Comparison of Measured Data between Pre- and Post-Radiotherapy in a Patient with Cardiac Resynchronization Therapy Defibrillator
A Hypothesis

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Summary
Although some researches proved the influence of radiation therapy (RT) on pacemakers and implantable cardioverter defibrillators, little has been reported on cardiac resynchronization therapy defibrillators (CRTDs). We experienced a case of RT on CRTD and had a new finding.

A patient with CRTD implanted for dilated cardiomyopathy was diagnosed with lung squamous cell carcinoma and started receiving RT. All the implanted devices, including the main body of CRTD, left ventricular lead (LV), right ventricular lead with high-voltage conductor, and right atrial lead, were from the same manufacturer. The radiation targeted the tumor of 67 mm in diameter in the right superior lobe for 5 min per session. The CRTD was outside the radiation field, which is 65 mm, but the leads were inside. Plan 1 used 2 Gy/fr with 8 megavolt photons, and Plan 1 was irradiated at 0° and 180° for 16 RT sessions. The dosage was increased to 3 Gy for Plan 2 for 4 sessions. Plan 3 used 2 Gy with 6 and 8 megavolt photons, and Plan 3 was irradiated at 27.7° and 200.7° for 11 RT sessions. Changes in measured parameters were assessed before and after RT.

Changes in impedance of LV and high-voltage lead exceeded prespecified threshold. However, no significant errors were detected in the CRTD on the dosages and energy we used.

We hypothesize that the lead insulator could have been affected by radiation.

Key words: Cardiac implantable electronic devices, CIEDs, CRTD, Radiation therapy

Case Report

A 68-year-old man with dilated cardiomyopathy underwent CRTD implantation in August 2015. All implanted devices were from the same manufacturer. In March 2016, he was diagnosed with lung squamous cell carcinoma and received RT from March to May 2016 (Figure A). The irradiation plans were based on the guidelines established by the Japanese Society for Radiation Oncology. The Linear accelerator was applied as the RT system control device. Plan 1 irradiated 2 grays per fraction (Gy/fr) with 8 megavolt photons (MVp), and the angle was adjusted at 0° and 180° for 16 RT sessions. Plan 2 irradiated 3 Gy/fr with 8 MVp, and the angle was adjusted at 0° and 180° for 4 RT sessions. Plan 3 irradiated 2 Gy/fr with 6 and 8 MVp, and the angle was adjusted at 27.7° and 200.7° for 11 RT sessions (Figure B). The CRTD was outside the radiation field, which is 65 mm. However, the three pacing leads were within the irradiation field.

During the pre-RT procedure, we examined the setup...
Figure. A: Image taken on the first day of hospitalization. The black triangle points to the tumor that is 67 mm in diameter. The white arrow points to the right atrial pacing lead (RA lead). The black arrow points to the left ventricular pacing lead (LV lead). The white triangle points to the right ventricular pacing lead with high-voltage conductor (RV lead, high-voltage lead). B: Irradiation angles on all the plans. It was irradiated from various angles. The CRTD was outside the irradiation field. The area framed by a red line was given 100% of the dose rate. That area included three pacing leads (pointed by the white arrow) besides the tumor. The black triangle points to the tumor that is 67 mm in diameter. The white triangle points to the CRTD device. C: Cross-sectional views of the leads. a: Left ventricular pacing lead (LV lead). b: Right ventricular pacing lead with high-voltage conductor (RV lead, high-voltage lead). c: Right atrial pacing lead (RA lead). CRTD indicates cardiac resynchronization therapy defibrillator; PTFE, polytetrafluoroethylene; and ETFE, ethylene tetrafluoroethylene.

to get the values on the items as shown in the Table and then disabled the defibrillation function of CRTD. During RT, we continuously monitored ECG while preparing the defibrillator with percutaneous pacing. And during post-RT, we enabled the defibrillation function of CRTD after checking on the items as follows and got the values by measuring them: pacing lead impedance, pacing lead threshold, and wave amplitude. Each value was calculated as post-RT minus pre-RT, respectively. Then, we compared the calculated values with the prespecified thresholds that Russo published. Furthermore, we checked on the adverse events during irradiation including artifact to ECG, inhibited pacing, unrecoverable errors with the programmer, loss of historical diagnostic data, spontaneous changes in programmed parameters, reset to backup mode, and loss of telemetry.

No noises or inappropriate pacing were observed during the irradiation. None of the adverse events for CRTD
were observed. The wave amplitude and pacing lead thresholds were not affected. In the pacing lead impedance, however, the session exceeding threshold was 18.8% in Plan 1, 50.0% in Plan 2, and 45.5% and 6.3% in Plan 3 (Table). The patient completed the RT with his tumor reduced in size in 2016. Then, the patient had follow-up visits at a clinic in his neighborhood.

Discussion

There were no significant changes that would have a clinical impact in the present case. However, we identified that the impedance values exceeded the prespecified threshold in two pacing leads (LV lead and high-voltage lead). The values for the RA and RV leads did not exceed the prespecified threshold. We thought that the insulation of the conductor might have been affected by irradiation, i.e., chemical reaction, which could have changed the impedance values. We considered that the factors for the change would be common in each lead. Then, the insulators coating the conductor caught our attention (Figure C). It is a type of polymer called (P)TFE (Figure Ca and Cb). In other word, only the insulator of the right atrial lead is made with silicone rubber. It has been reported that (P)TFE is an inconvenient polymer for radiation resistance, whereas silicone rubber is known as a radiation-resistant polymer. It has also been reported that irradiation can break molecular binding in the molecular weight polymers, leading to scission in macromolecules. The scission process usually produces deleterious effects, and the radiation damage to organic materials may depend not only on the absorbed dose but also on the irradiation duration and dose rate. Furthermore, the oxygen existing there reacts very rapidly with free radicals produced by irradiation. Unfortunately, human intravascular condition is oxygen rich.

In general, RT can affect the function of the generator, but the CIED leads are considered to be resistant to these effects. (P)TFE is known to be vulnerable in terms of radiation resistance, but the manufacturers recognize that the radiation intensity is much higher than the radiation dose used for cancer therapy. It is possible that (P)TFE may be denatured by heat as an immediate effect, but because the melting temperature of (P)TFE exceeds 280°, it does not seem appropriate to consider that it can happen in the human body.

On the other hand, only one case report presented a course of RT where direct irradiation was suspected to have caused malfunction of an ICD shock lead, leading to the reimplantation of the device. Therefore, we have not ruled out the possibility to support our hypothesis and remind ourselves that we should manage and maintain the effects of radiation at adequate levels. For the present case, the following changes could have been made as suggested in the previous study: (1) a remote monitoring system with daily evaluations should have been considered.

### Table.

Changes between Pre- and Post-Radiation Therapy and Measured Values

| Pacing lead impedance (ohms) * | Plan 1 (n = 16) | Plan 2 (n = 4) | Plan 3 (n = 11) |
|---------------------------------|-----------------|----------------|-----------------|
| % of sessions exceeding threshold | % of sessions exceeding threshold | % of sessions exceeding threshold |
| **Mean change (SD)** | **Mean values Pre** | **Mean values Post** | **Mean values Pre** | **Mean values Post** | **Mean values Pre** | **Mean values Post** |
| RA lead | 3.6 (8.1) | 413.6 (13.6) | 417.3 (12.7) | 0 (0) | 0 (0) | 407.5 (13.4) | 407.5 (15.0) | 0 (10.5) | 0 (11.6) | −3.0 (58.3) | 420 (96.5) | 417 (68.8) | 0 ± 50 |
| LV lead | 25.5 (39.3) | 872.7 (62.1) | 903.6 (33.2) | 18.8 (55.9) | 20.0 (128.4) | 18.9 (18.9) | 50.0 | −4.0 (0.0) | 852.5 (58.3) | 880 (96.5) | 45.5 ± 50 |
| RV lead | −4.5 (9.3) | 368.2 (14.0) | 363.6 (8.1) | 0 (9.6) | −7.5 (22.1) | 23.8 (15.9) | 0 | −9.0 (0.0) | 379 (15.9) | 370 (28.5) | 45.5 ± 50 |
| High-voltage lead | −0.4 (1.4) | 48.7 (1.4) | 48.4 (1.2) | 0 (1.0) | −0.5 (2.2) | 1.5 (2.4) | 0 | −0.7 (0.0) | 49 (2.4) | 48.3 (1.9) | 6.3 ± 3 |

Pacing lead threshold (volts at 0.5 ms) *

| *Pacing lead | RA lead | LV lead | RV lead | High-voltage lead |
|-------------|--------|--------|---------|------------------|
| **Mean values Pre** | **Mean values Post** | **Mean values Pre** | **Mean values Post** |
| RA lead | 0.0 (0.0) | 0.5 (0.0) | 0.5 (0.0) | 0.5 (0.0) | 0.5 (0.0) | 0.5 (0.0) | 0.5 (0.0) | +0.5 |
| LV lead | 0.0 (0.1) | 0.82 (0.12) | 0.82 (0.12) | 0.1 (0.13) | 0.81 (0.14) | 0.87 (0.0) | 0 (0.0) | 0.75 (0.0) | 0.75 (0.0) | +0.5 |
| RV lead | 0.0 (0.0) | 0.98 (0.08) | 1.0 (0.0) | 0 (0.0) | 1.0 (0.0) | 1.0 (0.0) | 0 (0.0) | 1.0 (0.0) | 1.0 (0.0) | +0.5 |

Wave amplitude (percent) †

| Wave amplitude (percent) † | Plan 1 | Plan 2 | Plan 3 |
|----------------------------|-------|-------|-------|
| P wave | −1.9 (14.5) | 4 (0.7) | 4.1 (0.5) | 1.7 (6.1) | 3.3 (0.3) | 3.4 (0.3) | −10.6 (16.3) | 4.3 (0.5) | 3.9 (0.6) | 0 ± 50 |
| R wave | 0.0 (0.0) | 11.9 (0.1) | 11.9 (0.1) | 0 (0.0) | 0.0 (0.0) | 11.9 (0.0) | 11.9 (0.0) | 0 (0.0) | 0 (0.0) | −25.0 ± 50 |

* Measured changes in device setting values = (post-RT − pre-RT) †Wave amplitude (%) = (post-RT − pre-RT) ÷ post-RT × 100 ‡Russo RJ, et al. Assessing the risks associated with MRI in patients with a pacemaker or defibrillator. N Engl J Med 2017; 376: 755-64.
instead of controls in the clinic or hospital; (2) the device evaluations should preferably be done, before the RT course, weekly during the RT course, and after the completion of the RT course, at least, but they were done even more frequently in this study; (3) the device evaluations should have been converted to evaluations after every fraction in case it needed a reset. Additionally, as a next challenge, we would like to start with a bench study to clarify the following: Is the molecular weight polymer really changing? How will the pacing lead impedance change by cumulative radiation doses or energy intensity?

In conclusion, we hypothesize that the molecular weight polymer of the lead insulator might be affected by radiation in the oxygen-rich condition, although the conductor inside the device body can be temporarily affected, and it can merely be a transient event. No significant errors were detected in the CRTD on the dosages and energy we used.

**Disclosure**

Conflicts of interest: The authors declare no conflict of interest for the present article.

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