Atrial-selective Sodium Channel Block as a Strategy for Suppression of Atrial Fibrillation.

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ABSTRACT: Antiarrhythmic drug therapy remains the principal approach for suppression of atrial fibrillation (AF) and flutter (AFl) and prevention of their recurrence. Among the current strategies for suppression of AF/AFl is the development of antiarrhythmic agents that preferentially affect atrial, rather than ventricular, electrical parameters. Inhibition of the ultrarapid delayed rectifier potassium current (I_{Kur}), present in atria, but not ventricles, is an example of an atrial selective approach. The present study examines the hypothesis that sodium (Na^+) channel characteristics differ between atrial and ventricular cells and that atrial-selective Na^+ channel block is another effective strategy for the management of AF. We demonstrate very significant differences in the inactivation characteristics of atrial vs. ventricular Na^+ channels and a striking atrial selectivity for the action of ranolazine, an inactivated-state Na^+ channel blocker, to produce use-dependent block of the Na^+ channels, leading to depression of excitability, development of post-repolarization refractoriness, and suppression of AF. Lidocaine and chronic amiodarone, both predominantly inactivated-state Na^+ channel blockers, also produced an atrial-selective depression of Na^+ channel dependent parameters (Vmax, Conduction velocity, Diastolic Threshold of excitation, and Post-repolarization refractoriness-PRR). Propafenone, a predominantly open-state Na^+ channel blocker, produced similar changes of electrophysiological parameters, which were not atrial-selective. The ability of ranolazine, chronic amiodarone and propafenone to prolong the atrial action potential potentiated their ability to suppress AF in coronary-perfused canine atrial preparations. Conclusion: Our data demonstrate important differences in the inactivation characteristics of atrial vs. ventricular Na^+ channels and a striking atrial selectivity for the action of agents like ranolazine to produce use-dependent block of Na^+ channels leading to suppression of AF. Our findings suggest that atrial selective Na^+ channel block may be a valuable strategy to combat AF

KEYWORDS: Electrophysiology, cardiac arrhythmias, atrial vs ventricular, sodium channels, lidocaine, amiodarone, ranolazine, propafenone

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