

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

Chengyu Wang¹, Bingxun Li¹, Mingjie Lin¹, Qiaomei Yang¹, Gang Li¹, Xiaoyan Liu¹, Qing Zhang¹, Shandong Yu¹, and Lin Wu¹

¹Affiliation not available

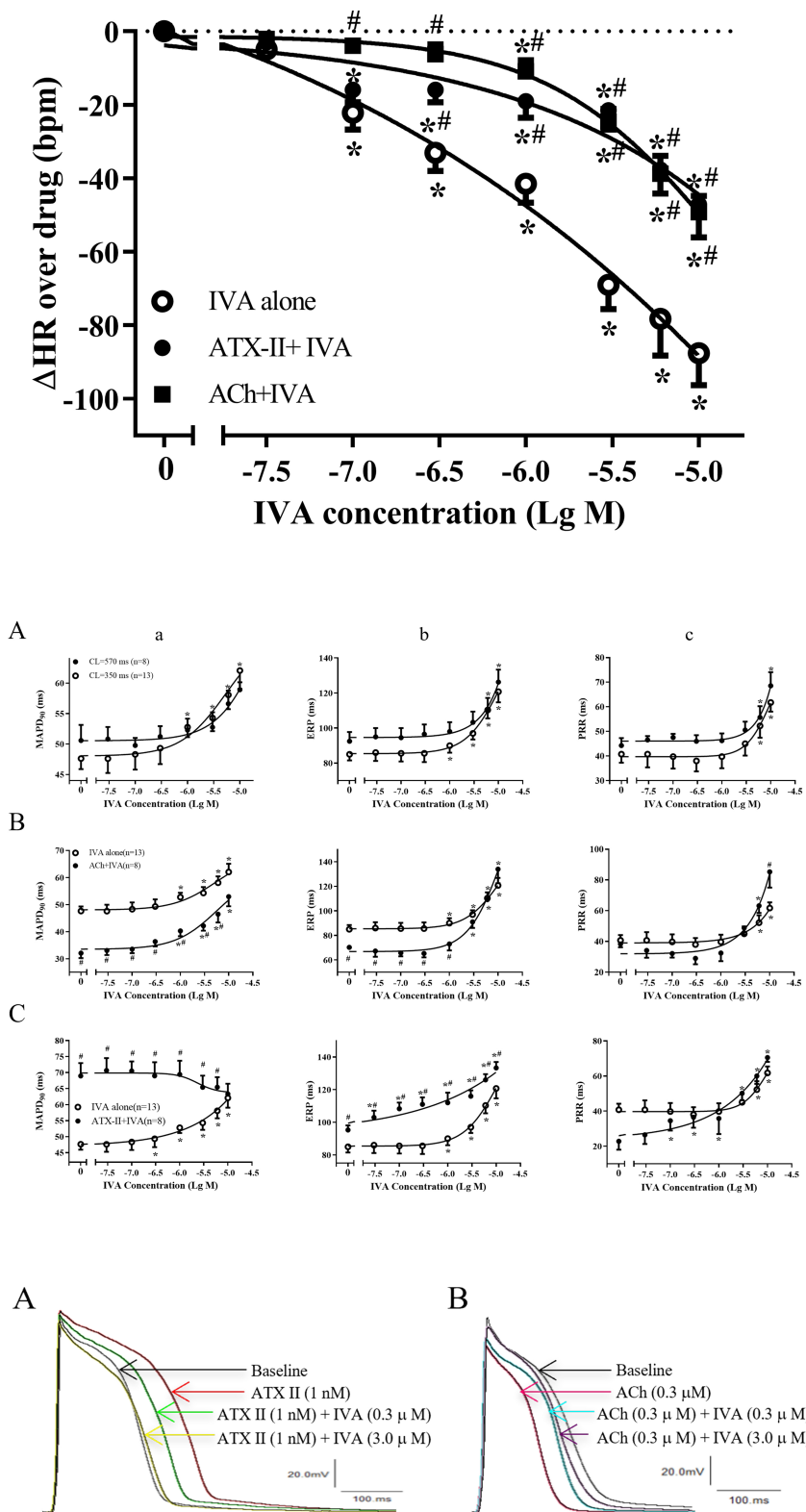
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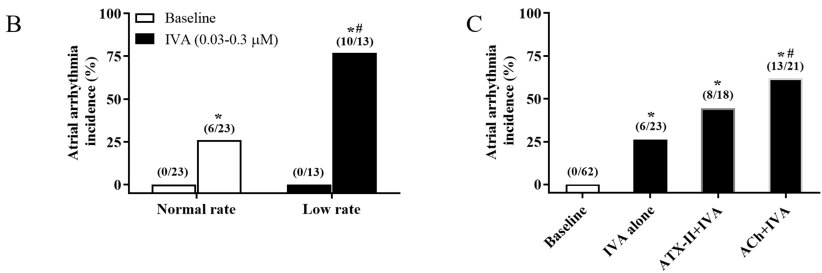
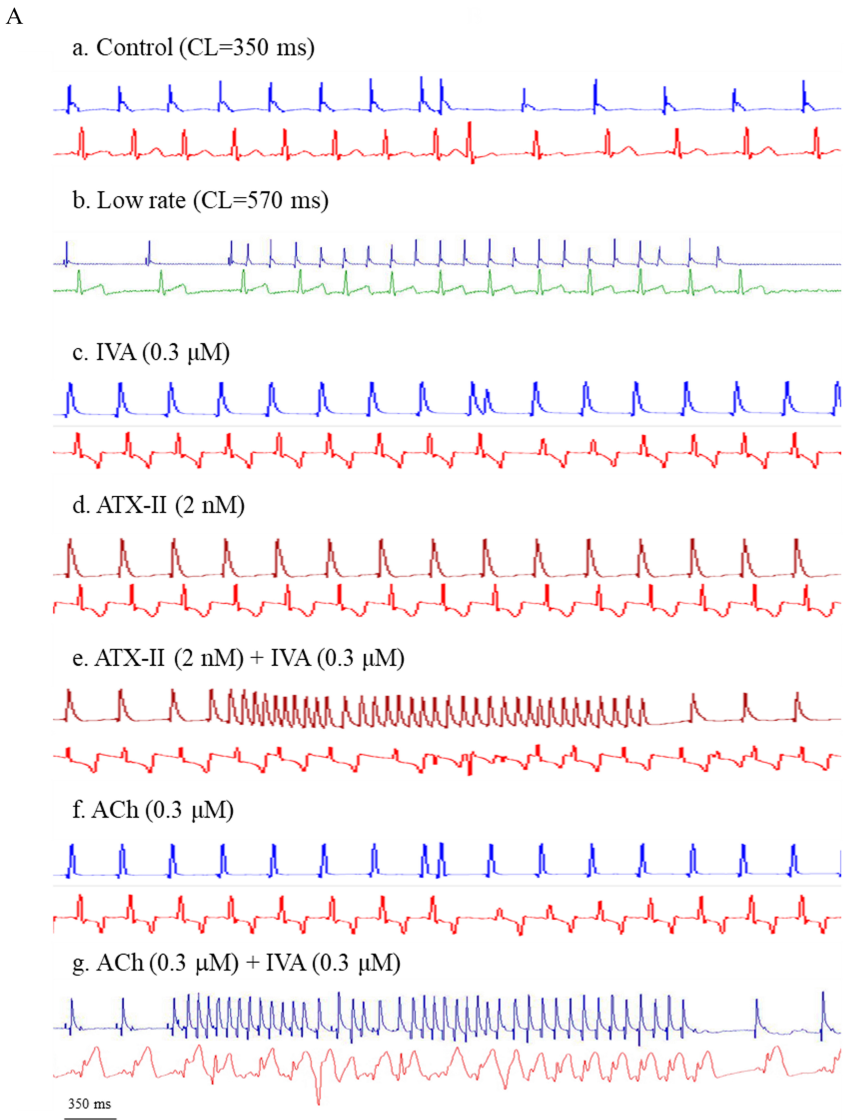
Abstract

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 Ca^{2+} 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 Ca^{2+} sparks and decreased Ca^{2+} 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 Ca^{2+} inhomeostasis.

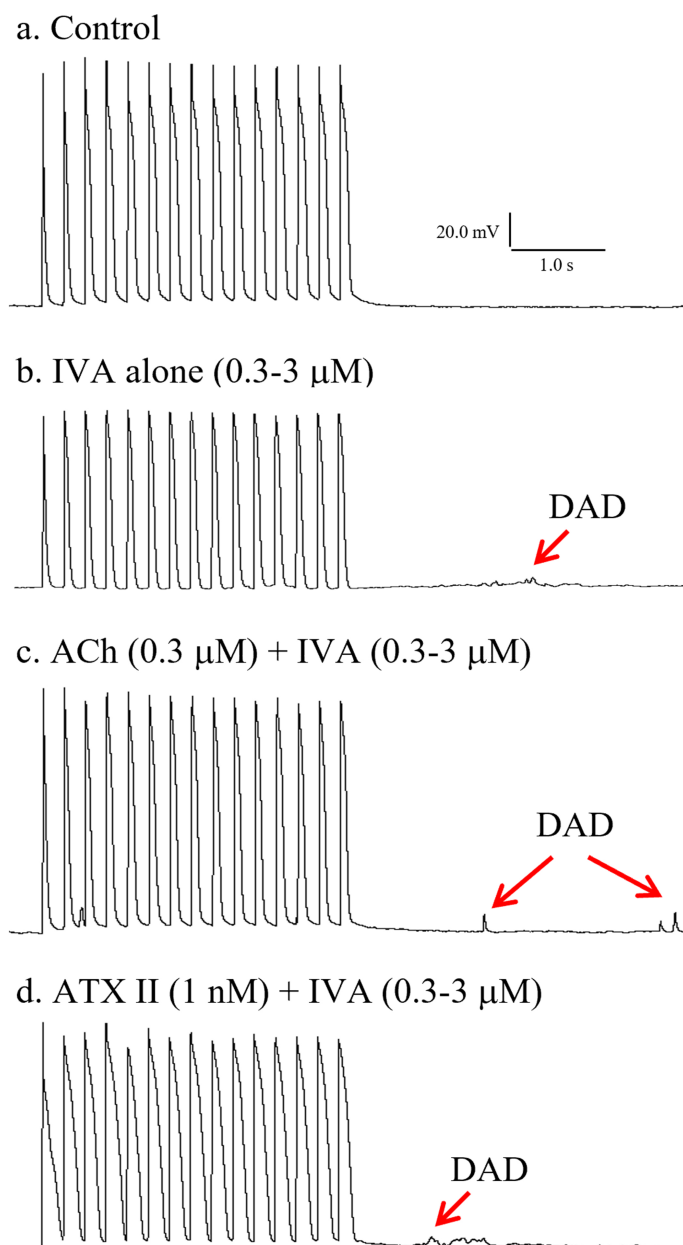
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