Not all Long-QTs Are The Same, Proarrhytmic Quantification with Action Potential Triangulation and Alternans

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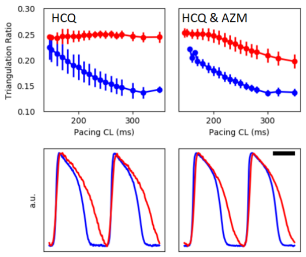
Aims: We aimed to characterize the mechanism under which QT-interval prolonging drugs and their combination can be less arrhythmic, examining arrhythmia susceptibility due to action potential (AP) triangulation and spatial dispersion of action potential duration (APD). Additionally, we aimed to elucidate that Torsades de Pointe (TdP) associated with long-QT are not necessarily caused by early-after-depolarization (EADs) but associated with the presence of action potential alternans in both time and space.

Method: Isolated Guinea Pig hearts were Langendorff perfused, and optical mapping was done with voltage dye sensitive dye. To study the effects of QT interval prolongation, two commonly used drugs at the beginning of the COVID-19 pandemic, hydroxychloroquine (HCQ) and Azithromycin (AZM) were added. The ventricular vulnerability was assessed by a burst pacing protocol consisting of a premature extra stimulus (S1-S2 protocol). Alternans in time and space were characterized by performing restitution pacing protocol.

Results: Comparing APs, HCQ prolongs APD during phase-III repolarization, resulting in a higher triangulation ratio than with AZM alone or AZM combined with HCQ. Lower triangulation ratios with AZM are associated with phase-II prolongation and were associated with lower arrhythmia susceptibility in S1-S2 protocols and lower incidence of spatially discordant alternans.

Conclusions: Long-QT associated with drugs prolonging phase-III repolarization is known to increase arrhythmia susceptibility. The addition of phase-II prolonging drugs as AZM results in a lower triangulation ratio and lower incidence of alternans at slower pacing rates. Arrhythmia susceptibility decreases even without a decrease of QT interval prolongation due to previously added phase-III prolongation drug as HCQ. Although the risk of TdP is often associated with EADs, this study shows that spatially discordant alternans are the mechanism leading to TdP and not necessarily EADs.



Triangulation and APs before (blue) and after (red) administrations of the HCQ and HCQ&AZM drugs.