Mechanisms of action of atrial-specific anti-arrhythmic drugs

IMPACT PARAGRAPH

Being the most common arrhythmia in clinical practice, atrial fibrillation (AF) represents a major challenge for public health. Aging of the population that is expected in the coming decades will result in substantial increase in the number of patients with AF. Having effective options for AF treatment is therefore essential. Currently available therapeutic approaches for management of AF are insufficient. The use of antiarrhythmic drugs (AADs) that are available for AF treatment is limited by severe side effects that can be potentially lethal. Therefore, there is an urgent need for development of new AADs as well as for better understanding of the mechanisms that are underlying the maintenance and termination of AF.

In this thesis, we studied new approaches for treatment of AF by AADs. We investigated two compounds, each working on a different principle, testing them in goats with AF. Our results demonstrate that both therapeutic approaches have a potential to become safe and efficient strategies for AF treatment. This finding can support development of new drugs that would work on the same or very similar principle, leading to improvement of the available pharmacological approaches for treatment of AF.

Performing a retrospective analysis of data acquired during AF terminations in goats, we demonstrated that cardioversion of AF in goats is associated with sudden changes in atrial electrophysiology during the last AF cycles before the arrhythmia termination, regardless of the presence or the type of AAD. This finding provides new insights into the mechanisms that lead to AF cardioversion and improves our understanding about the process of AF termination itself. In long-term perspective, this knowledge may facilitate the design of new approaches for treatment or prevention of AF.

To improve the current pharmacological strategies for treatment of AF, it is necessary to develop AADs that would be efficient in patients with long-standing complex AF and safe in patients with underlying structural heart disease that are at increased risk of developing severe adverse events. The new method for identification of small fibrillatory waves that is presented in this thesis will facilitate studying of complex atrial conduction. It has a potential to improve our understanding why AADs lose their efficacy when AF becomes complex and difficult to terminate. By further development of this method, we showed that during AF the pattern of atrial repolarization resembles the pattern of previous activation, which is a phenomenon that favors AF stability. The methods developed in this thesis may facilitate studying of antiarrhythmic as well as possible proarrhythmic effects of AADs. From this perspective, the presented tools can be used for improvement of current pharmacological strategies for treatment of AF.