Mechanisms of action of atrial-specific anti-arrhythmic drugs

SUMMARY

Atrial fibrillation (AF) is a rhythm disorder characterized by fast and irregular activations of the atria. Being a major cause of stroke, heart failure and overall cardiovascular morbidity, AF represents a considerable challenge for public health and a significant socioeconomic burden. In many patients the AF episodes are asymptomatic and terminate spontaneously. However, due to the progressive behavior of the disease the episodes prolong until AF becomes persistent. Early diagnosis and effective treatment of AF are therefore essential for successful clinical management of the arrhythmia.

The recently published Early treatment of Atrial fibrillation for Stroke prevention Trial (EAST) showed that early treatment of AF by antiarrhythmic drugs (AADs) or by catheter ablation slows down the progression of the arrhythmia. However, neither of the strategies achieves satisfying success rates in the later stages of the disease. Moreover, the use of currently available AADs is limited by their side effects, especially by an increased risk of development of drug-induced ventricular arrhythmias. This creates an urgent need for development of new AADs that would be safe and efficient at the same time, as well as for better understanding of the mechanisms that are responsible for perpetuation of AF. This thesis aims to provide new insights in both fields. We investigated the potential of pharmacological inhibition of two ion currents that are both considered as promising targets for treatment of AF. In addition, we studied the mechanisms of AF termination under various conditions. Finally, we present a new analysis tool for studying complex atrial conduction and the interaction between activation and repolarization waves during both pacing and AF.

In **chapter 2** of this thesis we studied the antiarrhythmic effect of a highly specific acetylcholine-activated potassium current (I_{KACh}) inhibitor XAF-1407 in a goat model of pacing-induced AF. We demonstrated that XAF-1407 is a potent AAD for AF termination in the goat. The administration of XAF-1407 was not associated with any ventricular arrhythmias and its effect on ventricular electrophysiology was only limited. Pharmacological inhibition of I_{KACh} by XAF-1407 resulted in more pronounced prolongation of atrial effective refractory period in electrically remodeled atria than in normal atria. This observation agrees with the hypothesis that the potency of I_{KACh} inhibition may be increased in electrically remodeled atria due to a constitutively active I_{KACh}. Our findings indicate that I_{KACh} inhibition has a potential to become not only atrial-selective, but also AF-selective strategy for treatment of AF, being safe in the ventricles at the same time.

Chapter 3 investigates the antiarrhythmic properties of a small conductance calcium-activated potassium current (I_{SK}) inhibitor AP14145, again in a goat model of pacing-induced AF. Showing that AP14145 is able to terminate persistent AF in goats, the study demonstrates that

AP14145 is an efficient antiarrhythmic agent for AF cardioversion. Rate-dependent reduction of conduction velocity observed during atrial pacing indicated a possible class I effect of the I_{SK} inhibition. The administration of AP14145 was not associated with any changes in ventricular electrophysiology, neither with ventricular proarrhythmic effects. Pharmacological inhibition of I_{SK} might therefore also represent a safe therapeutic strategy for treatment of AF. The AF terminations in presence of AP14145 were preceded by gradual prolongation of AF cycle length. However, to our surprise, the decrease of AF complexity before cardioversion was sudden, occurring just in the last AF cycles before the arrhythmia termination.

To investigate the process of AF termination more in depth, in **chapter 4** we performed a retrospective analysis of several studies in the goat model of pacing-induced AF, including the studies presented in **chapter 2** and **chapter 3**. We analyzed bi-atrial high-density electrical mapping data that were acquired during pharmacologically-induced as well as spontaneous AF terminations. The study demonstrates that cardioversion of AF was always preceded by increased spatiotemporal organization of fibrillatory conduction during the final seconds before the arrhythmia termination. This process was associated with abrupt changes in electrophysiological parameters. Our findings are highly suggestive that conduction through Bachmann's bundle might play an important role in the last activation cycles before AF termination.

The studies presented in **chapters 2-4** investigated the antiarrhythmic effects of AADs in animals with electrically remodeled atria when the fibrillatory patterns were relatively simple and AF could be pharmacologically cardioverted. With the progression of AF however, more complex conduction patterns occur and the arrhythmia is more resistant to termination. To understand the reasons why currently used AADs fail to cardiovert complex AF, it is essential to have methods that allow in-depth investigation of complex conduction patterns. Optical mapping proved to be a useful tool for exploration of the mechanisms driving cardiac arrhythmias because it allows recording of optical action potentials with high spatial and temporal resolution.

Chapter 5 presents a novel method that is tailored for detection of atrial activations in optical mapping recordings of AF. The method was designed to be highly sensitive to reveal small fibrillatory waves that occur during complex atrial conduction. The study demonstrates that the method is capable to identify optical action potentials with low magnitude and slow upstroke that are associated with slow, discontinuous conduction. The method can be considered as a first step for further analysis of optical mapping recordings acquired during cardiac fibrillation, allowing advanced analysis of activation patterns and identification and tracking of excitation waves.

Developing further the above-mentioned method, **chapter 6** investigates the interaction between atrial activation and repolarization patterns in perfused hearts of goats with persistent AF. It demonstrates that atrial repolarization during pacing shows rather synchronous behavior, resulting in local prolongation of action potential duration at the site of stimulation. In contrast, during AF atrial repolarization shows wave-like propagating behavior with a pattern that resembles the preceding activation. This similarity favors the tendency of subsequent excitation waves to follow the same direction of propagation, which is a phenomenon known as 'linking' of fibrillatory waves. The close resemblance of activation and repolarization patterns during AF therefore facilitates stabilization of functional reentry and perpetuation of the arrhythmia.

Taken together, the work presented in this thesis describes the antiarrhythmic mechanisms of novel AADs, showing that inhibition of I_{KACh} and I_{SK} has a potential to become safe and efficient therapeutic strategy for AF cardioversion. The work provides new insights into the mechanisms underlying AF termination, demonstrating that regardless of the presence or the type of AAD, cardioversion of AF in goats is associated with increased organization of the fibrillatory process and with abrupt changes in electrophysiological parameters. Applying a new method for analysis of optical mapping data, the work also provides new insights into the mechanisms underlying perpetuation of the arrhythmia, showing that during AF the pattern of atrial repolarization tends to resemble the pattern of preceding activation.