Catheter-free arrhythmia ablation using scanned carbon ion beams in a porcine model

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Introduction

Cardiac arrhythmias are a wide-spread disease associated with reduced quality of life, increased risks of stroke and sudden cardiac death. Catheter ablation and isolation of arrhythmogenic structures in the heart is the current standard treatment, but is invasive, complex, and shows varying effectiveness especially for progressive disease.

The most common form is atrial fibrillation (AF), a too fast and ineffective contraction of the atria. AF often originates from the pulmonary veins (PV) and can be cured by isolating the veins. For persistent AF, the ablation of the AV node can be a last resort to prevent the AF from affecting the ventricles.

The irregular scars caused by an infarct can lead to ventricular tachycardia (VT), which can cause sudden cardiac death. Homogenizing the scars can cure VT, but is difficult in the left ventricle, where the thick muscle tissue cannot be penetrated completely with catheter ablation.

In this study, scanned carbon ions were investigated as a non-invasive alternative to induce the required electrically isolating fibrosis in the myocardium.

Material and Methods

Eighteen pigs were randomized to irradiation of AV node (AVN), LA-PV junction (PVI), freewall LV, and sham-AVN. Prior to treatment, mapping of cardiac electrophysiology (EP), fiducial marker, and pacemaker implantation were performed at the University of Heidelberg. Cardiac 4DCT images were acquired both with and without contrast agent at HIT Heidelberg. Target and organs-at-risk (OAR) were contoured on the contrast enhanced CT, also used for deformable image registration. The resulting vector maps were transferred to the native 4DCT for treatment planning with GSI's TRiP4D.

PVI and LV were targeted using 40 Gy. AVN was targeted with 25, 40, and 55 Gy. For AVN and PVI, field-specific ITVs were calculated from the 4DCT after adding 5 mm isotropic margins. For LV, only range margins of 2 mm and 2% were used. Up to 15 rescans were applied to counter interplay.

Pigs were anesthetized, respirated, and positioned in a custom-built fixation. Both imaging and treatment were carried out under enforced breath-hold at end-exhale. All animals were irradiated using two opposing fields at GSI Cave M, monitored by online PET. In-room time was in the order of 1.5 to 3h, with most time used for positioning with orthogonal X-rays.

Animals were followed for up to 6 months with extensive analyses ongoing. Skin biopsies were taken before irradiation and in the final follow-up. Skin reaction was closely monitored for up to 12 weeks. Blood samples were collected before and after 4, 8, 12 and 24. The final follow-up included detailed electrophysiological mapping and macroscopic pathological examination.

Cardiac tissue obtained from the targeted area, and areas in the entrance channel of the beam, and out of the beam field, were fixed in 4% formaldehyde and processed for histological analysis or fixed on dry-ice for protein extraction. Control samples of the heart which were not irradiated were also taken.

Results

Analysis of PET images showed accurate targeting. 4D-dose reconstruction showed successful motion mitigation.

After 3 and 6 months, electrophysiological changes and scar formation were observed in the LV target regions. After 4 months, complete AV-block was detected in 40 and 55 Gy animals on surface ECG, persisting until study end in the 55 Gy animal. Lesion formation for PV isolation was almost completely achieved in one animal, leaving only a small gap detectable in EP mapping.

First histological analysis revealed fibrotic changes, i.e. the presence of fibroblasts instead of cardiomyocytes and proteins of the extracellular matrix in tissue 3 months after treatment. The sham control showed a well-organized structure of cardiomyocytes.

A total of 3 animals died from pacemaker infection, 2 further showed signs of infection during the follow-up, with one of those animals from the sham group No irradiation-induced side effects in organs at risk such as skin, oesophagus, aorta or trachea were observed.

Discussion

In conclusion, this study showed the feasibility of non-invasive arrhythmia ablation using scanned carbon ion beams. The ongoing evaluation of tissue samples, in the target and non-target area, will reveal the late effects and radiobiological mechanisms: cell death, inflammation, changed signal transmission, vascular damage, and fibrosis. Together with more detailed electrophysiological analysis this data will form an important foundation for future studies and eventual clinical application.

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