Doxapram is a promising new antiarrhythmic drug for an atrial-specific therapy of atrial fibrillation

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Topic(s):
Cellular Electrophysiology

Citation:
Background: TASK-1 (K2P3.1) is an atrial-specific two-pore domain potassium channel that is significantly upregulated in atrial fibrillation (AF) patients resulting in shortened atrial action potential duration (APD). Inhibition of TASK-1 in human atrial cardiomyocytes reverses AF-related APD shortening to values observed in patients with sinus rhythm (SR). By in silico-modelling and experimental characterization of drug binding sites, doxapram was identified as specific inhibitor of TASK-1.

Purpose: In this study, we investigated the antiarrhythmic efficacy of doxapram in a porcine model of AF to convert and suppress AF.

Methods: We established a new porcine model of persistent AF without induced tachymyopathy. AF was induced in domestic pigs by intermittent atrial burst stimulation using implanted pacemakers. During AF episodes, burst stimulation was inhibited by an integrated pacemaker biofeedback algorithm. AV-node ablation was performed to prevent AF-associated heart failure. All pigs underwent catheter-based electrophysiological investigations prior to and after 14 days doxapram treatment. Pigs in the treatment group received intravenous applications of doxapram twice per day. Rhythm status was continuously recorded by intracardiac long-term ECG monitors. The application of doxapram for cardioversion and long term suppression of AF in pigs with persistent AF was evaluated. Subsequent to the doxapram treatment, porcine cardiomyocytes were isolated from right and left atria and electrophysiologically investigated by patch-clamp and multi-electrode experiments. Atrial electrical remodeling was characterized by analyses of ion channel expression at mRNA and protein levels.

Results: TASK-1 mRNA, protein and transmembrane current were significantly increased in AF pigs compared to SR controls, resulting in shortened atrial APDs. In doxapram-treated AF pigs the AF burden was significantly reduced. After 14 days treatment with doxapram, TASK-1 currents and atrial APDs recorded in porcine cardiomyocytes were reduced and similar to values of SR animals. Doxapram could be successfully applied for cardioversion in pigs with persistent AF. On average, cardioversion was observed 3 minutes after doxapram application.

Conclusion: Doxapram significantly suppressed AF episodes and normalized cellular electrophysiological characteristics in a porcine model of AF through inhibition of the TASK-1 ion channel. Furthermore, doxapram rapidly converted AF into SR in pigs. Therefore, doxapram might serve as a new antiarrhythmic drug to treat AF in patients.