Cellular consequences of non-ablative radiotherapy, a novel approach to ventricular tachycardias

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Abstract:
Background. Catheter ablation is currently among the main approach for the treatment of drug-resistant ventricular tachycardia (VT). A single application of ionizing radiation (RT) has been recently suggested as a non-invasive alternative to ablate the substrate of VT. Preliminary data revealed that RT may suppress the arrhythmia without tissue ablation, thus suggesting a functional mechanism. In a murine model, the latter consists of faster conduction supported by increased expression of NaV1.5 channels and connexin 43.
Aims. i) To investigate whether the increased expression of Na^+ channels could enhance also the late component of Na^+ current (I_{NaL}); ii) to study the effects of RT on electrical activity of mouse ventricular cardiomyocytes (CMs).
Methods. Cells isolated 2 weeks after RT with low-dose (15 Gy) or high-dose (25 Gy) were compared to those of non-treated mice (CTRL). We evaluated: i) the transient (I_{NaT}) and late (I_{NaL}) I_{Na} components; ii) the action potential (AP) contour and the incidence of Early After Depolarizations (EADs) of proarrhythmic significance (*patch-clamp*); iii) CaMKII phosphorylation (*Western blot*), and iv) ROS (DCFDA fluorescence intensity through *THUNDER LIVE imaging system*).
Results. 25 Gy RT increased I_{NaT}, the AP amplitude and the maximum upstroke velocity (dV/dt_{MAX}), consistent with the previously reported increment in conduction velocity. RT preferentially enhanced I_{NaL}, resulting in a higher I_{NaL}/I_{NaT} ratio. With 15 Gy the same trends were observed, but changes were smaller (dose-dependency) and achieved statistical significance for I_{NaL} only. AP duration (APD) was increased (i.e., the refractory period was prolonged) and EADs tended to occur more often in RT CMs. CaMKII phosphorylation was reduced, but ROS levels were increased with 25 Gy RT, thus providing a likely mechanism for I_{NaL} enhancement.
Conclusions. An increase in I_{NaT} may underly the RT-induced effect on conduction velocity. I_{NaL} enhancement and the resulting APD prolongation is an additional mechanism reducing the re-entry inducibility. On the other hand, I_{NaL} enhancement (likely by ROS) may compromise electrical stability (EAD increased) and impair intracellular ionic homeostasis. This suggests the use of corrective measures (selective I_{NaL} blockade, ROS scavenging) during the RT procedure.