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Commentary

Non-invasive ablation of cardiac arrhythmia. Is proton radiation therapy a step forward?

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Implantable cardioverter defibrillator (ICD) implantation is a life-saving procedure in patients at risk of malignant ventricular arrhythmias. However, recurrent ICD shocks increase morbidity and mortality and decrease quality of life.

Scar-related reentry is the most common cause of sustained ventricular tachycardia (VT) in patients with structural heart disease (SHD). Since antiarrhythmic drugs are of limited value due to modest efficacy and potential for toxicity and proarrhythmia, increasing focus is given to research aimed to map and eradicate the arrhythmic substrate. Invasive activation and entrainment mapping during VT accurately define the VT circuit critical isthmus, which can be eliminated by radiofrequency (RF) catheter ablation. Since RF ablation produces a coagulative necrosis with limited transmural extension (5–6 mm), epicardial access through subxiphoid puncture was developed to reach epicardial scars. Endo/epicardial RF ablation is the current gold standard for patients with SHD and recurrent scar-related VT [1]. However, despite technological improvements and repeated ablation procedures, recurrence rates at one year are still high: 30–60%. Several mechanisms are involved, including lack of inducibility or hemodynamic intolerance of the clinical VT leading to unrecognized VT circuits, inadequate mapping, deep (intramural) or protected substrates and evolving substrates. Invasive VT ablation absorbs large resources and is associated to important complications, including death. Research is ongoing to improve resolution of invasive mapping systems and to increase lesions transmurality, both with RF and other energy sources. Cardiac sympathetic denervation may markedly reduce the burden of ICD shocks in patients with recurrent VTs [2]. However, the presence of slow monomorphic VTs is associated with a high recurrence rate after denervation, highlighting the need for more effective ablation strategies in these patients. Stereotactic arrhythmia radioablation (STAR) is an emerging approach in this setting.

STAR with X ray (photons) for refractory VTs in SHD was first described in 2013 [3]. Case reports and few case-series, all using single fraction high dose (25 Gray, Gy) of photons, have been reported, including an American phase I/II prospective study (ENCORE-VT) in 17 patients [4]. The STAR leading principle relies on the possibility of non-invasively and precisely ablating the arrhythmic substrate, using single-dose radiotherapy and minimizing toxicity for the surrounding tissue/organs, similarly to stereotactic body radiation therapy (SBRT) in oncology. Specific challenges in translating SBRT to cardiac substrates include the VT substrate target delineation on Computer Tomography (CT) and its transfer to the Treatment Planning System (TPS) and the irradiation of an actively moving target. Moreover, understanding of the biophysical effects of radiation at cardiac level is still very limited. Accordingly, VT recurrence rate in studies with follow-up ≥6 months is still high (66–100%) despite a reduction in VT burden and duration. The STAR short-term safety profile appears acceptable, with no severe acute toxicity reported. In ENCORE-VT, which applied a very large median final target volume (or planned target volume, PTV) of 99 ml (IQR 61–299), possible treatment-related serious adverse events (SAEs) included worsening of heart failure (11%), delayed pericarditis/effusion (28%) and pneumonia (11%). These SAEs were not reported in case series with lower median PTV. Recently reported longer-term safety data (2-year median follow-up) of ENCORE-VT and of an 18 patients European cohort (mean PTV 34 ± 17 ml [5]), disclosed one pericardial effusion and one gastro-pericardial fistula requiring surgical repair, the first study and two cases of mitral regurgitation significant progression, one requiring surgery, the second one. In both studies, cardiac mortality was high, but no specific warning for a probably or definitely STAR-related impact on cardiac function was raised.

To identify the electrophysiological target volume (clinical target volume, CTV), electro-anatomical mapping data, obtained from previous ineffective RF ablation and/or from *ad hoc* electrocardiographic imaging (ECGi) were used. ECGi has a great potential for a completely non-invasive VT ablation, but spatial accuracy is still sub-optimal, particularly for endocardial

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exit sites: a median distance of 21 mm between true and predicted pacing locations was recently reported [6].

Targeting cardiac structures requires to consider both breathing motion and heartbeat. There is still no reliable solution to account for both components. Standard 4D-cardiac tomography (CT) captures only one of the two motions, while 5D image reconstruction tools are still unavailable. Recording an adequate number of motion phases over the heartbeat for at least one full breathing cycle would likely result in unacceptable X-ray exposure. All groups performing STAR used either respiratory-gated 4D-CT or dynamic tracking of fiducial markers, by means of X-ray fluoroscopy, to compensate for respiratory movements. Some also used expiratory breath-hold ECG-gated CT scan to accurately compensate for heart contractions. The addition of internal motion compensation to the CTV provides the so-called internal target volume (ITV). Finally, a direct intraprocedural target motion monitoring system (*e.g.* CyberKnife's Synchrony) is highly desirable to minimize the PTV and increase accuracy. Indeed, target motion monitoring was not used in ENCORE-VT, resulting in a median PTV of 99 ml, as opposed to a median ITV of 31 ml. The first-in-man usage of MR-Linac, an MRI-based system for target motion monitoring, has been reported in the STAR setting [7].

Radiotherapy-related cardiotoxicity is a well-known late consequence of conventional treatment administered to oncological lung, breast or Hodgkin's lymphoma patients. In the case of photon or ion beam treatment for cardiac arrhythmia ablation, the problem of hitting the target while sparing the remaining heart tissue is even more pronounced. On one side, delivering doses >20 Gy on the target volume may be associated with middle and long-term negative effects on normal cardiac tissue. On the other side, doses >25 Gy in animals led to a more consistent dense scar formation on the pulmonary vein antrum/atrioventricular node, with a response kinetics ranging from 2 to 4 months. Electrophysiological effects were observed starting from 25 Gy.

Accordingly, the few available autoptic examination of human hearts after STAR with photons (all <3 months after STAR) showed a variable combination of edema and endothelial cells vacuolization with mild fibrosis inside the PTV [8]. Transmural fibrosis was never observed, although long-term histological data are lacking. Yet, electron microscopy data revealed disruption of intercalated disc/gap junction areas of vital cells, in agreement with pre-clinical evidence, showing an increased expression of connexin 43 after radiation exposure on tumoral cells and cardiomyocytes. The connexin 43 activation and its potential effect on conduction velocity (increase), together with acute (vasogenic and cytokine-release related) edema, may explain the relatively acute responses to STAR observed in some patients. Consistently, anecdotal invasive bipolar mapping, performed 11 months after STAR, showed the persistence of fragmented, late and low voltage potentials within the dense scar.

Particle therapy (protons, Carbon-12 and Helium) has a theoretical advantage over photon beams due to the Bragg peak (Fig. 1), a higher dose at the end of the particle range, potentially allowing for a high dose deposition on very small cardiac targets. Indeed, the application of 2–4 fields of a particle therapy can result in complete sparing of critical structures, whereas photons can only achieve a similar dose conformity by cross-firing many fields, exposing large cardiac tissue volumes to low or medium-dose levels. The comparison of simulation plans with protons (35 Gy to ITV, 25 Gy to PTV), instead of photons in ENCORE-VT patients, showed a significant sparing in non-target heart tissue (mean dose 1.9 Gy as compared to 6.2 Gy), while meeting the organ at risk constraints [9]. From a clinical standpoint, particle therapy would allow to provide irradiation on previously X-ray treated patients and possibly to perform additional procedures in case of recurrences (a hardly feasible option with photons). Heavier ions (Carbon-12 and Helium), could potentially obtain a smaller beam focus and less lateral scattering, and, in principle, a higher Relative Biological Effectiveness than photon

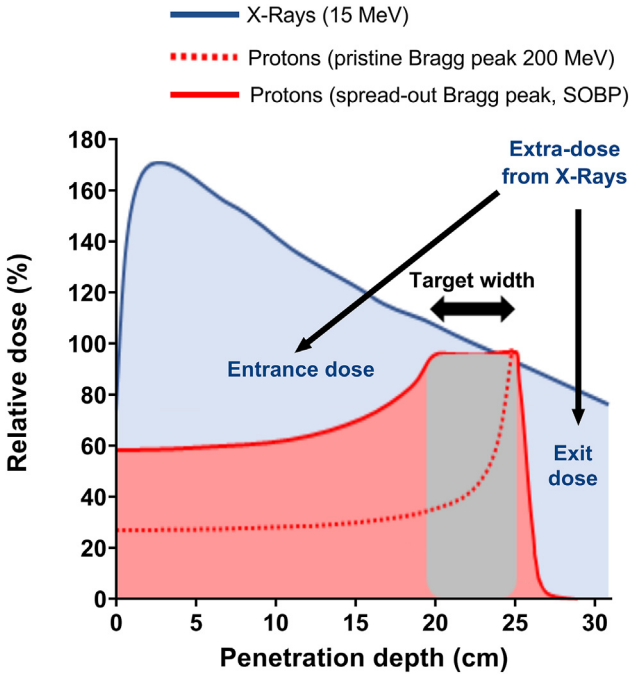

Fig. 1. Comparison of relative depth dose distributions of X-Rays (blue) *versus* protons (red). The gray depicts the target region. Protons, like other particles such as 12 Carbon ions and Helium, enter and travel through the tissue with minimal dose deposition along the path until the end of their paths, where a peak of energy deposition occurs. This phenomenon is known as the Bragg peak. For protons, the dose deposited before reaching the Bragg peak is approximately 30% of the Bragg peak maximum dose, whereas beyond the Bragg peak, the dose falls practically to zero. In order to cover the target with a uniform dose, a so-called spread-out Bragg-peak (SOBP) is created. The features of Bragg-peak are similar, although not equivalent, for heavy ions. Both 12 Carbon ions and Helium have a lower entrance dose deposition than protons, whereas 12 Carbon ions have a bigger tail dose than both protons and Helium. MeV = Megaeletronvolt. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and protons. Helium beams show less fragmentation tail than Carbon-12 and less lateral scattering than protons. However, proton radiation systems are more diffuse and several randomized trials using proton therapy in breast cancer patients are ongoing. *In vivo* STAR pre-clinical studies with carbon ions are also ongoing since 2016 [10].

The problem of breathing and heartbeat movements may be even greater in particles, as compared to photon therapy, and target irradiation with small spots could produce hot or cold spots. Beam ECG gating is a promising technology for the next future, correlated to online target motion monitoring by means of ultrasound imaging or MRI. The first-in-man STAR case using protons has been recently performed in Pavia (Italy) and no acute toxicity was reported in the press release. (http://www.ansa.it/english/news/science_tecnology/2020/01/22/protons-treat-heart-arrhythmia_f0ff4012-e8c8-49b7-b624-a5c25062e44c.html).

In conclusion, STAR is a promising treatment for refractory scar-related VT, particularly in case of slow VT, that poorly respond to sympathetic denervation. Particle therapy may potentially offer advantages over photons, but several challenges are present. They include the improving electrophysiological target definition and its transfer to the treatment planning system, the developing of a 5D-CT image, a 4D dose calculation and a gating system for breathing and heartbeat, triggered to scanning beam, an online target imaging system without X-ray exposure and, ideally, the capability to accelerate Helium beam. Research should continue using both photons and particles to better characterize the potential of both approaches for non-invasive ablation of recurrent ventricular tachycardia.

References

[1] E.M. Cronin, F.M. Bogun, P. Maury, P. Peichl, M. Chen, N. Namboodiri, et al., HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias, Heart Rhythm. 2019 (2019).

[2] M. Vaseghi, P. Barwad, F.J. Malavassi Corrales, H. Tandri, N. Mathuria, R. Shah, et al., Cardiac sympathetic denervation for refractory ventricular arrhythmias, J. Am. Coll. Cardiol. 69 (25) (2017) 3070–3080.

[3] P.C. Zei, S.G. Soltys, B. Loo, et al., First-in-man treatment of arrhythmia (ventricular tachycardia) using stereotactic radiosurgery, Heart Rhythm. 10 (2013) 1–554.

[4] C.G. Robinson, P.P. Samson, K.M.S. Moore, G.D. Hugo, N. Knutson, S. Mutic, et al., Phase I/II trial of electrophysiology-guided noninvasive cardiac radioablation for ventricular tachycardia, Circulation. 139 (3) (2019 Jan 15) 313–321.

[5] Long-term safety of stereotactic body radiotherapy for ablation of ventricular tachycardia: a multicentric study. J. Cvek, L. Knybel, R. Neuwirth, O. Jiravsky, M. Sramko, P. Peichel et al. European Heart Journal 2019; 40: ehz745.0048.

[6] S. Hohmann, M.E. Rettmann, H. Konishi, A. Borenstein, S. Wang, A. Suzuki, et al., Spatial accuracy of a clinically established noninvasive electrocardiographic imaging system for the detection of focal activation in an intact porcine model, Circ. Arrhythm. Electrophysiol. 12 (11) (2019 Nov), e007570.

[7] Mayinger M, Kovacs B, Tanadini-Lang S, Ehrbar S, Wilke L, Chamberlain M, et al. First magnetic resonance imaging-guided cardiac radioablation of sustained ventricular tachycardia. Radiother Oncol. 2020 Feb 14. pii: S0167–8140(20)30020–7. doi: https://doi.org/10.1016/j.radonc.2020.01.008. (Epub ahead of print).

[8] M.S. Lloyd, J. Wight, F. Schneider, M. Hoskins, T. Attia, C. Escott, et al., Clinical experience of stereotactic body radiation for refractory ventricular tachycardia in advanced heart failure patients, Heart Rhythm. 17 (3) (2020 Mar) 415–422.

[9] Feasibility of Noninvasive Cardiac Ablation Utilizing Intensity Modulated Proton Therapy to Treat Ventricular Tachycardia. Goddu SM, Hilliard J, Knutson N, Zhao T, Hugo GD, Mutic S. Int Journal of Radiation Oncology, Biology, Physics 2018; 102: S58.

[10] H.I. Lehmann, C. Graeff, P. Simoniello, A. Constantinescu, M. Takami, P. Lugenbiel, et al., Feasibility study on cardiac arrhythmia ablation using high-energy heavy ion beams, Sci. Rep. 6 (2016) 38895.