Analysis of depolarization abnormality and autonomic nerve function after stereotactic body radiation therapy for ventricular tachycardia in a patient with old myocardial infarction

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Introduction

Japan experiences an estimated 70,000 cardiac deaths annually, mostly due to ventricular arrhythmias. While radiofrequency catheter ablation (RFCA) is an effective treatment option, stereotactic body radiation therapy (SBRT) is emerging as a complementary therapy when catheter ablation fails or is not desirable.[1] The greatest advantage is that irradiation takes an average of 15 minutes under consciousness, requiring no anesthesia, greatly reducing the patient's psychological and physical strain.[2] However, the electrophysiological mechanisms of the antiarrhythmic effect remain unclear. To the best of our knowledge, we performed the first SBRT for ventricular tachycardia (VT) in Japan. Herein, we report novel insights into the noninvasive parameters of electrocardiography (ECG) before and after treatment.

KEY TEACHING POINTS

- After stereotactic body radiation therapy (SBRT) treatment for refractory ventricular tachycardia, we used high-resolution ambulatory electrocardiography and observed changes to noninvasive parameters that are consistent with a less arrhythmogenic substrate.
- The metrics of ventricular depolarization and vagal tonus showed improvement over time, but the effect of radiation on cardiac sympathetic nerves remains unclear.
- Further studies regarding the antiarrhythmic effect of cardiac SBRT are warranted.

Case report

A 75-year-old woman presented with old anterior myocardial infarction (MI) and a low ejection fraction (27%). She underwent percutaneous coronary intervention for stenosis of the right coronary artery and standard pharmacotherapy at 53 years of age (in 1998). The left anterior descending artery was not operated because of chronic total occlusion. In 2012, an implantable cardioverter-defibrillator (ICD; Boston Scientific, Tokyo, Japan) placement was performed for sustained VT (Figure 1A). Previously documented ECG findings indicated complete right bundle branch block (CRBBB) morphology with an inferior axis (in the first 2 beats) and superior axis (in the following 3 beats), and V_6 QS pattern at the rate of 270 beats per minute (Figure 1B).

In 2019, she came to our emergency department by ambulance after receiving the first ICD shocks. ECG showed no obvious ischemic ST-T change, but echocardiography revealed severe hypokinesis/akinesis in the anterior septum, severe wall thinning, and aneurysmal changes in the apex. We performed a coronary angiography followed by percutaneous coronary intervention for the right coronary artery region where restenosis occurred and administered additional beta-blockers. One month later, ICD shocks were again applied; however, stress technetium-99m scintigraphy showed no signs of ischemia. Since RFCA was deemed appropriate, the physician explained the procedure to the patient and her

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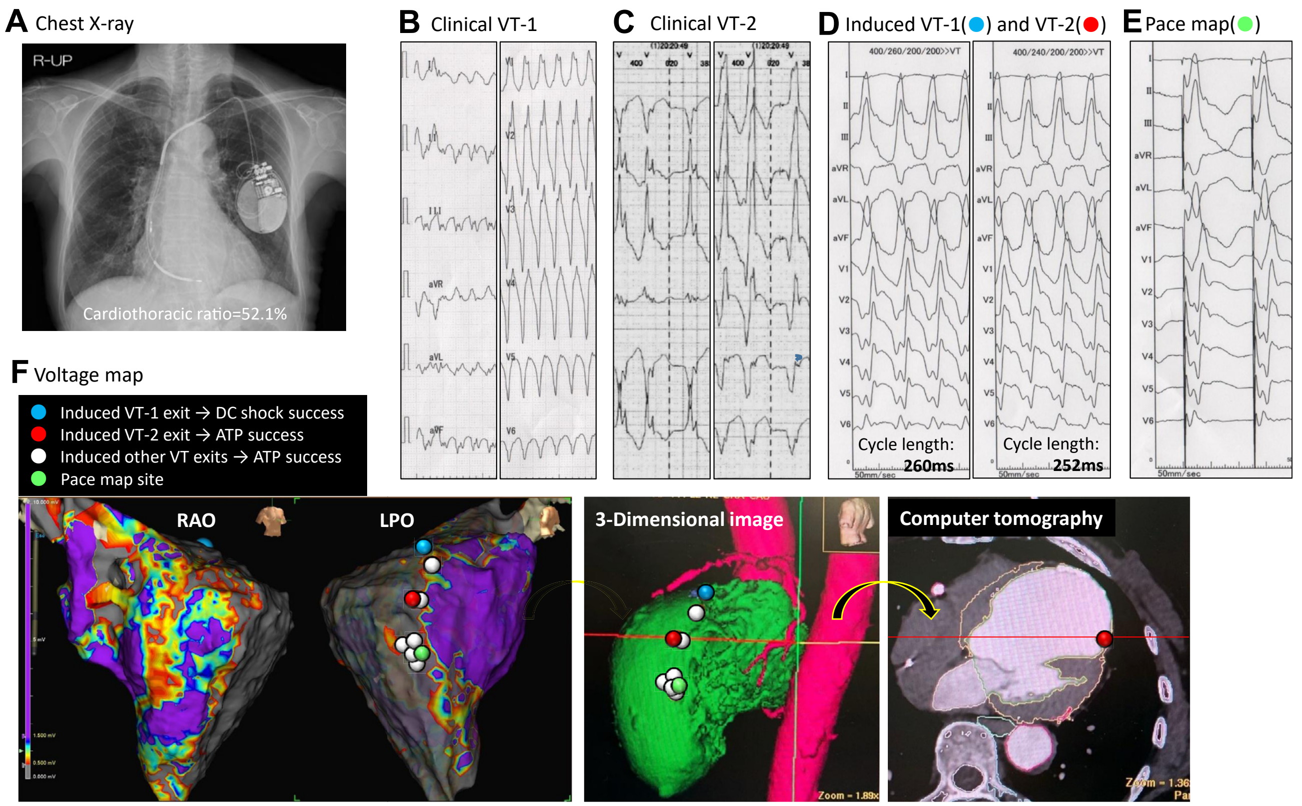


Figure 1 Electrophysiological findings. **A:** Chest radiograph with implantable cardioverter-defibrillator insertion and mild cardiac enlargement. **B, C:** Two types of clinical ventricular tachycardia (VT). **D, E:** Induced VTs and pace map morphology differed from clinical VTs. **F:** Multiple VT exits, and pace map site marked in the border zone of the endocardial voltage map. ATP = antitachycardia pacing; DC = direct current; LPO = left posterior oblique view; RAO = right anterior oblique view.

family. However, she chose not to undergo ablation because of concerns about the risk of electrophysiological study (EPS) and RFCA.

At the 2-month follow-up period, she complained of frequent presyncope, which was consistent with the nonsustained VT (CRBBB, inferior axis and V_6 QS pattern) documented by ambulatory ECG (Figure 1C). Therefore, 2 other physicians independently recommended RFCA, but informed consent was not obtained. As an alternative, SBRT was proposed as another treatment option after approval from a clinical research committee (Japan Registry of Clinical Trials: jRCTs, CRB3180004). The patient and her family were informed that this was the first case in Japan, irradiation may involve adverse effects, and an EPS was needed (Supplemental Data 1). We designed a treatment plan in collaboration with Washington University investigators at the Center for Noninvasive Cardiac Radioablation.

During EPS, an endocardial bipolar voltage map was obtained using the EnSite Precision system (Abbott, Abbott Park, IL), revealing an extensive low-voltage (<1.5 mV) area with left ventricle anterior septum scarring. Programmed stimulation from the right ventricular apex elicited more than 2 nonclinical VTs (Figure 1D). Left ventricle endocardial pace mapping failed to show the same morphology as the clinical VTs (Figure 1E). It was suggested that the reentry circuits responsible for clinical VT were located in the myocardium or epicardium (Supplemental Data 2). Electroanatomical substrates were marked on 3-dimensional images and exported to cross-sectional computed tomography (CT) images (Figure 1F).

Using the QRS axis-based algorithm in the 17-segments American Heart Association model, we identified segments with scars from the echocardiography, CT, scintigraphy, and positron emission CT (PET) data (Supplemental Data 3). Based on the results of all examinations, segment 17 was excluded from the target and segments 7, 12, 13, and 16 were included for irradiation (Figure 2A). Commercial software (Eclipse Ver 13.7; Varian Medical Systems Inc, Palo Alto, CA) was used to perform contouring for treatment planning with reference to the blood flow information from the merged images taken during the contrast-enhanced CT and PET examinations (Figure 2B). The gross target volume was 8.34 cm^3 (used instead of gross tumor volume); internal or planning target volume was created with a margin of 3 mm or 5 mm, respectively. A linear accelerator (True Beam STx; Varian Medical Systems Inc) was used for SBRT while the patient was awake and lying in the supine position on a vacuum-fixed cushion (Figure 2C). A single dose of 25 Gy was administered to provide maximum coverage within the treatment volume while minimizing peripheral organ risk. The procedure was based on the American Association of Physicists in Medicine Task Group 101 report. The total

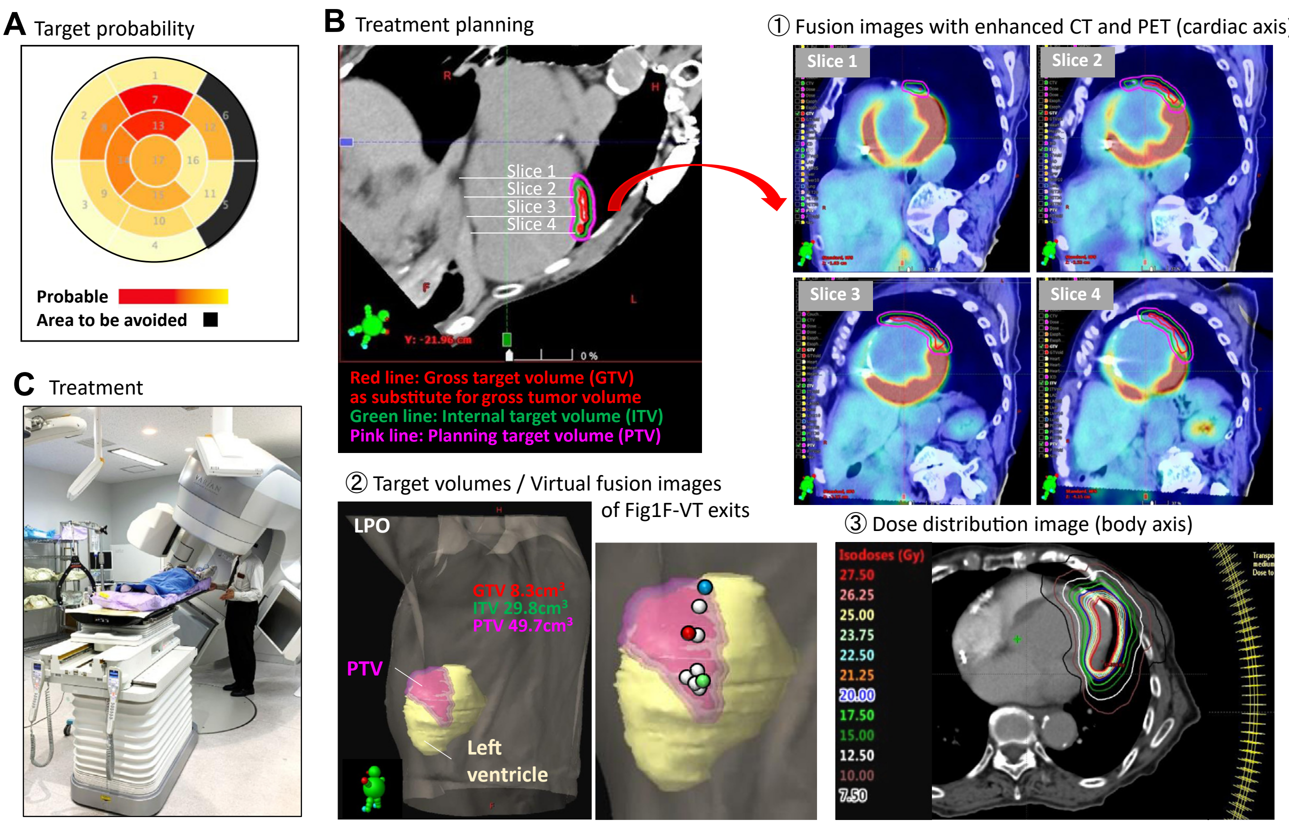


Figure 2 Radiation treatment plan. **A:** Target and non-target areas. **B:** Cardiac computed tomography (CT) with positron emission CT (PET) fusion images is used for contouring. **C:** Breathing instruction and treatment without anesthesia and pain-free conditions. LPO = left posterior oblique view.

procedure time was 51.5 minutes (beam-on time was <4 minutes). The patient's vital signs, ECG monitoring, and ICD equipment showed no abnormalities.

During the 6-month follow-up period, safety (Table 1) and antiarrhythmic effects (Table 2) were prospectively assessed. Since the patient had a history of pulmonary toxicity to amiodarone, only beta-blocker was used before and after SBRT. Quality-of-life scores and 6-minute walk distance improved (Table 1). No significant changes were found in laboratory or respiratory tests. The patient progressed well through monthly visits, without any adverse events (pericarditis, heart failure, or pneumonia) recognized on Common Terminology Criteria for Adverse Events Version 5.0. Analysis of cardiac episodes recorded with the ICD showed a 99% reduction in the total number of seconds of VT detected after radiotherapy, with no evidence of antitachycardia pacing and shock sequences (Table 2).

A high-resolution 24-hour ambulatory ECG (Spiderview Synescope; MicroPort, Paris, France) indicated a decrease in nonsustained VT and improvement of various noninvasive prognostic factors (Table 3), negative shift in late potential (LP; depolarization abnormality) at 6 weeks, increased heart rate variability (HRV; vagal activity) at 3 months, and

Table 1 Physical and mental assessments

	Baseline	1 week after RT	1 month after RT	4 months after RT	6 months after RT
QOL (points)	87	-	109	117	112
6MWT (m)	350	400	370	380	380
/min SpO_2 (%)	92%	96%	96%	97%	97%
BNP (pg/mL)	225.3	342.6	192.8	119.1	244.1
KL-6 (U/mL)	306	283	280	312	356
Respiratory function		-	-	-	
%VC	84.2				102.3
%FEV_1	98.0				98.4
%DLco	114.2				111.3
Adverse events	None	None	None	None	None

BNP = brain natriuretic peptide; DLco = lung diffusion capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; KL-6 = sialylated carbohydrate antigen KL-6; min SpO_2 = minimum percutaneous oxygen saturation; QOL = quality-of-life scores assessed by Medical Outcomes Study Short-Form 36-Item Health Survey; RT = radiotherapy; VC = vital capacity; 6MWT = 6-minute walk test.

Table 2 Arrhythmia episodes recorded by ICD

	Before RT	After RT
VT burden (s/during 6 months)	756.4	7.2
Nonsustained VT duration (average ± SD)	76.7 ± 51.3	1.1 ± 1.4
ATP sequences (times/during 6 months)	5	0
ICD shocks (times/during 6 months)	4	0

ATP = antitachycardia pacing; ICD = implantable cardioverter-defibrillator; RT = radiotherapy; VT = ventricular tachycardia.

normalized heart rate turbulence (HRT; baroreceptor sensitivity) at 6 months, including turbulence onset and turbulence slope (TS).

^{123}I-metaiodobenzylguanidine scintigraphy (^{123}I-MIBG; Fuji Film RI Pharma, Tokyo, Japan) showed an overall uptake deficit and increased washout both before and after treatment, which is consistent with the findings of chronic heart failure. Regionally, there was a marked reduction in uptake at the anterior free wall to the apex and increased washout at the inferior-posterior walls. A slight improvement was observed in the mismatch between early and late images, heart to mediastinum ratio, and washout after SBRT treatment (Figure 3).

Discussion

The initial goal of SBRT treatment was based on the concept of inducing fibrosis by tissue ablation of X-rays to create a conduction block in the reentry circuit.[1] However, the fact that VT suppression was achieved much earlier than 3–6 months before histological changes were observed suggests that additional radiobiological effects may contribute to antiarrhythmic effects.[2,3] Radiation directly affects tissue DNA, RNA, mitochondria, and proteins; the indirect effects include inflammatory responses, fibroblast proliferation, bystander effects, and immune activity; however, little is known about its effects on cardiomyocytes.

As previously reported,[1,2] we observed antiarrhythmic effects immediately after irradiation (Table 2) using 25 Gy and X-ray irradiation (Figure 2). We believe this is the first study to use high-resolution ambulatory ECG to determine changes in noninvasive parameters after radiotherapy (Table 3). Positive LP in patients with MI reflects heterogeneous and delayed conduction, while lack of LPs is associated with lower risk of VT and sudden cardiac death.[4] MI patients with spontaneous VT have shown decreased vagal tone,[5] and HRV indices are considered significant independent prognostic indicators of overall and cardiovascular mortality.[6] HRT, which reflects sympathovagal regulation against fatal cardiac arrhythmias, is a strong predictor of long-term cardiovascular mortality in patients with previous MI.[7] Turbulence onset reflects the ability of the baroreflex to increase heart rate after premature ventricular contraction, whereas TS reflects the ability to decrease heart rate in subsequent stretching. It has been reported that increased TS with beta-blockers is the result of improved baroreceptor control of heartbeat dynamics by suppression of sympathetic overactivation.[8]

In this case, LP negative conversion in the early postirradiation period suggests an improvement in depolarization abnormalities, while increased high-frequency power implies a predominance of vagal function. Furthermore, the normalized TS in the HRT may be related to the restoration of regulation in heart rate reduction via the baroreceptor reflex. Although it is not known whether irradiation induces suppression of the enhanced sympathetic nervous system, the ^{123}I-MIBG results might reflect organic degeneration of the sympathetic distribution or functional changes in adrenergic innervation. If heterogeneous nerve sprouting could be homogenized by irradiation-induced denervation, this could

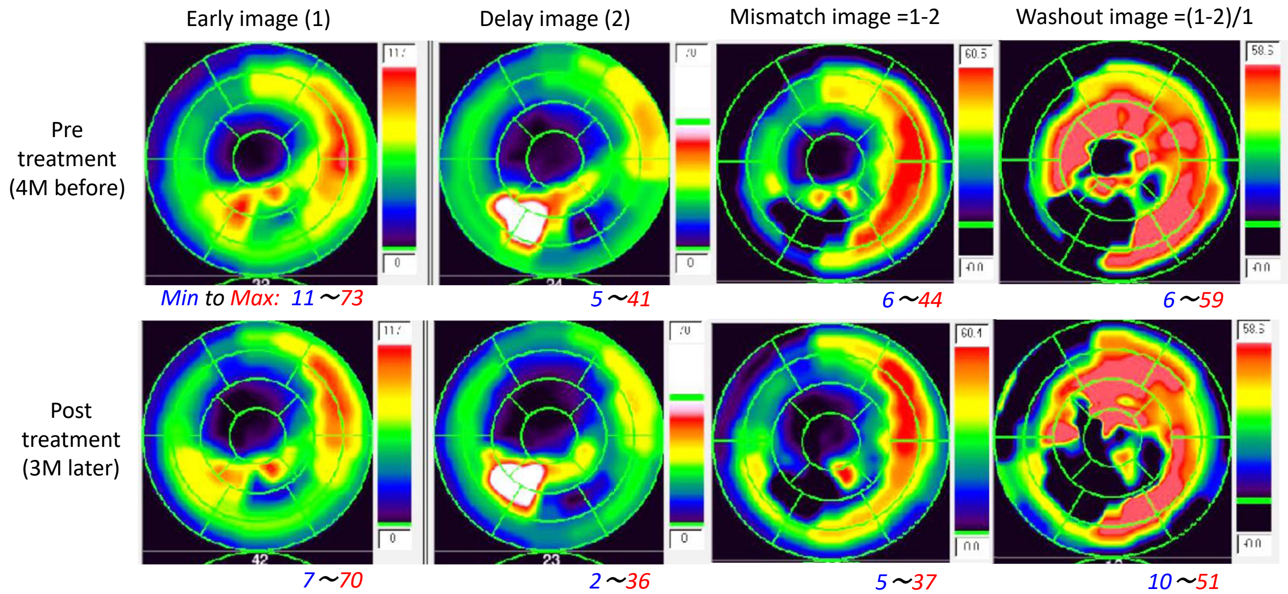
Table 3 Arrhythmia counts and noninvasive parameters determined by ambulatory electrocardiography

	2 months before RT	6 weeks after RT	3 months after RT	6 months after RT
Total heart rates (beats/24 h)	100,392	107,861	96,198	95,919
PVC (counts/24 h)	1508	1879	1303	414
Nonsustained VT (time/24 h)	3 [max 20 run]	1 [max 3 run]	1 [max 11 run]	0
Ventricular late potential†	Positive	Negative	Negative	Negative
F-QRS (ms)	156	156	154	153
LAS40 (ms)	43	31	32	30
RMS40ms (μV)	22	28	25	27
Heart rate variability				
LF (ms^2)	191	193	329	527
HF (ms^2)	240	202	475	602
LF/HF	0.79	0.96	0.69	0.88
Heart rate turbulence‡				
Category	Risk 1	Risk 1	Risk 1	Risk 0
TO (%)	-0.001	-0.015	-0.009	-0.02
TS (ms/R-R interval)	1.97	1.98	2.10	2.57

F-QRS = filtered QRS duration; HF = high-frequency power; LAS40 = duration of the terminal low-amplitude signal <40 μV; LF = low-frequency power; PVC = premature ventricular contraction; RMS40 = root mean square voltage of the terminal 40 ms of the F-QRS; RT = radiotherapy, TO = turbulence onset; TS = turbulence slope; VT = ventricular tachycardia.

†Ventricular late potentials was considered positive when 2 of the following 3 conditions were met: F-QRS ≥ 114 ms, LAS40 ≥ 38 ms, and RMS40 < 20 μV using the worst values obtained for 24 hours.

‡Heart rate turbulence was categorized as risk 0 with TO < 0% and TS > 2.5 ms/R-R, risk 1 with either TO ≥ 0% or TS ≤ 2.5 ms/R-R, or risk 2 with TO ≥ 0% and TS ≤ 2.5 ms/R-R.



Parameters	Pre treatment	Post treatment
Mismatch between early and delay images (Average ± SD)	19.2±12.7	16.1±9.4
Heart-to-Mediastinum activity ratio (H/M, normal value: 2.2) ▪ Early (Heart: count/pixel, Mediastinum: count/pixel) ▪ Delay (Heart: count/pixel, Mediastinum: count/pixel)	 1.77 (H:15.6, M:8.9) 1.78 (H:8.0, M:4.5)	 1.96 (H:13.4, M:7.3) 1.94 (H:8.0, M:4.4)
Washout ratio of whole heart (Normal range: 9. 6±5. 8%)	38.2%	30.5%

Figure 3 Sympathetic activity. ^{123}I-metaiodobenzylguanidine scintigraphy before and after treatment. The difference between early and delayed (3 hours later) phase provided the mismatch image. Washout images were created by dividing the mismatch image by the early-phase image.

reduce the repolarization dispersion under sympathetic stimulation, leading to reduced arrhythmogenesis.[9]

Previously, we conducted animal experiments with heavy ions and found that exposing a rabbit MI model to 15 Gy of carbon ion beams increased the expression of the gap junction protein connexin 43 (Cx43) at 2 weeks, leading to improved conduction abnormality, reduced spatial heterogeneity of repolarization, and decreased VT vulnerability.[10] The upregulation of Cx43 persisted for at least 1 year.[11] In the canine MI model, increased Cx43 expression was present 1 year after irradiation, alongside improved LP and decreased VT vulnerability.[12] In a study of patients with mediastinal carcinoma of the thoracic mediastinum requiring carbon beam therapy, noninvasive ECG parameters were analyzed before and after inevitable cardiac irradiation. LP and HRV improved, and arrhythmia decreased promptly after treatment in few cases.[13] Although the aforementioned studies examined the effects of carbon beams,[10–13] the favorable electrophysiological findings in our study (Table 3) suggest that X-rays may have similar biological effects to carbon ions. Basic experiments on the influence of X-rays on cell-cell coupling are warranted.

Limitation

The HF component reflects the fluctuations in the frequency of neurotransmitter impulses reaching the sinus node and may not necessarily suggest reduced or impaired cardiac vagal activity. The LF component is defined by arterial pressure and strongly influenced by baroreceptor reflex sensitivity. Since LF/HF is dependent on HF changes, sympathetic function cannot be directly assessed. MIBG helps detect sympathetic activity. In this report, whether the HRV improvements are due to a direct radio-modification in vagal function or a secondary response for sympathetic denervation is unclear. While acute antiarrhythmic effects are recognized, most long-term autonomic interventions for arrhythmias (sympathetic denervation/stellate ganglionectomy, renal denervation, etc) require several weeks to present their definitive antiarrhythmic effects, hence configuring the blanking periods. Changes in autonomic function in the chronic phase should be carefully monitored.

Conclusion

In MI patients with VT, SBRT rapidly reduced arrhythmic episodes and improved depolarization abnormalities, while also recovering vagal activity and baroreflex function. These findings may partly explain the mechanism of the antiarrhythmic effects of X-ray irradiation while demonstrating the utility of high-resolution ambulatory ECG in objectively assessing electrophysiological instability.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2021.01.023.

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