Combining Pharmacokinetic and Electrophysiology Modeling for Studying Vulnerability to Alcohol-Induced Arrhythmia

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Introduction: Alcohol consumption increases arrhythmia occurrence. The effects of ethanol on cardiac electrophysiology have been described for concentrations that reflect only partially the blood alcohol concentrations (BACs) associated with recreational drinking. This study investigates the acute effects of commonly observed BACs on atrial arrhythmia vulnerability, with particular focus on sex-specific differences in ethanol pharmacokinetics.

Methods: Ethanol pharmacokinetics were modeled using a 3-compartment model with specific gastric emptying, elimination and absorption rates, and Michaelis constant for a male and a female subject. Peak BACs were obtained for ethanol doses of 10-50 g, corresponding to 1-5 standard drinks, respectively (Fig. A). A homogeneous 2D sheet of virtual atrial tissue (8x8 cm, resolution 400 μm, the same electrophysiology for male and female) was constructed and the ethanol effect on ionic currents was modeled according to Sutanto et al. (*J Mol Cell Cardiol* 2020, 146, 69-83). Re-entry was induced by an S1S2 cross-field stimulation, considered inducible if persisted for >1 s, and monitored for 10 s. The simulations were performed under control and chronic atrial fibrillation (cAF; Grandi et al., *Circ Res* 2011, 109, 1055-1066) conditions, and in the presence of normal (80 cm/s) and low (50 cm/s) conduction velocity (CV).

Results: An increased duration of re-entrant arrhythmia was observed in the presence of ethanol in cAF simulations (Fig. B). No re-entry was inducible in the control simulations with normal CV. Only small differences in total arrhythmia duration were observed between the simulations with male- and female-specific BACs (cAF 50 cm/s: 156 [152-168] s vs. 170 [156-170] s, p = 0.3125; cAF 80 cm/s: 56 [38-61] s vs. 55 [38-61] s, p=1.0).

Conclusion: Recreational drinking increases stability of re-entrant arrhythmia in cAF. The sex-specific differences in ethanol pharmacokinetics play only a minor role in acute alcohol-induced atrial arrhythmia.