Inward rectifier potassium channels determine cardioversion threshold and success rate by regulating post-shock refibrillation

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Purpose: Termination of atrial fibrillation (AF) by electrical cardioversion (ECV) remains the mainstay of AF treatment in symptomatic patients. Still, energy requirements for successful ECV (the cardioversion threshold [CT]) are well above the pain threshold, and success rate of ECV diminishes during the progression of paroxysmal to chronic AF. Hence, the use of ECV is limited by the increasing necessity for painful shocks with AF progression. Remodeling of inward rectifier potassium channels (e.g., increased activity of IK1 and IK,Ach, resp.) is associated with the progression of AF. However, it is unknown whether and how these ion channel activities contribute to the CT and success rate. Therefore, we investigated the effects of IK1 and IK,Ach blockade of CT in AF.

Methods: Neonatal rat atrial cardiomyocyte monolayers were burst paced to induce reentry-based AF and subjected to biphasic truncated exponential shocks (10 ms duration) of 20–100 V (10 V increments) to determine CT. To study the effects of IK1 and IK,Ach on the CT, cultures were treated with BaCl2 and Tertiapin or transduced with lentiviral vectors encoding Kcnj5-specific shRNAs. Optical mapping was used to assess electrophysiological parameters prior to, during and after ECV attempts.

Results: Successful ECV depended on full synchronization of all phases around phase singularities. ECV below CT failed because of incomplete synchronization or post-shock refibrillation. Post-shock refibrillation occurred at significantly higher voltages than incomplete synchronization (58 ± 21 vs 34 ± 8 V). BaCl2 and Tertiapin significantly increased wavelength during reentry (0.80 ± 0.28 and 0.48 ± 0.14 cm in controls), which correlated strongly with CT (R²=0.69), in contrast to conduction velocity (R²=0.06), cycle length (R²=0.35), APD80 (R²=0.44), and complexity (R²=0.50). As a result, IK1 and IK,Ach blockade significantly decreased CT (27 ± 0.4 and 32 ± 11 vs 60 ± 25 V in controls, respectively). Transduction with Kcnj5 shRNA containing lentiviral vectors confirmed these results.

Conclusions: These results suggest that remodeling of IK1 and IK,Ach during AF progression could increase CT by shortening of wavelength during reentry and decrease ECV success rate. Hence, this study provides new mechanistic insight into failing ECV and identifies IK1 and IK,Ach as possible targets to increase effectivity of ECV while decreasing its harmfulness.