Potential role of $\text{K}^+$ currents in the repolarization reserve: the importance of cardiac repolarization reserve in understanding the proarrhythmic side effects of antiarrhythmic drugs

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Background: Although antiarrhythmic drugs are prescribed to reduce an arrhythmia, they may have the paradoxical effect of actually exacerbating that arrhythmia or causing new or more serious forms. Proarrhythmia is a new or more frequent occurrence of pre-existing arrhythmias, precipitated by antiarrhythmic therapy, which means it is a side effect associated with the administration of some existing antiarrhythmic drugs, as well as drugs for other indications. In other words, it is a tendency of antiarrhythmic drugs to facilitate emergence of new arrhythmias. The CAST and SWORD trials were the first that revealed this dangerous side effect of antiarrhythmic medication. Extensive investigations started then to elucidate the mechanisms which cause proarrhythmia, and in particular special interest was paid to understand the proarrhythmic effect of non-cardiac medication. An important discovery in the investigation of this phenomenon was the introduction of the term of repolarization reserve by Roden [1]. This term helped to understand how the cardiac repolarization is modified by pharmacological tools.

Methods: This study compared the contribution of the four main potassium currents $I_{K1}$, $I_{to}$, $I_{Kr}$ and $I_{Ks}$ currents to cardiac repolarization in mammalian (including human) ventricular preparations by in vitro and in vivo electrophysiological and molecular biological techniques.

Results: In pathological settings, when repolarization reserve is impaired, the relatively mild block of additional $\text{K}^+$ current can cause marked APD/QT interval prolongation. When this normal repolarization reserve is attenuated the otherwise minimal or moderate potassium current inhibition can result in excessive and potentially proarrhythmic prolongation of the ventricular action potential duration. Congenital ion channel defects, ion channel remodeling due to myocardial infarction, heart failure, diabetes mellitus etc. can lead to impaired repolarization reserve.

Discussion: We should re-evaluate our safety pharmacology concept related to possible QT lengthening effects of drugs to apply tests in preparations where the repolarization reserve is impaired instead of using preparations where this reserve is normal.

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