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Review Article

Use of Stereotactic Radioablation in Experiments on Large Animals: Non-Invasive Interventions in Arrhythmology

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ABSTRACT

Due to the wide prevalence of various cardiac arrhythmias, new strategies for the treatment and management of patients with arrhythmias are being developed. One of the promising strategies for the correction of rhythm disturbances refractory to modern methods of treatment is stereotactic radio ablation of tachyarrhythmia's using linear particle accelerators.

The publication presents an overview of experimental in the field of radio ablation of various parts of the heart in order to influence the substrate of arrhythmias; own experience of using stereotaxic radio ablation of the heart in an experiment on domestic pigs is described.

Keywords: Ventricular tachycardia; Stereotactic radio ablation; Noninvasive arrhythmology

INTRODUCTION

The prevalence of tachyarrhythmia's in the population determines the development of methods for the treatment of this pathology. New approaches to treatment aimed at improving the efficiency and safety of already known methods of treatment are a priority in the development of future arrhythmology.

The technology of catheter ablation of tachyarrhythmia's, which appeared in the late 90s of the XX century, quickly became widespread and evolved into a highly effective method for treating the vast majority of cardiac arrhythmias (with an efficiency close to 100%, for example, in Wolff-Parkinson-White syndrome). The technique is reflected in any section of arrhythmology and clinical guidelines with high levels of evidence base for efficacy and safety. However, the use of this technique may not always have good results [1]. For example, in interventional catheter treatment, for example, Atrial Fibrillation (AF), the long-term effectiveness of this method varies greatly from 10%-15% with long-term forms of AF to 50%-75% with paroxysmal AF [1,2]. Radiofrequency Ablation (RFA) of Ventricular Tachycardia's (VT) is used in patients with ischemic cardiomyopathy for the treatment and prevention of recurrent VT [2]. This technique is the first class of indications for electrophysiological investigation and ablation of polymorphic and monomorphic VTs in patients with implanted cardioverter-defibrillator and repeated "shocks" due to recurrent sustained VT [3]. The effectiveness of this technique ("freedom" from ventricular tachycardia in patients with ischemic VT and implanted ICD) according to randomized trials is 20-48% during the follow-up period of up to three years, which may be due to the inaccessibility of localization and the large volume of the "target zone", the impossibility performing trans mural exposure in the ventricles of the heart, since the thickness of the myocardium of the left ventricle of the heart can reach 30 mm or more. Hemodynamic instability during tachycardia mapping is a common problem during this procedure, which in some cases may require the patient to be provided with bypass used circulation [4]. This category of patients is characterized by the presence of severe concomitant diseases and conditions, such as chronic cardiac, respiratory and renal insufficiency, which may increase the risk of performing, and be an absolute contraindication to such procedures.

Among the complications of methods of catheter ablation of tachyarrhythmia's, "mechanical" damage to the atria and ventricles of the heart (with the outcome in cardiac tamponade) and closely located organs (atrioesophageal fistula, damage to the

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phrenic nerve) prevails; as well as embolic complications during and after the ablation procedure (stroke, transient ischemic attack, air embolism). The frequency of the above complications can range from 0.6% to 3%, and the mortality from them is about 0.1% [5]. In addition, interventional procedures in the treatment are quite long in time and are carried out using fluoroscopy.

In recent decades, stereotaxic irradiation of pathological foci of various nature using installations with multiple sources of Co-60, electron accelerators, and heavy charged particles has become an increasingly common method of radiation therapy in oncology (mainly for brain tumors). In stereotactic radiation therapy and radiosurgery, modern technologies are used that allow radiation to be delivered to the "target" from a large number of directions, with a high degree of precision and selectivity. This provides conformal (coinciding in volume with the volume of the pathological focus) irradiation, minimizing the impact on the surrounding normal tissues and minimizing acute and delayed radiation complications [6].

Non-invasive stereotaxic treatment using linear electron accelerators can be considered a promising alternative to catheter ablation in patients with tachyarrhythmia's, which has been demonstrated in a number of works on the experimental and clinical application of this technology.

The high efficiency and safety of stereotactic radiation therapy using electron and proton accelerators, the advent of navigation systems and the improvement of methods for planning and calculating dose distributions, including taking into account the movement of various anatomical structures, made it possible to apply this method of treatment in diseases of continuously moving organs, for example, diseases of the respiratory and cardiac systems. The similarity of the tasks of oncologists and cardiac electrophysiologist (creation of persistent and precise damage to the organ tissue with the subsequent formation of fibrosis and, as a result, a "conduction block") made it possible to start experimental and preclinical studies on the use of this technology for the treatment of tachyarrhythmias [7].

LITERATURE REVIEW

Experimental studies on animals have shown the high efficiency of stereotactic radio ablation in creating stable functional damage to heart tissues.

In a study by Refaat, et al. performed on domestic pigs, to evaluate the effectiveness of the stereotaxic method for the treatment of arrhythmia, ablation of the AV Node (AVN) was performed with various loading doses (35 Gy and 2-40 Gy). The control of the occurrence of AV blockade was carried out using a previously implanted pacemaker. On average, AV block developed within 2 months. At autopsy for histological examination, materials were taken from the AVN and adjacent organs. In the preparations of the AV node, the phenomena of violation of tissue architectonics and disorganization of intracellular structures, as well as necrosis and fibrin deposits were observed. Histological examination in preparations of the liver, lungs, and esophagus did not reveal any pathological changes [8].

Zei, et al. conducted a study of the possibility of performing stereotaxic radioablation of the orifices of the pulmonary veins (radiation doses of 15-35 Gy). The experiment was performed on dogs and pigs with subsequent remote observation. Before and after stereotaxic irradiation, an electrophysiological study was performed using electroanatomical mapping of spike activity zones in the pulmonary vein (Carto 3. Bioscence Webster USA). Control electroanatomical mapping was carried out on the third and sixth months of observation. Pulmonary vein isolation was 100% effective in the 25 and 35 Gy groups, 80% in the 20 Gy group, and was ineffective in the 15 Gy groups [9].

Many authors have faced the problem of taking into account and compensating for the movement of the heart muscle in space and time, which can significantly complicate the procedure. Several different methods have been proposed as solutions to this problem. So, in the study of John, et al. described a technique for compensating respiratory movements, which can be achieved in three ways: limiting chest excursion by abdominal wall compression or anesthesia, setting the radio ablation system so that the exposure is performed at a certain point in the respiratory cycle (gating), as well as the installation of special marks (including the electrodes of the pacemaker/ICD systems) for tracking and compensating for displacements during irradiation (tracking) [10].

Graeff and Bert raise the issue of the complexity of accounting for respiratory and cardiac cycles for a more accurate and targeted impact on the area of interest. Referring to the experience of treating chest tumors, the authors proposed a method that excludes sufficiently significant changes in the position of the target in space during respiration. During breathing, the amplitude of movement of the chest organs is quite large (sometimes many times greater than the size of the intended impact zone itself), so it was proposed to perform the impact during a deep breath with a delay or with restriction of chest excursion through compression of the abdominal wall with an anesthetic aid that limits respiratory movements. All this could simplify the task, but it is risky for the patient and increases the duration of exposure [11].

During the cardiac cycle, the ventricle of the heart moves in three planes (compression and rotation), which greatly complicates the targeted action in the target. The proposed concept of heart rate accounting, which correlates with the R-R interval on the Electrocardiogram (ECG), is a priority in the development of "synchronization" of the radio ablation technique and navigation support, but this direction needs to be improved.

This paper also describes the use of intracardiac gold markers near the target. According to the authors of the study, ICD/pacemaker electrodes can be used as markers, which will help solve the problem with movement [11].

Our study was performed on 4 domestic pigs. The age of the animals was 3 months, the average weight was 30 ± 1.5 kg. The study was carried out on a True Beam linear accelerator (Varian, USA). Animals were divided according to the zones of expected exposure: 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 vein (dose 30 Gy) 4th-AV node and free LV wall (dose 45/40 Gy, respectively). Before the study, all animals underwent CT of the heart with contrast. These data were used for treatment planning in the Eclipse system (Varian, USA) (Figure 1). The average exposure time was 16 ± 4.2 minutes (Table 1). No intraoperative complications were noted. The planned period of long-term follow-up is 6 months, followed by a morphological and histological study of the autopsy material. The main objectives of the study were to assess the conformity and homogeneity of exposure, as well as the analysis of the electrophysiological effect after stereotaxic radio ablation.

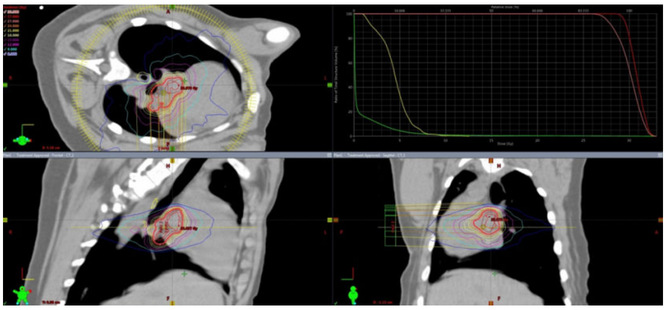

Figure 1: Radioablation planning. Contouring of the target exposure area (pulmonary veins). The figure shows a series of CT scans of a pig's heart in three planes. The esophagus is marked with a yellow outline. According to the dose planning and distribution, the target volume (red curve) is irradiated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

	Dose 1	Dose 2		Dose 3	Dose 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
Dose of radiation, Gy	35	40	35	30	45	40
GTV, cm^3	2.4	3.7	2.4	5.6	7.9	1.9
GTV-PTV +margings, mm	3	3	3	3	3-Feb	5
PTV, cm^3	7.9	9.6	7.5	15.2	20.9	13
Beam energies, MeV	6 X	6 X -FFF		6 X -FFF	6X-FFF	
Beam intensity, me/min	600	1400		1400	1400	
Treatment time	23 min 44 sec	8 min 20 sec		6 min 16 sec	9 min 38 sec	

Abbreviations: AV node: Atrioventricular Node; PV: Pulmonary Veins; LV: Left Ventricle; LVFW: Left Ventricle Free Wall; GTV: Gross Target Volume; PTV: Planning Target Volume; FFF: Flattening Filter-Free

Table 1: Treatment planning parameters for all dose groups and targets.

The average observation period after the experiment was maximum 189 days-minimum 20 days.

AV node radiation group

In macroscopic examination, in all cases, in the area of the AVN, noticeable changes were noted in the area of influence, which had clear, but not even, boundaries of the damage zone, which did not go beyond the planned ones. The impact zone in the planning system completely coincided with the impact zone on the macro preparation, i.e. the impact was precise. Irradiation conformity was achieved with AVN radio ablation in all animals.

Microscopic examination revealed changes in all layers of the AVN localization zone, represented mainly by mature granulation tissue among unchanged myocardial fibers, stained bright red by picrofuxin according to van Gieson and blue by Masson's trichrome. In AVN preparations, some cardiomyocytes showed complete (true) transverse tears, coagulation and vacuolization of the cytoplasm, which are characteristic of an acute stress reaction. At the same time, the degree of histological changes was most pronounced at the maximum loading dose of 45 Gy.

In the same zones, the presence of single intact cardiomyocytes belonging to the conduction system was noted.

According to the loop recorder AV-blockade of the 3rd degree was detected in animal's No. 2 and No. 4. In animal No. 1 for the entire period of observation, rhythm and conduction disturbances were not registered. In animal No. 2, AV blockade had a transient character, mainly at night: the minimum heart rate was 16 beats. Per minute, rhythm pauses for more than 2 seconds, in the amount of 1868 episodes over the entire observation period-173 days, the maximum duration of ongoing AV blockade-42 minutes, the blockade was first detected on the 108th day from the implantation of the registrar. Animal No. 4 died on the 21st day of the experiment from a systole due to the development of complete AV block.

Pulmonary Veins (PV) and Left Atrium (LA) radiation group

Macroscopic examination of the preparation of LA and PV shows the presence of altered areas of the myocardium in the area of the orifices of the PV in the form of hemorrhagic impregnation and areas of calcification. The impact zone in the planning system completely coincided with the impact zone on the macro preparation, which indicates a high degree of conformity of the impact.

Histological examination of the area taken from the mouths of the pulmonary veins and in the thickness of the wall of the left atrium in the area of the impact, foci of calcification, edema and loose connective tissue are noted. Myocardial stroma in the indicated areas with focal edema. When examining organs adjacent to the affected area (lungs, esophagus, bifurcation lymph nodes), no foci of necrosis and fibrosis were found.

For the entire period of observation, no rhythm and conduction disturbances were recorded in animal No. 3.

Left ventricle radiation group

In macroscopic examination, the treatment area has clear boundaries, which almost completely coincide with the planned volume of exposure before the procedure (animal No. 2-the LV apex and part of the ventricular septum, animal No. 4-the free LV wall).

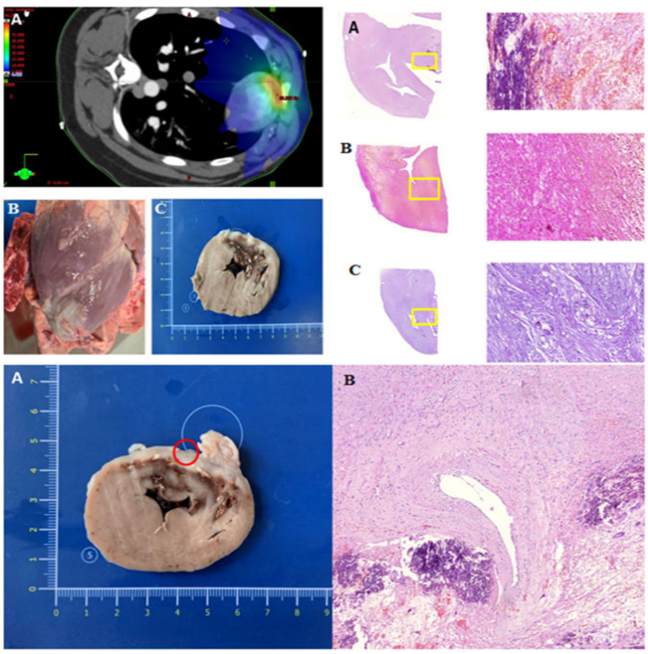

Figure 2: Left upper images-A: The porcine left ventricular apex on contrast-enhanced CT scans in the treatment planning system. B: A macroscopic sample of the procine heart. Fibrosis in the area of the apex. C: A macroscopic sample after radio ablation. The modified area corresponds to the affected area. Right upper images-A microscopic sample of the left ventricular apex after radio ablation. A: hematoxylin-eosin staining. B: van Gieson's staining. Magnification: 40-200. C: PAS staining. Bottom images-A: A macroscopic sample of the porcine left ventricle after radio ablation. The red circle denotes the LAD projection. B: A microscopic sample of the left ventricular wall at the LAD level. Hematoxylin-eosin staining. Magnification: 200.

Histological examination of the myocardium of the apex of the left ventricle with the interatrial septum (animal No. 3) shows a trans mural nature of the changes: massive fields of fibrous tissue of varying degrees of maturity (with a predominance of sub epicardial) with focal hemorrhages of various prescription and granulations are surrounded by cardio myocytes with coagulation and vacuolization of the cytoplasm. In animal No. 4, attention was drawn to the presence of granulations, foci of necrosis, Tran's mural fibrosis (and foci of calcification, hemorrhage in the affected area) throughout the exposure. At the same time, the anterior inter ventricular artery, partially passing through the zones of the planned impact in both animals, had no signs of damage and was not thrombosed, however, in the subendothelial zone, edema and partial destruction of the integumentary plate were noted, which indirectly may indicate the possibility of parietal thrombosis in the long term (Figure 2).

In the group of effects on the left ventricle in animal No. 2 and No. 4, according to the loop heart monitor, ventricular arrhythmias were not recorded. Animal No. 4 died from a systole against the background of complete AV blockade on the 21st day of observation.

Thus, according to the analysis of macroscopic preparations of hearts, the interventions performed turned out to be precise with a high degree of conformity.

According to microscopic examination, the impacts were transmural, in these areas there were phenomena of necrosis and calcification, which indicates a homogeneous damage to myocardial areas with subsequent formation of fibrosis.

According to the data recorded using a loop heart monitor, it was revealed that exposure to AVN with a dose of 35 Gy does not lead to the development of persistent.

DISCUSSION

Conducted large experimental studies prove that the use of stereotaxic radioablation demonstrates sufficiently high rates of effectiveness and safety of the technique for creating persistent myocardial damage in experimental animals, the main provisions of studies conducted abroad were reproduced in our experiment. In our study, we achieved functional damage to the myocardium in the area of the AV junction of both transient AV blockade (at a dose of 40 Gy on day 108 of observation) and permanent AV blockade of the 3rd degree. (45 Gy on day 21) using a 6 MeV photon beam. The volumes of radiation damage to heart tissues analyzed at autopsy positively correlated with the dose distribution around the target damage volume, i.e. impacts were highly conformal (coincident in volume) and precise.

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 Cyber Knife 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 mappingwas 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 38 Gy to80 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 (thirdgrade AV block) on day 21 day. Histological examination revealed similar changes in the affected areas as reported by Sharma, et al.

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. Lehmann, et al. divided 17 pigs into 4 groups according to the pretreatment zones. Group 1 underwent the radioabaltion of AVnode 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].

Rapp, et al. focused on the pathology and patho morphology of radiation injury. No radiation-induced effects on the esophagus, trachea, phrenic nerve, and skin were observed by histological and immune histochemical examination suggesting the precision and selectivity of stereotactic radio ablation. 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].

CONCLUSION

Stereotactic radiosurgery using linear electron accelerators is a technology that demonstrates high efficiency and safety and is widely used and successfully used in oncology. One of the main advantages of the method is its non-invasiveness, which makes it possible to inflict high-precision and effective "damage" to any localization. The use of this technology for the treatment of tachyarrhythmia's definitely has high prospects in modern arrhythmology as an alternative method of ablation in patients with an ineffective catheter approach, as well as in patients with contraindications for interventional procedures. Further development of this technology in arrhythmology definitely requires both experimental and extended clinical studies to determine the level of effectiveness and safety of the method. A number of complex issues and tasks remain open, such as determining the required therapeutic dose to create functional and homogeneous damage to the myocardium of the heart at various localizations of exposure; ensuring the accuracy of exposure, taking into account the continuous movement of structures and organs in the chest cavity; possible reversibility of the created myocardial damage; possible "proarrhythmogenicity" of the performed actions; the prospect of creating a "true (pathogenetic) antiarrhythmic" effect, which is the subject of further research.

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