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# Correlation between radiation dose and myocardial remodeling after stereotactic radiation therapy for ventricular tachycardia: First assessment of dose-effect relationship in human

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**Running title:** Correlation between radiation dose and myocardial remodeling after stereotactic radiation therapy for ventricular tachycardia in human

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Cardiac stereotactic body radiation therapy (SBRT) is an emerging treatment for refractory ventricular tachycardias (VT) resistant to medication and/or catheter ablation (CA)(1). Data regarding myocardial remodeling resulting from cardiac SBRT in humans are scarce. We aimed to describe the correlation between radiation dose received and the resulting electrophysiological effect.

A 62-years-old man with non-ischemic cardiomyopathy was referred for cardiac SBRT for refractory VT after unsuccessful CA procedures, most likely due to an intramural location of the substrate. Using Versa HD linear accelerator (Elekta, Crawley, UK), a single radiation dose of 25 Gy was delivered to the basal inferolateral left ventricle (LV), over a planning target volume (PTV) of 85 cc (*Figure 1A*). Eight months later, the patient presented with a new VT different from the one initially targeted, requiring redo CA. Both procedures were performed using CARTO® 3D system (Biosense Webster Inc., California, USA). High density voltage maps (Pentaray®) were performed in sinus rhythm (*Figure 1B*). Dense scar, low voltage areas and normal myocardium were defined as bipolar voltage < 0.5 mV, 0.5-1.5 mV and > 1.5mV, respectively. Pre- and post-radioablation electroanatomical data were registered to the cardiac computed tomography (CT) using automatic registration (Coherent Point Drift probabilistic algorithm), manually corrected and validated by two cardiologists (RPM, KB). Dose distribution was registered to the cardiac CT using automatic rigid registration based on intensity correlation with the corresponding thoracic CT, manually corrected by a cardiologist (RPM) and a radio-oncologist (RDC). Each pre-SBRT measurement with bipolar voltage > 0.5mV was linked to the nearest post-SBRT point. Pre-SBRT measurements with no corresponding post-SBRT measurements closer than 3mm were not considered. The study was approved by local ethical committee.

Based on this matching, 631 pairs of voltage measurements were analyzed. Regarding radiation dose, 82 (13.0%), 116 (18.4%), 106 (16.8%), 87 (13.8%), 84 (13.3%) and 156 (24.7%) voltage pairs received a dose of 0-5 Gy, 5-10 Gy, 10-15 Gy, 15-20 Gy, 20-25 Gy and above 25 Gy, respectively. LV myocardium receiving less than 15 Gy had no significant change in mean bipolar voltage between pre- and post-SBRT. Conversely, LV myocardium in the 15-20 Gy, 20-25 Gy and >25 Gy dose ranges had a significant change in mean bipolar



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voltage, decreasing from 3.9±3.3mV to 0.4±0.5mV ($p<0.001$), 1.1±0.7mV to 0.3±0.2mV ($p<0.001$), and 1.0±0.6mV to 0.2±0.3mV ($p<0.001$), respectively (*Figure 1C*).

Cardiac SBRT is a promising technique for the treatment of refractory VTs. Pre-clinical studies have specified the dose-effect relationship leading to the current radiation dose of 25 Gy(2). However, there is no data regarding myocardial remodeling resulting from SBRT in humans, particularly the dose-effect relationship in real-world SBRT setting. *Amino* et al previously reported in rabbit hearts the same threshold of 15 Gy for reducing ventricular arrhythmias vulnerability(3). *Zhang*'s paper recently suggested that cardiac SBRT would promote an increase in conduction velocities through cellular reprogramming, potentially explaining the observed acute effects of SBRT, even for low radiation doses. Our work suggests the existence of a delayed radioablative effect with reduced bipolar voltage and dense scar formation in myocardial regions receiving a radiation dose ≥15 Gy. These two electrophysiological mechanisms most likely coexist after cardiac SBRT, at different degrees depending on the delay from treatment delivery.

In conclusion, this case of remapping 8 months after SBRT shows a reduction in bipolar voltages for myocardium exposed to radiation doses ≥15 Gy. This result and recent works suggest that for doses below 25 Gy, two anti-arrhythmic effects of SBRT may coexist: an early effect explained by electrical cell reprogramming and a delayed ablative effect explained by increased scar formation. However, there is no data regarding the durability of these low-dose effects on the control of ventricular arrhythmias. Although further studies are needed to confirm these results, these data may be of interest to optimize future cardiac SBRT treatment plans, particularly in complex cases where organs at risk are close to the PTV.



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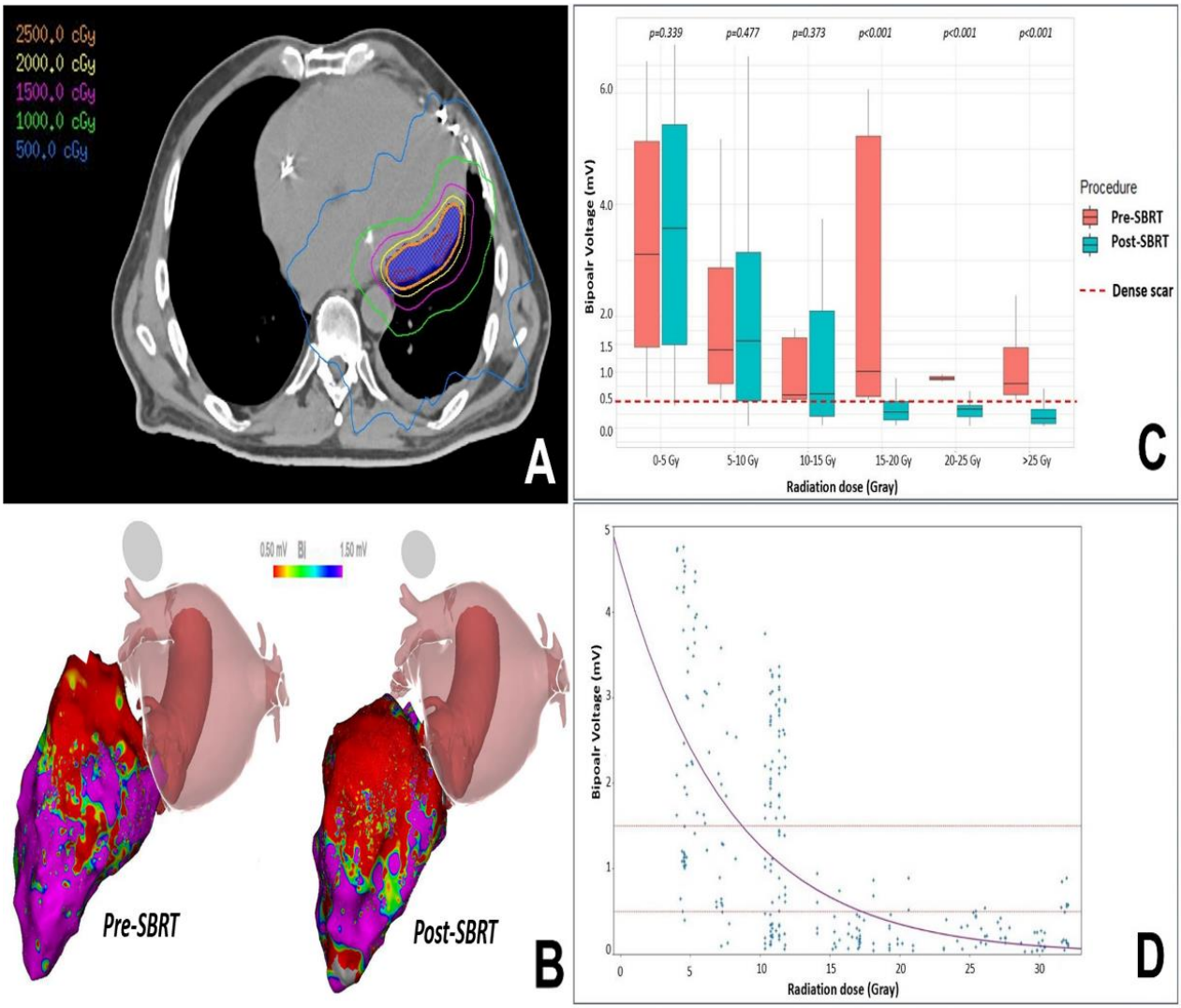
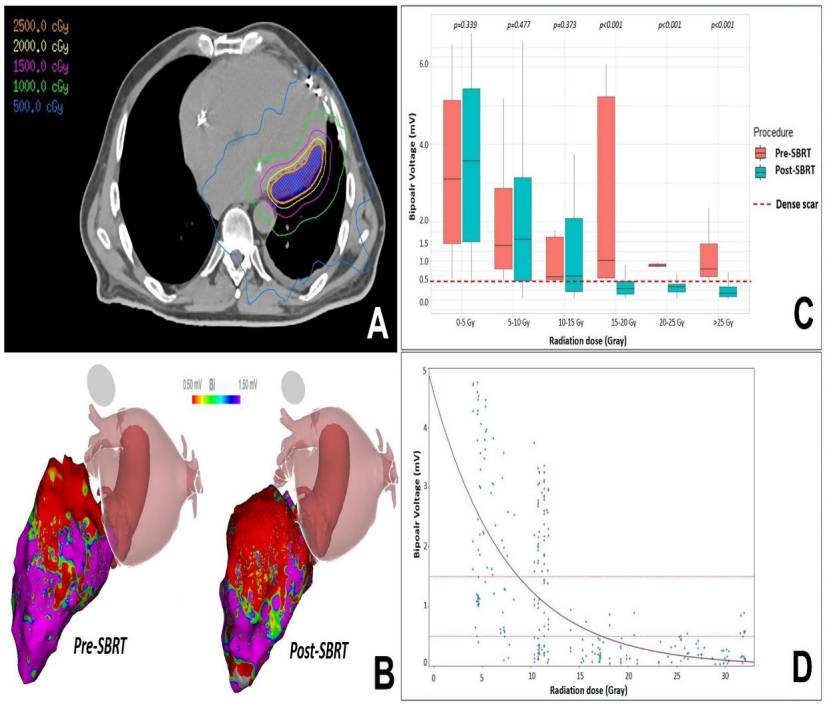



*Figure 1: Panel A – Cardiac SBRT target volume and dose distribution. Panel B– Pre/post SBRT voltage maps of the LV. Panel C– Evolution of bipolar voltages between pre and post SBRT depending on the radiation dose received. Panel D – Post-SBRT bipolar voltage as a function of the radiation dose received for points with pre-SBRT voltage >1.5mV.*



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