

# Insights Gleaned from Multiscale in Silico Simulations

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## Editorial

Acute overconsumption of ethyl alcohol (ethanol) changes cardiac electrophysiology and may cause cardiac arrhythmias, as seen in 'holiday heart syndrome.' In cardiomyocytes, ethanol affects a variety of targets, including ion channels, Ca<sup>2+</sup>-handling proteins, and gap junctions. However, due to the various electrophysiological targets involved and their possible interactions with preexisting electrophysiological or structural substrates, the mechanisms underlying ethanol-induced arrhythmogenesis remain poorly understood and difficult to research experimentally. To describe the acute effects of ethanol on cardiac electrophysiology and arrhythmogenesis, we used in-silico studies at the cellular and tissue levels.

Reduced I<sub>Na</sub>, I<sub>Ca,L</sub>, I<sub>to</sub>, I<sub>Kr</sub>, and I<sub>Kur</sub>, dual effects on I<sub>K1</sub> and I<sub>K,ACh</sub> (inhibition at low concentrations and augmentation at high concentrations), and increased INCX and SR Ca<sup>2+</sup> leak were all observed in human atrial and ventricular cardiomyocyte computer models. Low ethanol concentrations prolonged atrial action-potential length (APD) without affecting ventricular APD in multiscale simulations in the absence or presence of preexisting atrial fibrillation or heart failure-related remodelling. High ethanol concentrations, on the other hand, shortened atrial APD and prolonged ventricular APD.

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prolonged ventricular APD. In tissue simulations, high ethanol concentrations promoted reentry, but the degree of reentry promotion was determined by the existence of altered intercellular coupling as well as the degree, form, and pattern of fibrosis. These findings add to our understanding of the possible proarrhythmic interactions between a preexisting substrate and acute changes in cardiac electrophysiology. Acute ethanol exposure, in particular, produces concentration-dependent electrophysiological effects that vary between the atria and ventricles, as well as between healthy and diseased hearts. Low concentrations of ethanol have anti-fibrillatory effects in the atria, while high concentrations facilitate the inducibility and maintenance of reentrant atrial and ventricular arrhythmias, implying that alcohol use should be limited as part of cardiac arrhythmia management.

Our multiscale in silico research sheds new light on the acute effects of ethanol on cardiac electrophysiology and arrhythmogenesis, demonstrating that ethanol has concentration-dependent electrophysiological effects that vary between the atria and ventricles, as well as whether disease-related remodelling is present or not. Low levels of ethanol in the atria may have antiarrhythmic effects, while high levels may promote reentrant arrhythmias. Gap-junction remodelling caused by ethanol is a key factor in ethanol-induced reentrant arrhythmias. The precise proarrhythmic risk is determined by the degree, form, and pattern of disease-related structural remodelling, as well as other co-factors such as autonomic nervous influences.

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