Ivabradine causes abnormal intracellular calcium handlings and delayed afterdepolarizations to induce atrial fibrillation in rabbit hearts

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Abstract

Objective: The present paper is to determine the effects and underlying mechanisms of ivabradine (IVA) on atrial fibrillation (AF). Methods: Electrophysiological changes were determined using Langendorff-perfused hearts and patch-clamp techniques. Parameters of Ca²⁺ handling were evaluated by using calcium imaging and western blotting. Results: IVA (0.1-10 μM) slowed HR in a concentration-dependent manner in isolated hearts of rabbit. IVA induced atrial arrhythmias in 26.1% and 76.9% of hearts paced at a basic cycle length of 350 and 570 ms, respectively. In hearts pretreated with either acetylcholine (ACh) or anemone toxin-II (ATX-II) which caused no inducible atrial arrhythmias, adding to IVA administration caused atrial arrhythmias in 61.9% (13/21) and 44.4% (8/18) of hearts, respectively. In atrial myocytes, IVA induced DADs by 41.7%, 62.5% and 50.0%, respectively, in the absence and presence of either ACh or ATX-II. IVA increased the frequency, amplitude and full width at half-maximum (FWHM) of Ca²⁺ sparks and decreased Ca²⁺ transport in association with increased protein expression of RyR2 and NCX1 and decreased SERCA2. Conclusion: IVA increases atrial proarrhythmic risk in hearts with a slow HR, enhanced vagal tone and increased late sodium current by inducing DADs resulting from an enhanced intracellular Ca²⁺ homeostasis.

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a. Control (CL=350 ms)

b. Low rate (CL=570 ms)

c. IVA (0.3 μM)

d. ATX-II (2 nM)

e. ATX-II (2 nM) + IVA (0.3 μM)

f. ACh (0.3 μM)

g. ACh (0.3 μM) + IVA (0.3 μM)