Metabolic modulators as a treatment of atrial fibrillation

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Summary

Atrial fibrillation, one of the most common arrhythmias in clinical practice, is characterized by the fast and irregular atrial activation and irregular ventricular rate. This chaotic atrial activation is associated with disturbed blood flow in the atria and consequent clot formation. In many patients AF is asymptomatic, but if not treated properly, it can cause devastating thromboembolic complications, including stroke. Therefore, due to its high prevalence and high complication rates, AF represent one of the major health problems that requires timely diagnosis and adequate treatment.

Present treatment strategies for AF could be roughly divided in three groups. The first, ‘rhythm control’, is aiming to restore and preserve sinus rhythm (SR) while the second one, ‘rate control’ is aiming to prevent cardiac and extracardiac complications by maintaining a normal heart rate while the atria remain in AF. The third one is focused on preventing the formation of the blood clots in the atria and consequent thromboembolic complications, by inhibiting different coagulation pathways. Although this strategy is satisfactory for some patients, in others, especially patients who experience direct symptoms, restoration and maintenance of sinus rhythm is desirable. For rhythm control, it is important to understand the natural course of the AF and the processes responsible for perpetuation of the arrhythmia.

AF often begins with short episodes (paroxysms) of the arrhythmia that become longer over time, until arrhythmia becomes persistent. This progressive course of AF is maintained through a number of remodeling processes that include changes in electrophysiological properties (‘electrical remodeling’), metabolic alterations (‘metabolic remodeling’) and finally changes of the atrial tissue structure (‘structural remodeling’).

The treatment strategies that are used to restore SR are counteracting these remodeling process, and include antiarrhythmic drugs and several ablation procedures. Antiarrhythmic drugs affect the function of ion channels, while ablation procedures impact atrial structure and conduction. However, currently there are no treatment strategies that are used to interfere with the metabolic alterations during AF and from that perspective contribute to the preservation of atrial structure and function.

Therefore, the main focus of this thesis was to investigate effect of metabolic modulators on different stages and different aspects of AF-induced atrial remodeling. The second chapter of this thesis gives an overview of the current knowledge about changes in myocardial metabolism and tissue perfusion during different stages of AF. In this chapter, we also propose ranolazine and trimetazidine as drugs that can affect metabolic processes of myocardial cells that may assuage metabolic compromise during AF and thereby inhibit remodeling processes and inhibit AF progression.
In addition to the effect of ranolazine on the metabolic shift towards glucose utilization, ranolazine is also a multi-ion channel blocker with reported high atrial selectivity in the blockade of the peak Na⁺ current (I_{Na}). To start investigating the potential use of ranolazine as a metabolic modulator for long-term treatment of AF, we have first assessed the direct effects of ranolazine in an awake goat model of lone atrial fibrillation at different stages of AF-induced atrial remodelling (chapter 3). Ranolazine decreased conduction velocity and prolonged atrial effective refractory period, irrespective of the stage of electrical remodelling, without apparent proarrhythmic effects on ventricles. Based on this evidence, ranolazine can be considered as a safe antiarrhythmic drug for AF treatment, allowing further study of its possible long term (metabolic) effects. However, short-term ranolazine administration was ineffective in cardioverting AF. Because there is still an unmet need for safe (i.e. atrial-selective), effective anti-arrhythmic drugs for pharmacological cardioversion of AF, we proposed inward-rectifier currents as an appropriate target. In chapter 4 we have shown that the inhibition of the inward rectifier K⁺ current (I_{K1}) with pentamidine analogue 6 (PA-6) can effectively cardiovert persistent AF in goats to sinus rhythm without proarrhythmic effects on the ventricles in either goats or dogs. We further propose that the acetylcholine-activated inward rectifier potassium current (I_{KACH}) may form a target with similar effects, but an even higher degree of atrial selectivity. Adequate tissue perfusion is a prerequisite for sufficient O₂ supply and therefore for adequate energy production. In the chapter 5 we have shown that chronic AF in goats increases the sensitivity of atrial resistance arteries to endothelium-dependent vasodilatation. The factor that was responsible for this shift is most likely endothelium-derived hyperpolarizing factor (EDHF). EDHF actually represents several different substances secreted by the endothelial cells. Unfortunately, in our experiments we were not able to identify exact pathway, but it was clear that chronic atrial fibrillation leads to notable changes in the regulation of the atrial vessels, which may represent an adaptive change to the higher energy demand of the fibrillating atrial myocardium. We have previously shown that AF causes a state of supply/demand ischemia that can persist for weeks. To investigate whether these and other AF-induced changes in atrial metabolism can contribute to atrial remodeling, we have studied the long-term effects of a metabolic intervention during AF. In chapter 6 we have performed an extensive characterization of the several metabolic parameters including production of, damage by and neutralization capacity for reactive oxygen species (ROS), mitochondrial function and structure during chronic AF in goats. We show that trimetazidine, a metabolic modulator, can attenuate several hallmarks of the AF-induced remodelling processes mainly by inhibiting excessive ROS production originating from mitochondria.