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EXPERIMENTAL USE OF STEREOTACTIC RADIOSURGERY FOR NON-INVASIVE INTERVENTIONS IN ARRHYTHMOLOGY

V.A.Vaskovskiy[1], I.A.Taymasova[1], D.V.Kalinin[1], N.A.Antipina[2], A.A.Nikolaeva[2], G.Y.Smirnov[2], A.V.Golanov[2], A.A.Potapov[2], A.Sh.Revishvili[1]

[1]A.V.Vishnevsky National Medical Research Center of Surgery, Russia, Moscow, 27 Bolshaya Serpukhovskaya str;
[2]N.N.Burdenko National Medical Research Center of Neurosurgery, Russia, Moscow, 16 Four Tverskaya-Yamskaya str.

Purpose. The experimental study aimed to study the effects of stereotaxic radioablation of various doses on the myocardium of the atria, ventricles and atrioventricular (AV) node in the long term (up to 6 months); as well as assessment of collateral damage during radioablation.

Methods. The study comprised 4 domestic pigs. The animals were 10-12 weeks old, the average weight was 30±2.7 kg. A linear accelerator was used for the experiment. Each animal underwent radiation exposure in different areas: 1st animal - AV node (dose 35 Gy), 2nd animal - AV node and the apex of the left ventricle (LV) (dose 40/35 Gy, respectively), 3rd animal - pulmonary veins (PV) and left atrium (dose 30 Gy), 4th - AV node and LV free wall (dose 45/40 Gy). Under intravenous sedation with hemodynamic monitoring, contrast-based CT of the heart was performed to assess the degree of displacement of the heart chambers in one respiratory and cardiac cycle and to assess the anatomy of the chambers of the heart and adjacent organs. The allocation and the contouring of the target zones were carried out in three projections: axial, frontal and sagittal. For electrocardiographic control, a loop recorder was implanted in each animal. The average exposure time was 11±7 minutes. After a follow-up period, morphological examination of the autopsy material was performed.

Results. The average follow-up period after ablation was 134.75±77.34 days. The electrophysiological effect of the ablation was achieved in cases of complete AV-block development. This effect was developed in 2 out of 3 animals, where AV-node was exposed: 2nd animal - 40 Gy on 108th day of observation and 4th animal - 45 Gy on 21st day of observation. No cardiac tachyarrhythmia was recorded in the animals. The results of myocardium macro- and microscopic examination showed significant changes in the target zones. These areas had precise but uneven damage boundaries, which were within the planned ones (conformal exposure with a high degree of precision). The transmural nature of the changes was noted as well. Massive fields of fibrous tissue of various degrees of maturity (with a predominance of subepicardial localization) with focal hemorrhages of various ages and granulations were detected, which were surrounded by cardiomyocytes with coagulated and vacuolated cytoplasm.

Conclusion. The use of non-invasive stereotactic treatment of tachyarrhythmias has high prospects in modern electrophysiology as an alternative ablation method.

Key words: stereotactic radioablation; ventricular tachycardia; noninvasive ablation

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Corresponding author: Valentin Vaskovskiy, E-mail: vvaskov03@mail.ru

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The high prevalence of tachyarrhythmias has emerged the need of developing novel treatment approaches. They are primarily focused on optimizing the existing methods by improving their efficiency and ensuring their safety.

The introduction of catheter ablation in the early 1990s has revolutionized treatment for tachyarrhythmia and shown superior clinical outcomes. It is almost 100% effective for treating patients with Wolff-Parkinson-White syndrome. Catheter ablation is recommended to patients with arrhythmias in the national and international clinical guidelines with a high level of evidence and clinical support for efficacy and safety. However, catheter ablation may be furtherly optimized [1] for patients with long-standing, persistent, and paroxysmal atrial fibrillation (AF). The long-term success of interventional catheter ablation for treating long-standing AF varies from 10% to 15% and for paroxysmal AF - from 50% to 70% [1, 2]. Radiofrequency ablation (RFA) is used to perform an electrophysiological examination, treat and prevent ventricular tachycardia (VT) in patients with ischemic cardiomyopathy [3]. RFA is the first-line treatment for polymorphic and monomorphic VT in patients with implantable cardioverter-defibrillators (ICD) and repeated shocks from ICD due to sustained VT [4]. The 3-year freedom from VT recurrence in patients with ICD varies from 20 to 48%. RFA can fail because of inaccessibility to the VT substrate, the large volume of interest, the transmural heterogeneity of ventricular myocardium with the thickness over 30 mm [4]. Hemodynamic instability precludes mapping during VT and may require the placement of the patient on extracorporeal circulation [5].

These patients commonly suffer from severe concomitant diseases, such as chronic heart failure, respiratory and renal failure. The presence of comorbidities increases the risk of procedure or becomes an absolute contraindication to RFA.

Mechanical trauma to the atria and ventricles (resulting in cardiac tamponade) and adjacent organs (atrial-oesophageal fistula, phrenic nerve) are recognized as the major risks of catheter ablation of tachyarrhythmias. It is also associated with an increased risk of periprocedural stroke, transient ischemic attack, and air embolism. The incidence of these complications can range from 0.6% to 3% with a mortality rate of 0.1% [6]. In addition, interventional procedures are time-consuming and require the need of fluoroscopy.

Recently stereotactic radiotherapy of malignant foci using cobalt-60 machines, medical linear accelerators (LIBAC) and heavy charged particles has become a promising modality for treating oncology. Novel technologies allow shaping the high-dose radiation beam to conform to the target volumes with high precision and selectivity. The delivery of conformal radiation minimizes the radiation exposure on the adjacent healthy tissues and minimizes acute and delayed radiation complications [7]. Jean Regis and John Adler, well-known experts in stereotactic surgery, have proposed the concept of neuromodulation to provide the rationale for functional radiosurgical interventions for hyperkinesis and pain syndromes. The radiation-induced neuromodulation principle suggests that the delivery of high doses of ionizing radiation allows both, the formation of a focus of destruction and the modulation of the function. Non-invasive stereotactic treatment using linear electron accelerators can be considered as a promising alternative to catheter ablation in patients with tachyarrhythmias. The beneficial potential of stereotactic therapy has been demonstrated in several experimental and clinical studies [8].

The high efficacy and safety of stereotactic radiotherapy using electron and proton accelerators, accurate navigation systems, digital methods for dose planning and distribution, precisely delineating anatomical structures, and motion tracking have opened new horizons in the treatment of respiratory and cardiovascular disease. Since oncologists and arrhythmologists share the single task to damage pathological tissues, promote the progression of fibrosis with the resultant conduction block, the green light has been given to the experimental and preclinical studies on radioablation to treat tachyarrhythmias. Several research groups have shown promising results of radiation-induced damage to arrhythmogenic cardiac tissues in animal experimental studies.

Our study is aimed at developing a novel radioablation technique to perform radiation-induced damage to arrythmogenic cardiac tissues and assessing the long-term accuracy, efficacy, and safety of radiation exposure in a porcine model.

MATERIAL AND METHODS

The experimental study was performed in the A.V.Vishnevsky National Medical Research Center of Surgery and N.N.Burdenko National Medical Research Center of Neurosurgery following the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes and the requirements of the All-Union State Standard ISO 10993-2.

A total of four pigs, two males, and two females Sus scrofa domesticus pigs, were used in the study. Animals were aged 10-12 weeks with a mean weight of 30±2.7 kg. Radioablation was performed in the period from December 2019 to February 2020. All animals underwent irradiation at the predetermined target zones. Animal 1 was irradiated with 35 Gy at the AV node. Animal 2 received radiation exposure at the AV node area and the left ventricular apex with a 40/35 Gy dose of radiation, respectively. Animal 3 underwent radioablation of the pulmonary vein orifice and left atrium with 30 Gy dose exposure. Animal 4 underwent radioablation of the AV node and the left ventricular free

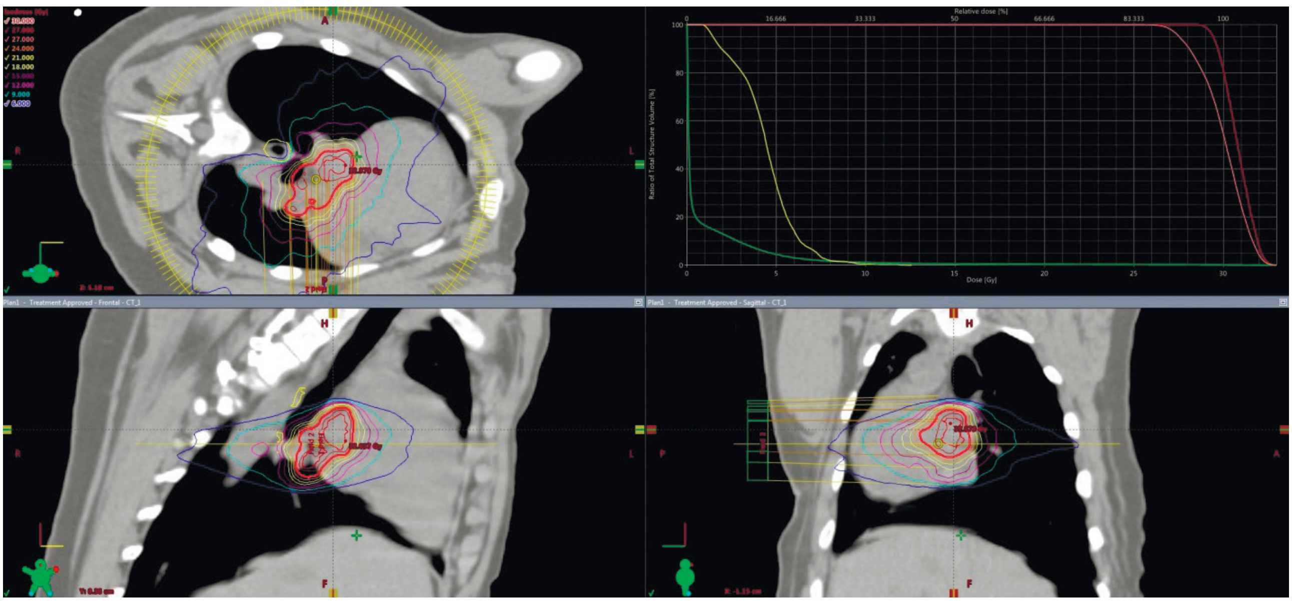

Fig. 1. Radioablation planning. Contouring of the target exposure area (pulmonary veins). The figure shows a series of CT scans of a pig's heart in three planes. The esophagus is marked with a yellow outline. According to the dose planning and distribution, the target volume (red curve) is irradiated with a given high dose, creating a dose fall-off at the esophagus (yellow curve) and minimizing the radiation exposure.

wall with 45/40 Gy dose exposure, respectively. Stereotactic radiosurgery doses were delivered by a TrueBeam STx linear accelerator (Varian, USA).

Animals were sedated with i.v. ketamine 4.4 mg/kg, zoletil 2 mg/kg. Animals were on spontaneous breathing with the supply of humidified oxygen. The following hemodynamic parameters were monitored: blood pressure, heart rate, SaO_2, and respiration rate. Laboratory animals were then immobilized on a special vacuum mattress. First, multislice computed tomography (MSCT) was performed. To ensure accurate target tracking during cardiorespiratory motion, native CT scans were recorded to mark the region of interest (Fig. 1). Contrast-enhanced CT scans were recorded to assess the anatomy of the heart chambers and adjacent organs. The tracking of the target zone was then performed using the MSCT image series in the axial, frontal, and sagittal planes. Treatment planning was performed with the Eclipse Treatment Planning System software (Varian, USA). The target zone was marked on each series of images with a step of 1.25-1.3 mm. A margin of up to 5 mm was extended from the target outline for untracked respiratory and cardiac motion (Fig. 2-5). The target zone was then assessed using the following parameters: gross target volume (GTV, the volume of the target zone that can be seen with the help of imaging), planning target volume (PTV, the final volume containing GTV and the additional margin of up to 5 mm), the proximity of critical structures to the region of interest (esophagus, lung tissue) (Fig. 1).

After all the parameters had been calculated, animals underwent radiation exposure. The characteristics of the target zones and exposure parameters are presented in Table 1. The mean exposure time was 11±7 minutes. There were no intraoperative complications. The next step included the implantation of a loop recorder (Reveal, Medtronic, USA) into the right lateral region of the chest to monitor the rhythm remotely during the follow-up (transmission of recordings every 14 days). The device programming parameters were as follows: pause episode detection - 1,5 sec, AT/AF detection, VT detection >300 ms.

The follow-up period was 6 months. At the end of the follow-up, animals were sacrificed. Biopsied tissues were referred to as morphological, macroscopic, and microscopic studies. All samples were documented by photographs, cut transversely into slices through 1,5 cm, and then fixed in 10% formalin solution buffered to pH 7.0-7.2 for 48 hours.

Biopsied tissues were taken from the target zones (a full-thickness sample of the heart, including the pericardium, myocardium, and endocardium, cardiac conduction system, including AV node, coronary arteries, and heart veins) and adjacent organs and tissues (lungs, esophagus, bronchi, peribronchial lymph nodes). A total of 167 samples were collected. Samples were placed in tissue cassettes and fixed then in 10% formalin solution buffered to pH 7.0-7.2 for 24 hours, washed with running tap water, and dehydrated with graded series of alcohol. Samples were embedded into paraffin blocks according to the standard protocol and then cut into 3-µm thick sections using an automatic rotary microtome HM 355 S (Thermo Scientific, Germany). Samples were mounted onto glass slides (Gerhard Menzel GmbH, Germany) and stained with hematoxylin and eosin according to the standard protocol. In addition, Masson trichrome staining and van Gieson's staining were performed to identify type I-IV collagen fibers. Periodic acid Schiff staining was performed to detect glycopolysaccharides in the cells of the cardiac conduction system.

The main objectives of the histological assessment included the examination of the conformity and homogeneity of exposure, as well as the evaluation of the electrophysiological effects following stereotactic radioablation.

RESULTS

The mean follow-up period after the indexed procedure was 134.75±77.34 (max. 189 days - min. 20 days) days. Animals 1, 2, 3 underwent the entire follow-up period of 6 months.

AV node radioablation

Macroscopic findings suggested that the presence of evident changes in the AV node area induced by radiation exposure. The changes had clear but rough boundaries that did not exceed the PTV. The exposure zone calculated in the planning system completely coincided with the resultant exposure zone, i.e. radiation exposure was precise

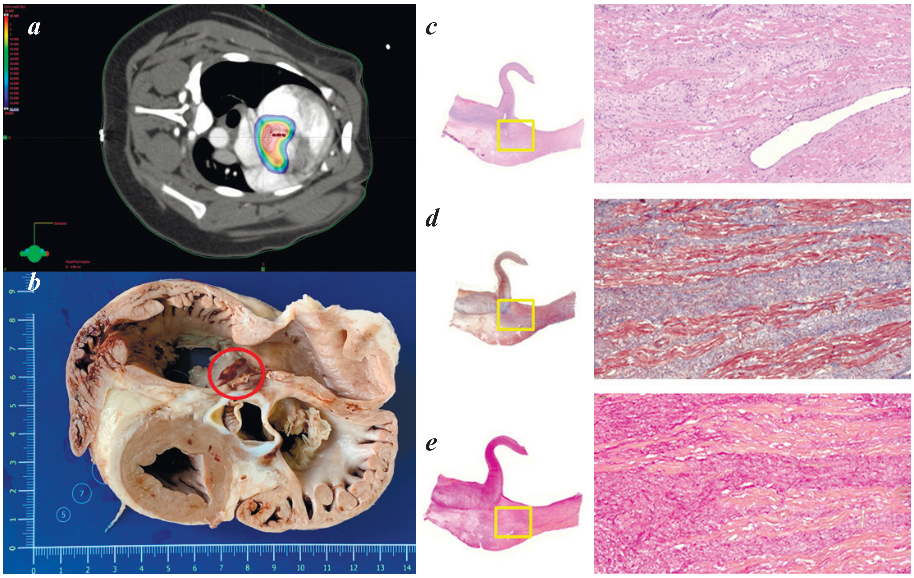

Fig. 2. a: Dose distribution in the target zone (AV node) and adjacent tissues on a series of contrast-enhanced CT scans of the pig heart in the axial plane calculated in the treatment planning system. b: A macroscopic sample of the porcine heart. The red circle marks the irradiation area. A microscopic sample of the AV node tissue after radiation exposure. c: hemotoxylin-eosin staining. d: Masson's trichrome staining. e: van Gieson's staining. Magnification: 40-200. AV node - atrioventricular node, CT - computed tomography.

(Fig. 2 a, b). Conformity of irradiation was achieved in all animals (animals 1, 2, 4).

Microscopic examination reported evident changes in all layers of the AV node area with mature granulation tissue among unchanged myocardial fibers (Masson trichrome staining and van Gieson's staining (Fig. 2 c, d, e). AV node samples proved that some cardiomyocytes were completely torn with resultant coagulation and vacuolization of the cytoplasm, suggesting acute stress response. Histological changes were more pronounced at a maximum radiation dose of 45 Gy.

Single intact cardiomyocytes from the conduction system were determined in the same zones.

The Reveal Insertable Cardiac Monitor showed that animals 2 and 4 had third-degree AV block. None rhythm or conduction disturbances were recorded in animal 1 within the follow-up. Animal 2 had transient third-degree AV block mainly overnight: the minimum heart rate was 16 beats per minute with the rhythm pauses over 2 secs. A total of 1,868 episodes were recorded within 173 days. The maximum duration of transient third-degree AV block was 42 mins. The AV block was first detected on day 108 after the implantable cardiomonitor implantation (Fig. 3). Animal 4 died on day 21 from asystole due to the development of a complete AV block.

Pulmonary vein radioablation

Macroscopic examination reported the presence of hemorrhagic impregnation and calcification deposits. The

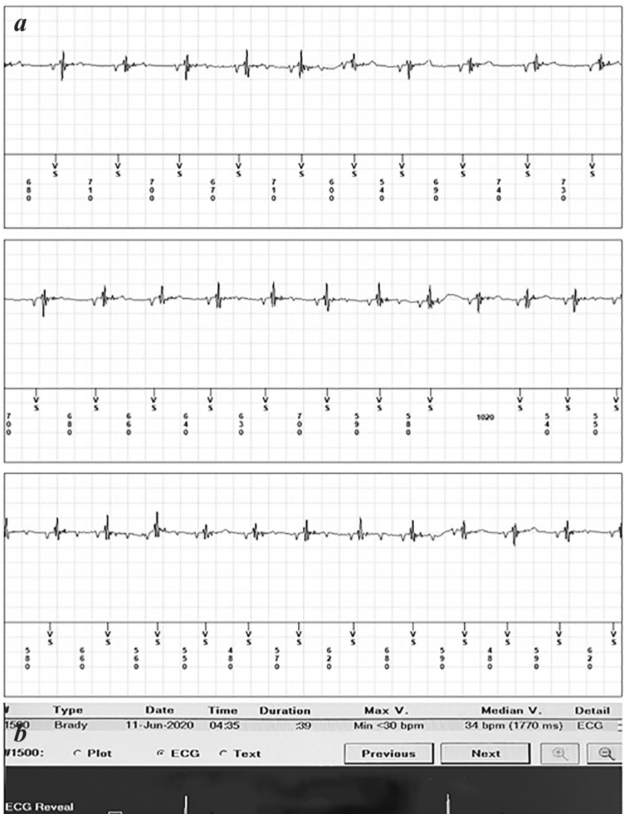

Fig. 3. a: ECG recorded with the Reveal ICM on day 1 of the experiment. The rhythm is sinus, the heart rate is 100 bpm. b: a single-channel ECG was recorded with the Reveal ICM on day 108. An episode of transient complete AV block is recorded with a heart rate of less than 30 bpm.

exposure zone in the planning system completely coincided with the resultant radiation exposure proving its high conformity.

Histological findings of the sample collected from the pulmonary vein orifice area and the thickness of the left atrial wall showed the presence of calcification foci, edema, and loose connective tissue after radiation exposure. Focal edema was found in the region of the myocardial stroma. None necrotic and fibrotic regions were found in the adjacent organs (lungs, esophagus, bifurcation lymph nodes) (Fig. 4).

No rhythm or conduction disturbances were recorded in animal 3 within the follow-up.

Left ventricular free wall and interventricular septum radioablation

Macroscopic examination reported clear boundaries of the exposure area, almost consistent with the PTV calculated before the procedure (animal 2 underwent the irradiation at the left ventricular apex and the part of the interventricular septum; animal 4 underwent the irradiation at the LV free wall (Fig. 5).

Histological examination of the myocardium at the left ventricular apex and interatrial septum (animal 3) reported transmural fibrosis of varying maturity degrees (mostly subepicardial) with hemorrhages of multiple ages and granulations surrounded by cardiomyocytes with coagulation and vacuolization. Samples collected from animal 4 reported the presence of granulations, necrosis, transmural fibrosis with the regions of calcification and hemorrhages (Fig. 5). Importantly, the anterior interventricular artery, partially passing through the exposure target zones, had no signs of damage and was not thrombosed. However, edema and partial destruction of the integumentary plate were found in the subendothelial zone increasing the risk of parietal thrombosis in the long-term period (Fig. 5).

No ventricular arrhythmias were recorded with the Reveal device in animals 2 and 4. Animal 4 died from asystole due to a complete AV block on day 21 of the follow-up.

Macroscopic examination confirmed high-precision radiation treatment with superior conformity.

Microscopic examination reported the presence of transmural lesions with necrosis and calcification, suggesting the production of homogeneous damage to the myocardium, followed by the formation of fibrosis.

The loop recorder reported that the radiation exposure at a dose of 35 Gy did not allow achieving stable electrophysiological effects, whereas 40-45 Gy doses produced AV blocks of varying severity.

DISCUSSION

The first report on the use of radiosurgery for treating arrhythmias in the experimental study was published by Sharma et al. in 2010. Sixteen mini pigs underwent radioblation with 25-80 Gy doses of exposure using the CyberKnife robotic stereotactic system (Accuray Inc., USA) with predetermined targets at the cavotricuspid isthmus, AV node, the left ventricular free wall, pulmonary veins, and left atrial appendage. Electrophysiological mapping was performed with the epi-endo approach using the navigation mapping system CARTO (Biosense Webster. USA) before and after the procedure. Two animals in the group of AV node exposure underwent pacemaker implantation. The long-term follow-up period was 6 months. The bidirectional cavotricuspid block was seen at 40 Gy one month after exposure. Energy ranged from 38Gy to 80 Gy and pulmonary vein–left atrial junction and left atrial appendage showed marked voltage reduction to less than 0.05 according to EPI data at 35 days. AV block was produced in one animal with a radiation exposure dose of 70 Gy at 49 days (one of the two animals was excluded from the study due to the infection at the site of pacemaker implantation). No other organ damage was seen. Despite the exact underlying mechanism affecting tissues and promoting cell damage that had not been determined, it provoked cell apoptosis and immune-inflammatory processes. Histological examination reported vacuolization, eosinophilic infiltration, vasculitis, ischemic damage with the development of fibrosis, and subsequent calcification of the exposure substrate. The absence of the thermal damage suggested the preservation of the vascular endothelium preventing capillary and arterial bed thrombosis [9]. In our study, the alteration of electrophysiologic properties was achieved earlier at a lower exposure dose (transient AV block was produced at 40 Gy within 108 days. A dose of 45 Gy resulted in the animal death from sudden cardiac arrest (third-grade AV block) on day 21 day. Histological examination revealed similar changes in the affected areas as reported by Sharma et al.

M.Refaat et al. (2017) assessed the effectiveness of the stereotactic radioablation of the AV node with various loading doses from 35 Gy to 40 Gy in a porcine model. Alterations of electrophysiological properties were recorded by the implanted pacemaker. AV block was produced within 2 months after stereotactic radioablation. Biopsied tissues included AV node tissues and adjacent organs. The histological assessment reported severe architectural disruption with loss of the smooth cellular organization, in addition to cellular necrosis and extensive fibrin deposition in the area. Sections from the surrounding tissues, however, including the liver, esophagus, and lungs, showed normal architecture [10].

P.C.Zei et al. (2018) assessed the feasibility of performing stereotactic radioablation of the pulmonary vein orifices with treatment doses ranging from 15-35 Gy using a canine and swine model. Before and after stereotactic irradiation, electroanatomic mapping of spike activity zones in the pulmonary vein orifices was performed with Carto 3 (Biosence Webster, USA). Control electroanatomical mapping was performed at months 3 and 6 after the indexed procedures. The effectiveness of pulmonary vein isolation was 100% in the groups with exposure doses of 25 and 35 Gy, while reduced to 80% in the group with an exposure radiation dose of 20 Gy. Stereotactic radioablation was ineffective at a dose of 15 Gy [11].

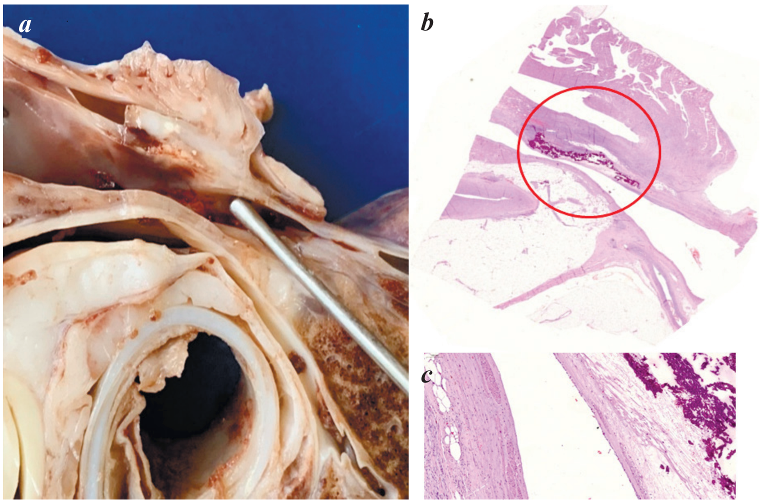

Fig. 4. a: A macroscopic sample of the pulmonary vein orifice after radioablation. b: A microscopic sample stained with hematoxylin-eosin. c: A magnified region marked with the red circle represents the affected area, stained with hematoxylin-eosin. Magnification: 40-200.

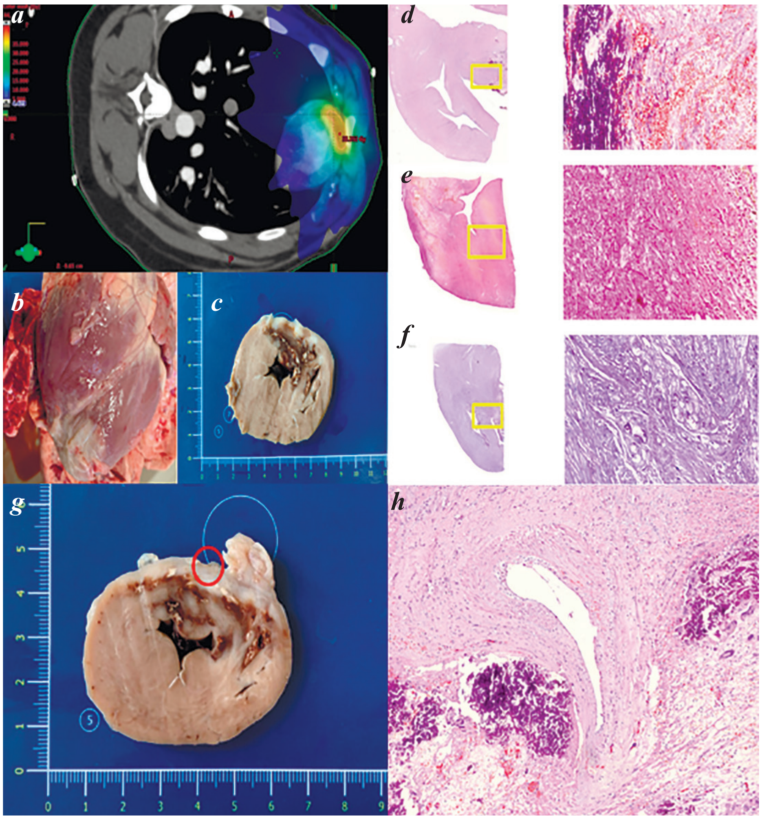

Fig. 5. Left upper images: a: The porcine left ventricular apex on contrast-enhanced CT scan in the treatment planning system. b: A macroscopic sample of the porcine heart. Fibrosis in the area of the apex. c: A macroscopic sample after radioablation. The modified area corresponds to the affected area. Right upper images: a microscopic sample of the left ventricular apex after radioablation. d: hematoxylin-eosin staining. e: van Gieson's staining. Magnification: 40-200. f: PAS staining. Bottom images: g: A macroscopic sample of the porcine left ventricle after radioablation. The red circle denotes the LAD projection. h: A microscopic sample of the left ventricular wall at the LAD level. Hematoxylin-eosin staining. Magnification: 200. LAD – left anterior descending artery.

Two studies conducted by research groups from Germany and the United States described similar effects. They used a porcine model (n = 17) and the same study design to assess the effectiveness of stereotactic radioablation using a linear carbon beam. I.Lehmann et al. (2016) divided 17 pigs into 4 groups according to the pretreatment zones. Group 1 underwent the radioabaltion of AV node with the application of 25, 40, and 55 Gy doses of (n = 8). Group 2 underwent irradiation of the right superior pulmonary vein with an exposure dose of 30-40 Gy (n = 3). Group 3 received irradiation of the left ventricular free wall with an exposure dose of 40 Gy (n = 3). Three animals were included in the control group. Irradiation was performed at the GSI Helmholtz Centre for Heavy Ion Research (Darmstadt, Germany) using a single horizontal beam line. The median follow-up was 20.3 weeks. Long-term results were assessed using positron emission tomography and electrophysiological studies at 1, 3, and 6 months after the indexed exposure. Histological assessment was performed to determine achieved effects. In two out of six animals, both irradiations with 55 and 40 Gy led to complete AV block. In the animal that developed complete AV block following 40 Gy, the block was not persistent until the end of follow-up at six months. Three animals were excluded from the study due to the infection at the site of pacemaker implantation. Researchers supposed that the obtained results were associated with the target contouring complexities (AV node). The pulmonary vein exposure resulted in a decrease in spike activity, including in the acute period at all doses delivered. When exposed to the left ventricular free wall, the accuracy of exposure was assessed using positron emission tomography and histological examination. Ablation lesions of the left ventricle were consistent with those of radiation exposure [12].

F.Rapp et al. focused on the pathology and pathomorphology of radiation injury. No radiation-induced effects on the esophagus, trachea, phrenic nerve, and skin were observed by histological and immunohistochemical examination suggesting the precision and selectivity of stereotactic radioablation. Coronary arteries in the treated area were not damaged and thrombosed. Hemorrhagic impregnation of the myocardium at the treated area with the migration of macrophages and sideroblasts was found. This finding positively correlated with radiation exposure. Immunohistochemical stainings were used to identify activated T-cells (CD45+), demonstrating that inflammatory reactions were mostly present in tissues irradiated with higher doses, and in regions where the tissue was visibly damaged. It is typical for the severity of fibrosis (the degree of collagen deposition) and myocytolysis [13].

Stereotactic radioablation has shown promising results in the treatment of tachyarrhythmias and may be considered as an alternative method for treating patients refractory to the catheter and medical treatment and those with contraindications to interventional procedures. Further development of this technology requires both experimental and extended clinical studies to accurately determine its effectiveness and safety. There are still gaps that should be addressed in further studies: the required therapeutic doses to produce functional and homogeneous damage to the myocardium at different localizations; ensuring the accuracy of irradiation concerning cardiorespiratory motion; possible reversibility of the produced myocardial injury; possible proarrhythmia of the treatment; the potential of producing a true (pathogenetic) antiarrhythmic effect.

LIMITATIONS

Our study had several limitations: a small number of animals included in the study, a significant difference in the anatomy of the heart and the location of adjacent organs from the human heart, although the pig heart is a generally accepted model for experimental research in cardiac surgery and arrhythmology, and delayed radiation side effects that are needed to be assessed when calculating the risks-benefit ratio. We did not use radiation doses over 50 Gy. Since the loop recorders were implanted immediately after the intervention, we could not exclude the presence of rhythm disturbances in animals before the procedure. We could evaluate the postmortem autopsy material, but could not monitor radioablation effects in the PV and ventricles using electrophysiological control in the mid- and long-term period. Electrophysiological control will be implemented in our future study.

Table 1.

Treatment planning parameters for all dose groups and targets

	№1	№2		№3	№4	
Date of experiment	7.12.2019	21.12.2019		18.01.2020	1.02.2020	
Gender	male	female		male	female	
Target zone	AV node	AV node	LV apex	PV	AV node	LVFW
Doze of radiation, Gy	35	40	35	30	45	40
GTV, cm3	2.4	3.7	2.4	5.6	7.9	1.9
GTV-PTV +margins, mm	3	3	3	3	2-3	5
PTV, cm3	7.9	9.6	7.5	15.2	20.9	13
Beam energies, MeV	6x	6x-FFF		6x-FFF	6x-FFF	
Beam intesity, me/min	600	1400		1400	1400	
Treatment time	23 min 44 sec	8 min 20 sec		6 min 16 sec	9 min 38 sec	

Note: AV node - atrioventricular node, PV - pulmonary veins, LV - left ventricle, GTV - gross target volume, PTV - planning target volume, FFF - flattening filter-free, LVFW - left ventricle free wall.

CONCLUSION

Each group demonstrated safe and precise radiation exposure. Histological examination confirmed alteration of electrophysiological properties produced at all applied radiation doses. We produced transient AV block at a dose of 40 Gy within 108 days of the follow-up and third-stage AV block at 45 Gy within 21 days using a 6 MeV photon beam. However, the dose of 35 Gy was not sufficient to promote electrophysiological changes when targeted at the AV node. Histological examination reported that ablation lesions were consistent with those of radiation exposure that was conformal and precise. Our experimental study along with other research groups has proven that stereotactic radioablation demonstrates high effectiveness and safety for producing persistent myocardial damage.

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