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Teaching Case

Direct Clinical Effects of Cardiac Radioablation in the Treatment of a Patient With Therapy-Refractory Ventricular Tachycardia Storm

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Introduction

Patients with recurrent ventricular tachycardia (VT) are treated with antiarrhythmic drugs and invasive catheter ablation(s).[1] Unfortunately, though some patients have an (urgent) indication for invasive catheter ablation, coexisting conditions may prohibit such procedures. Cardiac radioablation, or stereotactic arrhythmia radiation therapy, is a new and promising noninvasive treatment modality for patients considered therapy-refractory or untreatable.[2] Although the mechanism of action of cardiac radioablation remains to be elucidated, based on previous data the antiarrhythmic effects of cardiac radioablation could take several weeks to several months. Importantly, the potential of direct antiarrhythmic effects of cardiac radioablation, in contrast to conventional ablations, are undecided.[2,3] Therefore, it is unknown whether cardiac radioablation is a suitable therapy in the setting of VT storm and incessant VT, although cases have been reported.[4-7] In this report, we present a patient with therapy-refractory VT storm and incessant VT who experienced direct clinical effects of cardiac radioablation.

Case Report

The run-up to cardiac radioablation

A 60-year-old male with an ischemic cardiomyopathy was admitted for VT storm. He suffered from an anteroseptal myocardial infarction at the age of 30, which was treated with thrombolytic medication. In 2011, at a left ventricular (LV) ejection fraction of 17%, he received a primary-prevention, subcutaneous, implantable cardioverter-defibrillator (S-ICD). During follow-up, the patient experienced several VT episodes that were treated by his ICD and necessitated medication adjustments. In

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2021, because of recurrent VT and an unchanged ejection fraction, the patient's S-ICD was explanted and he received cardiac resynchronization therapy (CRT-D). A cardiac magnetic resonance imaging (MRI) scan between the S-ICD explant and CRT-D implant revealed a previously unrecognized LV thrombus (for which treatment via vitamin K antagonist was started) beside the previous large antero-septal. antero-lateral myocardial infarction.

The patient was admitted 10 days later to a secondary hospital with a subsequent VT storm and he was eventually transferred to our academic hospital for further treatment via a tertiary referral hospital. During VT, the patient was hypotensive necessitating external electrical cardioversions. A repeat diagnostic work-up did not reveal new triggers. Over the course of his hospitalization, he was given several combinations of high-dose antiarrhythmic drugs, including high-dose intravenous amiodarone, multiple beta-blockers, mexiletine, and quinidine, all of which proved ineffective in preventing VT. Antibiotic therapy was started because the patient became septic, potentially as a consequence of a peripherally inserted central catheter. Blood cultures soon revealed a *Staphylococcus aureus* bacteremia and the antibiotics were adjusted accordingly. Although physical examination, echocardiography, and a positron emission tomography using [18F]fluoro-deoxyglucose / x-ray computed tomography scan ([^{18}F]FDG-PET/CT) with an endocarditis protocol (including preparation with a carbohydrate-free diet for 24 hours, fasting for 12 hours, and an intravenous infusion of heparin 15 minutes before [^{18}F]FDG-administration) showed no signs of endocarditis; however, antibiotics were continued in a high enough dose to treat endocarditis because of the recent CRT-D implantation and lower diagnostic yield of the FDG-PET scan during antibiotic therapy while the patient was critically ill. An urgent catheter ablation was considered. However, the apical thrombus was still present despite adequate anticoagulation therapy, and several of his multiple VT morphologies were inferred to originate from underneath this thrombus. Consequently, the patient was considered unsuitable for the procedure. While the patient was being treated with high-dose antiarrhythmic drugs (daily doses of 200 mg metoprolol, 400 mg amiodarone, and 600 mg mexiletine), VTs recurred, and the patient eventually required sedation and intubation. Adjustment of antiarrhythmic medication temporarily decreased the incidence of VT and the patient was extubated. Despite an additional percutaneous left stellate ganglion blockade, the VTs recurred.[8]

By then, the patient had been hospitalized for more than a month and experimental cardiac radioablation was considered. The therapeutic options and their advantages and disadvantages were extensively discussed with the patient and his family, including continuing current therapy with antiarrhythmic medications, discontinuation of therapy, high-risk catheter ablation, and (compassionate use of) experimental cardiac radioablation. The patient opted for cardiac radioablation. In our center, 6 patients have previously been treated with cardiac radioablation within the prospective STARNL-1-study (Netherlands Trial Registry number: NL7510), with promising direct effects, albeit none of these patients had such VT storm and incessant VT. The patient gave written informed consent for the publication of this case report.

Radioablation targeting and treatment

In our center, targeting is guided by the American Heart Association (AHA) Segmented Model.[9] Segments with electro-anatomic alterations such as VT exit sites, delayed enhancement on cardiac MRI, and wall-thinning on cardiac CT are translated to a semiautomatically segmented treatment-planning 4D-CT-scan.[10] An earlier cardiac MRI and CT scan revealed myocardial scar in the anteroseptal segments (Figure 1). Echocardiographic deformation imaging revealed abnormal strain percentages in all but the basal inferior segment, which was the only segment with normal shortening of >18%. During admission, 9 different VT morphologies were recorded with inferred exit sites both from the basal anterior and the inferolateral apex (Figure 1). The final target included 1 (partly), 2, 7, 8, 12 (partly), 13, 14, 16, and 17 (Figure 1). The clinical target volume (CTV) was 67 cm^3 and an internal target volume (ITV) was created to correct for cardiorespiratory motion based on the 4D-CT. Isotropic expansion with a 5-mm uncertainty margin was performed, which led to a planning target volume (PTV) of 300 cm^3, to which a dose of 25 Gy was prescribed. A 3-arc volumetric-modulated arc therapy (VMAT) plan was created, for which 95% of the PTV received at least the prescribed dose and where the dose in the ITV was escalated up to 34 Gy (RayStation 9A, RaySearch, Sweden). The patient was treated on the Agility^{TM} (Elekta, Sweden).

Efficacy

Before cardiac radioablation, the patient had 77 sustained VT-episodes during 37 days of hospitalization (a mean of 2.1 VT-episodes/day). Of those episodes, 25 required termination by electrical cardioversion. One VT recurred 4 hours after cardiac radioablation (again requiring electrical cardioversion), but no further VTs occurred after that episode. After 13 days the patient was transferred back to the initial secondary hospital for further recovery. After 14 more days without VT-episodes and completion of his antibiotic regimen, the patient was sufficiently recovered and discharged home. During the remaining follow-up of 4 months, no further episodes of VT occurred. Even during a COVID-19 infection there were no VT episodes. Figure 2 shows the number of VT episodes per day, as well as the medication regimen.

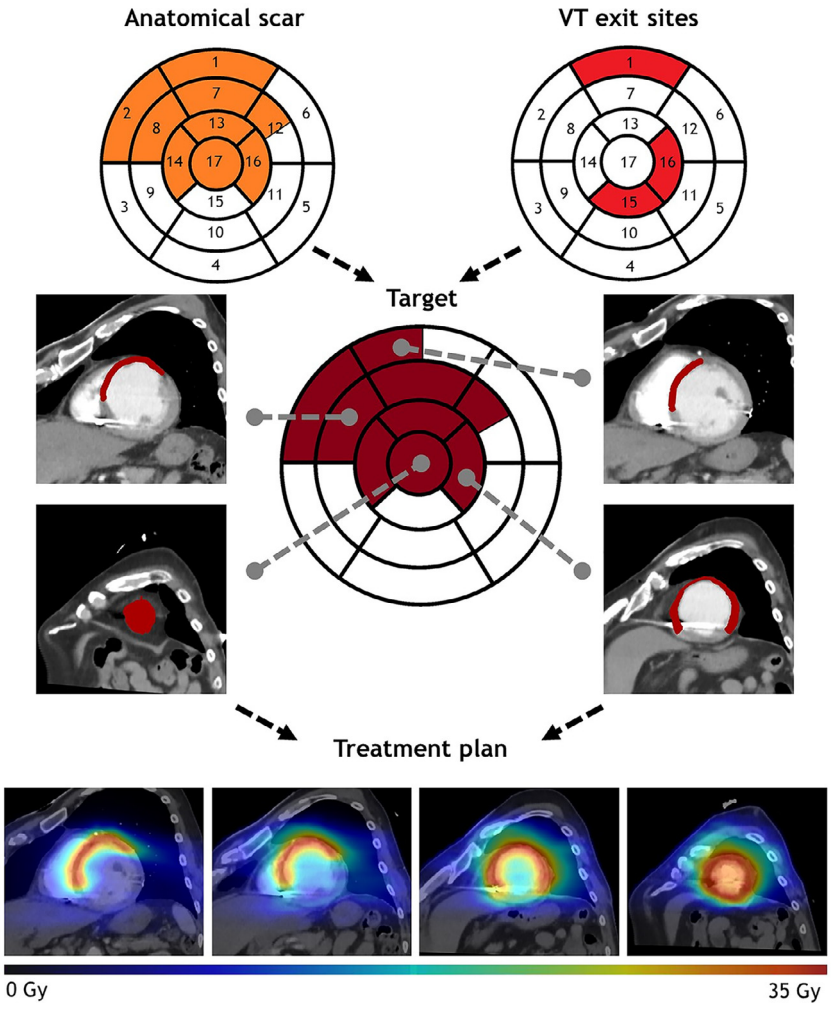

Figure 1 The anatomic scar and VT exit sites determining the target for cardiac radioablation visualized by the American Heart Association Segmented Model, and the angulated short axis-view of the heart and the target and radiation therapy dose distribution. *Abbreviation*: VT, ventricular tachycardia.

Currently, the patient is doing well, has started cardiac rehabilitation therapy and his antiarrhythmic drugs are being tapered off.

Safety

No signs of myocardial injury were seen, the patient's hs-Troponin-T levels did not change from baseline at 3, 12, and 24 hours after treatment, and the echocardiographic ejection fraction remained unchanged, as did his electrocardiogram. Furthermore, no other acute untoward myocardial effects were observed. The NT-ProBNP was reduced by 77% and no pericardial effusion was observed on echocardiography 24 hours and 3 months after treatment. Two days after treatment, the patient developed (likely radiation-induced) nausea and vomiting which lasted for 7 days (CTCAE grade 1) and was treated effectively with antiemetic medication. No other adverse events or complications were observed.

Imaging after treatment

A whole body [^{18}F]FDG-PET/CT-scan after endocarditis preparation protocol (alike the previous scan) was repeated to exclude active endocarditis one month after radioablation and 6 days after the cessation of antibiotic therapy. Fortunately, there were no signs of endocarditis. The left ventricle showed extensive ^{18}F-FDG uptake in the perfused areas of the heart, which had not been seen before therapy. Increased metabolic activity was also seen in parts of the left ventricle that had received lower doses (Figure 3). The actual treatment target, the anteroseptal scar, was, as expected, not metabolically active. The LV thrombus will be evaluated with follow-up CT-scans.

Discussion

In this case report we present a patient with therapy-refractory VT storm and incessant VT who

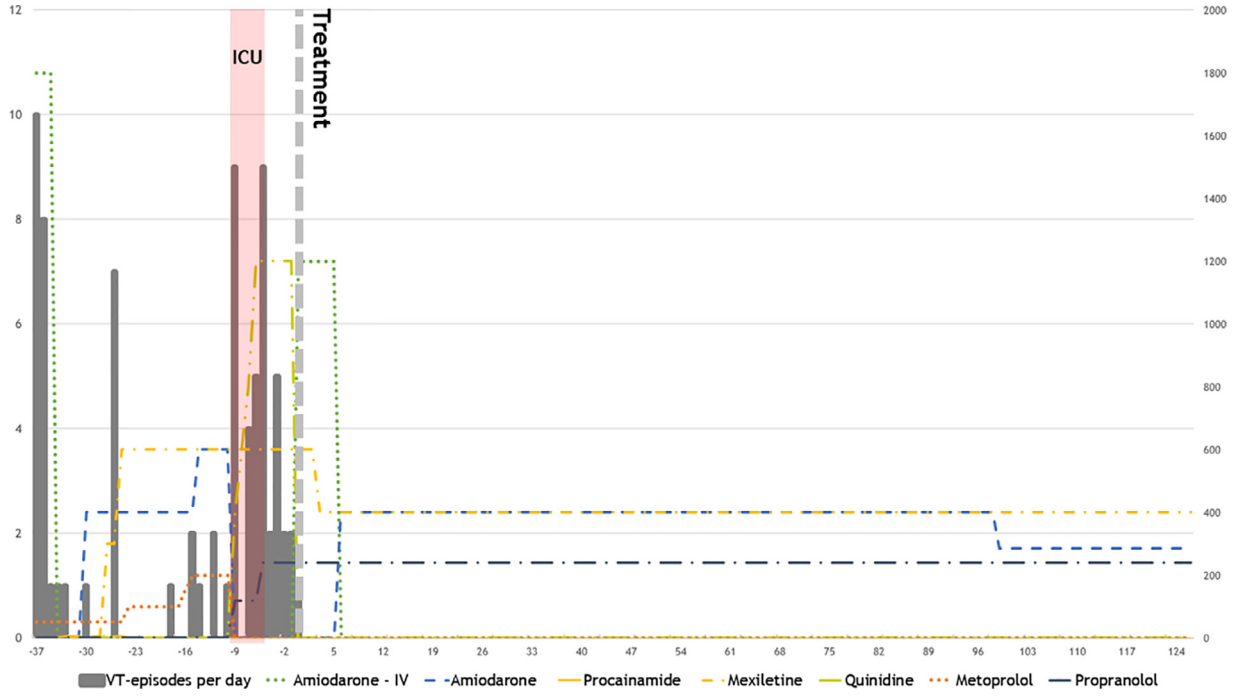

Figure 2 Number of VT episodes per day (left vertical axis) and the doses of antiarrhythmic medication per day in mg (right vertical axis). The red square indicates admission into the intensive care unit. The vertical gray dotted line indicates the moment of cardiac radioablation treatment. *Abbreviations*: IV, intravenous; VT, ventricular tachycardia.

experienced an apparent direct VT-reducing effect of cardiac radioablation. We believe that presenting this case could affect future treatment of patients with therapy-refractory VT storm in an acute setting when catheter ablation is unsuccessful or deemed unsuitable.

Patients with VT usually have structural abnormalities leading to re-entry as the mechanism for VT.[11,12] Conventional therapies aim to prevent VT by modulating cardiac electrophysiology with either medication or by means of catheter ablation. Antiarrhythmic medication decreases the conduction velocity and/or increases the

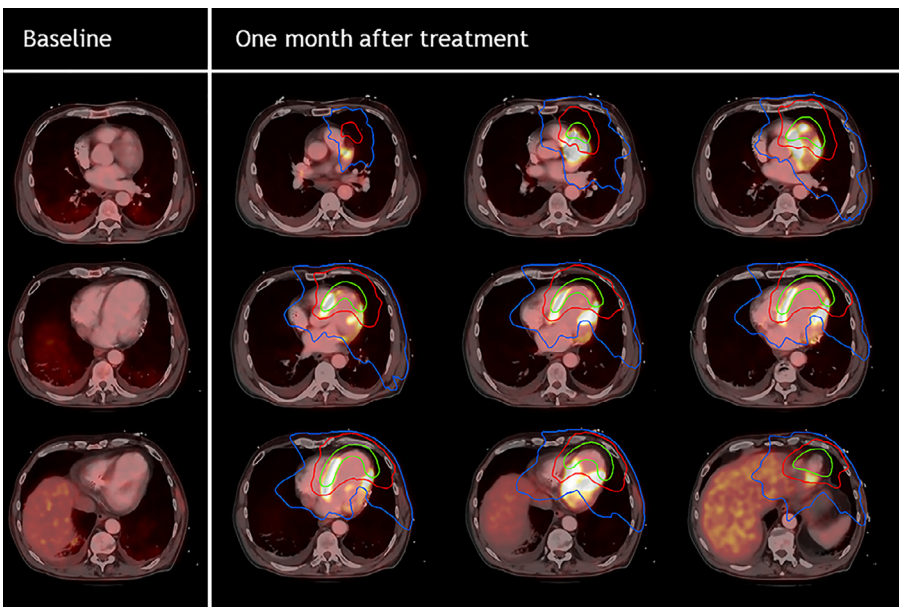

Figure 3 Representative transversal slices of the matched [^{18}F]FDG-PET/CT scan and the planning CT scan with the isodose lines. In green, the area receiving at least 25 Gy (100%); in red, 12.5 Gy (50%); and in blue, 5 Gy (20%) Increased metabolic activity is also seen in parts of the heart receiving lower radiation doses.

refractory period, altering the conditions required for re-entry, whereas catheter ablation aims to identify and disrupt the VT-pathways.[13]

Based on preclinical and clinical evidence, it was previously thought that cardiac radioablation would induce apoptosis as a consequence of double-strand DNA breaks inducing transmural myocardial fibrosis, which eliminates the zigzag conduction associated with re-entry.[2] However, fibrosis maturation is a process that takes several weeks to months and, as earlier effects of cardiac radioablation are observed, induction of fibrosis cannot explain its direct antiarrhythmic effects.[14-16] In our center, based on unpublished and published clinical experience indicating that cardiac radioablation could take many weeks to months to exert antiarrhythmic effects, we had not considered cardiac radioablation as an urgent treatment for patients with VT storm, despite the fact that in 2006 it was reported that irradiation could alter cardiac electrophysiology within 2 weeks after treatment.[17] In the current case, cardiac radioablation was expected to provide long-term antiarrhythmic effects and pharmacologic therapy was applied to bridge this period. However, the timing and magnitude of the effect with regards to VT reduction was remarkable and could only be due to direct electrophysiological alterations. These alterations were previously observed in preclinical work and were explained by the observation that the gap-junction protein connexin-43 was functionally upregulated 2 weeks after cardiac irradiation, leading to an increased conduction velocity.[17] This effect has been confirmed and shown to be durable, lasting at least a year.[18,19] It has recently been shown that in addition to connexin-43, voltage-gated sodium channels are upregulated within 6 weeks after cardiac irradiation. This radiation-induced reprogramming of cardiac electrophysiology resulted in supraphysiologic electrophysiology with increased conduction velocity.[3] Cardiac irradiation even reversed the slowed conduction in the border zone of myocardial scar.[3] Because a slowed conduction pathway is required for re-entry, increased conduction velocity could partly explain the antiarrhythmic effects of cardiac radioablation.[3,11] The extensive increased metabolic activity that was noted in this case on the repeat [^{18}F]FDG-PET/CT-scan 1 month after radiation therapy shows that radiation indeed caused increased myocardial metabolic activity, as described earlier.[20] This could indicate (cascade) inflammation and/or enhanced (repair) mechanisms, including the electrophysiological reprogramming of cardiomyocytes. Still, the exact mechanisms are yet to be elucidated. Preclinical work has shown that this increased metabolic activity is persistent even 12 months after irradiation and led to fibrosis and cardiac dysfunction.[21] Despite direct antiarrhythmic effects, irradiation does not appear to acutely cause myocardial injury, as indicated by stable troponin levels and the unchanged ejection fraction.

Although clinical and preclinical reports and inferred working mechanisms indicate a longer time to effect a result,[2] the direct clinical effects we observed are in line with several previous reports of patients with VT storm and incessant VF.[4-7] These reports also showed direct clinical effects in reducing the (short-term) arrhythmia burden combined with promising safety results.[4-7] Therefore, we believe there could be a role for cardiac radioablation in patients with VT storm when conventional therapy fails, although more data are necessary to confirm these results.

Conclusions

We present the case of a patient with VT storm and incessant VT who experienced direct clinical effects of cardiac radioablation. Therefore, even in patients with therapy-refractory VT storm and incessant VT, cardiac radioablation could be considered as a therapeutic option. The timing of the antiarrhythmic effect further supports the preclinical findings that not only induction of fibrosis, but (direct) electrophysiological reprogramming may play a key mechanistic role in cardiac radioablation.

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