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Letter to the Editor – Initiation and sustenance of re-entry are promoted by two different mechanisms

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We read with great interest the study by Hsueh et al. (1), which substantiates mechanistic links between atrial arrhythmias and heterogeneity of action potential duration (APD) in the atria (2,3). The study shows that APD heterogeneity and arrhythmogenesis in the canine atria both are promoted by blockade of small conductance Ca^{2+} activated K^+ (SK_{Ca}) channels (1), and concludes that such a blockade is proarrhythmic. However, this conclusion appears to conflict with another recent experimental study (4), in which SK_{Ca} channel blockade in the canine atria has been linked with antiarrhythmic effects. Biophysical modelling of the canine atrial tissue (5) may reconcile apparently contradictory experimental results (1,4). SK_{Ca} channel blockade is reported to be proarrhythmic (1) based on its effect of promoting the initiation of atrial re-entry, and antiarrhythmic (4) based on its effect of preventing the sustenance of atrial fibrillation (AF). *Re-entry initiation* can arise from a breakdown of electrical waves in regions of high APD heterogeneity (3,5) – such wave breaks and transient re-entry are clearly seen in the canine atria with the ADP heterogeneity increased by SK_{Ca} channel blockade (1). However, the blockade results in relatively high APD values in the healthy canine atria (1). Modelling predicts that re-entry is unlikely to sustain in such conditions and self-terminates after several rotations (5). *Re-entry sustenance* requires a reduction of the APD, which occurs due to AF induced remodelling of the atria (2). Thus, re-entry and AF are sustained only under conditions of remodelling in both experimental (4) and modelling (5) studies of the canine atria. Blockade of K^+ channels in the remodelled atria can then increase the APD and terminate reentrant waves and AF (4,5). Therefore, K^+ channel blockade can promote both proarrhythmic (1) and antiarrhythmic (4) mechanisms. Proarrhythmic effects, such as re-entry initiation, are more likely to arise in healthy atria due to highly increased APD heterogeneity (1,5). Antiarrhythmic effects, such as efficient re-entry termination, are likely to arise in remodelled atria due to the drug

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induced increase in APD (4,5). Importantly, the APD can be increased and APD heterogeneity decreased simultaneously, in response to the same K^+ channel blockade (1,4,5). Various experimental (1,4) and modelling (5) studies of the canine atria have utilized somewhat varying conditions (including specific atrial pacing protocols, channel blockers, regions of interest in the atria), but we believe that phenomena observed in these studies can be explained by congruent underlying mechanisms.

Abbreviations

APD	action potential duration
SK_{Ca}	small conductance Ca^{2+}activated K^+
AF	atrial fibrillation

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