Basic mechanism of atrial and ventricular arrhythmia suppression by heavy ion irradiation in hypercholesterolemic elderly rabbits

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Background: Recent development of electrophysiology-guided noninvasive cardiac radioablation therapy for ventricular tachycardia attracts a great deal of attention as a novel antiarrhythmic strategy (Robinson CG, Circulation 2019). As to underlying mechanisms, however, much remains to be clarified. We reported before that a single targeted heavy ion irradiation (THIR 15Gy) to rabbit hearts increased connexin43 (Cx43) expression, and a reduction of vulnerability to ventricular arrhythmias after myocardial infarction.

Purpose: We investigated the effects of THIR on in-vivo cardiac electrophysiology and vulnerability to atrial and ventricular tachyarrhythmias in aged rabbits with hypercholesterolemia.

Methods: Sixteen three-year old rabbits were fed with high fat/cholesterol chow (0.5% cholesterol and 10% coconut oil) for 14 weeks. A single THIR 15Gy was applied to 8 rabbits (HC+THIR) with a heavy ion medical accelerator. Eight rabbits without THIR were used as control (HC).

Results: Serum cholesterol levels in the HC and HC+THIR were 1545+386 and 1569+328 mg/dl (n=8, NS). Atrial (P-wave) late potential in signal-averaged ECG in HC+THIR showed a significantly larger root mean square voltage (RMS) than those in HC (12+0.5 vs. 2+0.5μV, n=4, $p<0.01$). Ventricular late potentials in HC+THIR showed significantly less fQRS-D than HC (81+5 vs. 89+7 ms); less LAS40 (21+7 vs. 30+4 ms), and larger RMS (99+27 vs. 44+13μV) (n=4, $p<0.04$). Atrial tachycardia or fibrillation (AT/AF) was induced spontaneously or by programmed/burst pacing of the left atria (LA) in 4 out of 4 HC, whereas in only 1 out of 4 HC+THIR. Ventricular tachycardia or fibrillation (VT/VF) was induced spontaneously or by programmed pacing or left stellate stimulation in 4 out of 4 HC rabbits, whereas in only 1 out of 4 HC+THIR. Immunolabeled Cx40 densities in LA and RA tissue from HC+THIR rabbits were significantly higher than those from HC rabbits by 44% and 60%, respectively (n=4, $p<0.01$). Comparable upregulation of immunoreactive Cx43 was observed in LV and RV tissue from HC+THIR rabbits. Sympathetic nerve densities in LA, RA, LV and RV tissues, which was labeled with anti-neuronal growth-associated protein 43 (GAP43) antibody and tyrosine hydroxylase (TH) antibody were both significantly less in HC+THIR than those in HC.

Conclusion: These results suggest that THIR may improve cardiac conductivity of HC rabbits in favor of reduction of vulnerability to atrial and ventricular tachycardia/fibrillation, and that this antiarrhythmic effect is attributed to upregulation of gap junction protein (Cx40 and Cx43) and in part to prevention of sympathetic nerve sprouting.