are intentionally targeted. Therefore these animal experiments were performed to investigate the accuracy and effect of

cardiac radiosurgical ablation.

In these animal studies, fiducials were surgically placed on the heart to track the target. Synchrony was used to track respiratory motion, and a margin was added to the target volume to compensate for cardiac motion. In humans, a temporary catheter, percutaneously placed in the heart, will be used as a fiducial for tracking. Imaging and phantom studies have confirmed accuracy of the technique, which will be reported in the future.

Conclusions

No good animal model exists to conduct a chronic study for atrial fibrillation. Animals cannot be sustained in atrial fibrillation and therefore animals treated have healthy hearts and are in sinus rhythm. Large animals such as porcine and canine models are required to study accuracy of radiosurgical treatments so that specific cardiac anatomy can be targeted and treated. Each model has significant shortcomings. Cardiac anatomy in both models is unique from humans. Pulmonary vein anatomy and the small vessel size often precludes placement of electrophysiologic catheters. The canine model is particularly poor for the study of cardiac radiosurgery due to the fact that motion of the pulmonary veins is far more extensive in dogs than human as a result of the incomplete formation of the pericardial sac. Porcine cardiac motion and alignment, although not the same as in humans, is more similar and provides a better animal model. Also, no comparative dose effect data among animal models is available for radiotherapy or radiosurgery in any organs, including the heart. Therefore, regardless of which animal model is used, clinical studies are needed to confirm safety and efficacy in humans.

Results from these animal studies were documented six months post radiation treatment. The potential exists for long term collateral damage that may result from radiation exposure to surrounding adjacent tissue such as the esophagus, the phrenic nerve, or the coronary arteries. In the future, long term clinical follow up will be important. The pre-clinical work recorded here and in other publications is leading to use of this technology in a human feasibility study.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** The Sutter Institute for Medical Research in Sacramento, CA Issued protocol number N/A. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** Patrick Maguire declare(s) an alternate financial activity from Cyberheart, Inc. President and CEO. Alice Jack declare(s) an alternate financial activity from Cyberheart, Inc. Executive Vice President. Edward Gardner, Luis Fajardo, Amin Al-Ahmad, Paul Zei, Patricia Takeda, and Elena Ladich declare(s) an alternate financial activity from Cyberheart, Inc. Consultants. **Intellectual property info:** There are provisional patents owned by CyberHeart Inc. The authors have no patents. **Other relationships:** All animals were treated with care in accordance with the “Principles of Laboratory Animal Care” formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and approved by the local animal care committee.

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