In silico prediction of the effects of ethanol on cardiac cellular electrophysiology and reentrant arrhythmias

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Introduction: Acute and chronic alcohol consumption alter cardiac electrophysiology and may promote arrhythmias, notably atrial fibrillation (AF). However, the underlying mechanisms and interaction between ethanol-induced and AF-related proarrhythmic remodeling remain incompletely understood. Here, we employ computational modeling to integrate recent experimental data about the acute effects of ethanol and study proarrhythmic consequences in the ventricles, and in the atria with and without AF-related remodeling.

Methods: Multi-scale simulations were performed in Myokit using the Courtemanche human atrial and Passini human ventricular models. To simulate the effects of ethanol in long-standing persistent (‘chronic’) AF (cAF), a cAF version of the human atrial model with electrical remodeling of cardiac ion channels was implemented. Acute electrophysiological effects of ethanol were incorporated in all three models based on previously published experimental data: reduced $\text{INa}$, $\text{ICa,L}$, $\text{IKr}$ and $\text{Ito}$, and dual effects on $\text{IK1}$ (inhibition at low concentrations, augmentation at high concentrations; Fig. A). The potential proarrhythmic effect of ethanol was investigated at the cellular and tissue level. Reentry was simulated using an S1S2 induction protocol in homogeneous tissue of 8x8 cm (400x400 units).

Result: Simulated application of 0.8, 80 and 400 mM ethanol had distinct effects on action potential duration (APD) and resting membrane potential (RMP) in human atrial and ventricular cardiomyocyte models (Fig. B). The lowest concentration of ethanol (0.8 mM) prolonged APD by ~5% in both control and cAF models and depolarized the RMP in the control atrial model, but had no effect on ventricular APD or RMP. However, 80 mM and 400 mM ethanol significantly reduced atrial APD and hyperpolarized RMP, particularly in the control atrial model, while significantly prolonging ventricular APD (Fig. B). At the tissue level, 0.8 mM ethanol slightly increased conduction velocity (CV) while shifting the vulnerable window (WoV) to the right in the control atrial model (Fig. C-E), but did not affect reentry in the ventricle (Fig. F-H). By contrast, 80 mM ethanol slightly reduced CV, shifted the vulnerable window to the left and prolonged the duration of reentry in the atria, but reduced the vulnerable window in the ventricle. The cAF model showed a large vulnerable window with unstable reentry and reentry duration was prolonged by ethanol (Fig. I-K).

Conclusion: Our simulations suggest that ethanol has concentration-dependent electrophysiological effects that differ between atria and ventricles, and in the absence or presence of AF-related remodeling. Low concentrations of ethanol could have anti-AF effects whereas moderate- and high-concentrations may promote AF. These findings facilitate a better understanding of the complex effects of alcohol consumption on cardiac electrophysiology.