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Pharmacological inhibition of atrial TASK-1 channels facilitates acute cardioversion of atrial fibrillation in a large animal model

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Background: The TASK-1 (hK2P3.1) two-pore-domain potassium channel was recently shown to regulate atrial action potential duration (APD). In the human heart, TASK-1 channels display atrial specific expression. Furthermore, upregulation of atrial TASK-1 currents was described in patients suffering from atrial fibrillation (AF). We therefore hypothesized that TASK-1 channels represent an ideal target for antiarrhythmic therapy of AF. In the present study we tested the antiarrhythmic effects of the high affinity TASK-1 inhibitor A293 for acute cardioversion in a porcine AF model.

Methods: 20 healthy German landrace pigs underwent electrophysiological studies in general anesthesia. Persistent AF was induced by right atrial burst stimulation via implanted pacemakers. Isolated atrial cardiomyocytes were analyzed using the patch-clamp technique.

Results: In porcine atrial cardiomyocytes isolated from pigs with persistent AF, inhibition of TASK-1 currents using the high affinity inhibitor A293 resulted in normalization of APD. Likewise, intravenous administration of A293 resulted in significant prolongation of atrial effective refractory period, measured at cycle lengths of 300, 400 and 500 ms, while QRS width, QT interval and ventricular effective refractory periods remained unchanged. After induction of AF episodes, administration of TASK-1 blockers could restore sinus rhythm within cardioversion times of 20 minutes.

Conclusion: Pharmacological inhibition of atrial TASK-1 currents exerts antiarrhythmic effects in vivo resulting in acute cardioversion of AF.