

Potential role of potassium currents in the repolarization reserve: the importance of cardiac repolarization reserve in safety pharmacology

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Cardiac repolarization is a delicate process and the determinants of repolarization in various species are poorly understood. This study compared the contribution of IK1, IKr and IKs to cardiac repolarization in canine and human ventricular preparations by applying conventional microelectrode, whole cell patch-clamp and molecular biological techniques. Pharmacological inhibition of IKr evokes modest prolongation of repolarization in the dog ventricle, while it largely lengthens it in the human. These results suggest that in human, in addition to its known effect to establish the resting membrane potential, IK1 is contributing only to the repolarization reserve, while in the dog, IK1 also plays a role to secure the normal repolarization. Therefore, the smaller IK1 in human comparing to the dog makes the ventricle more sus-

ceptible to repolarization lengthening in the human than in the dog. This should be taken into consideration when pharmacological results from the dog studies are extrapolated to the human, i.e. the effect on repolarization of drugs potentially blocking IKr/HERG channels can be underestimated in the human based on experiments performed in the dog. We conclude that humans show much greater repolarization-delaying effects of IKr-block than dogs, because of lower repolarization-reserve contributions from IK1 and IKs. These results are relevant to understanding species-specific determinants of repolarization and emphasize the limitations of animal models for the human disease.

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