

Dynamics of propagation patterns and anti-arrhythmic mechanisms during atrial fibrillation

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Valorization

Atrial fibrillation (AF) is a rhythm disorder that is often observed in the elderly population.¹ AF increases the risk for several cardiovascular diseases and in particular stroke.² The impact of AF on daily life, e.g. exercise tolerance and cognitive function, can be significant. The psychological burden of not knowing when and for how long AF occurs is substantial in symptomatic AF patients too. This becomes apparent when one reads the posts of AF patients on fora like www.atriumfibrilleren.nl. The joined goal of basic and clinical scientists is to reduce the incidence of AF and limit the burden of AF in daily life for those who already developed AF.

The prevalence of AF is as high as 3% for adults above 20 years of age. About a quarter of middle-aged people are expected to develop AF at some point in their life.¹ This estimate projects 14-17 million AF patients in the European Union in 2030.¹ Healthcare costs as a consequence of AF are considerable. In a combined evaluation of the Cardiovascular Health Study and the Framingham Study, healthcare costs increased by \$18,000 for a patient in the year after the first diagnosis of AF.³ Moreover, 70-80% of AF patients get hospitalized at some point during their disease.⁴ Once hospitalized, costs are about 3-fold higher than hospital costs for the average patient.⁵ The total financial burden of AF on the US healthcare system is estimated between \$6-26 billion.⁵

AF is also an extremely challenging scientific topic. Although it was initially identified as an electrical disorder, AF is a disease that has a more complex nature. Multiple regulatory responses (e.g. inflammation, electrical remodeling) and different cell types are affected during the progression of AF. These all together interact with other comorbidities.⁶ Hence, a highly challenging topic to investigate. The large social and economic impact of AF and its scientific challenges are valid justifications for worldwide efforts being made to come to a better understanding and treatment of the disease.

The work presented in this thesis is primarily focused on the scientific understanding of AF as a disease, with the eventual aim to improve treatment of patients. The data presented in this thesis are mostly obtained from experimental animal studies to address basic mechanism that cannot be studied in humans at the level of detail presented here. However, the topics discussed do directly link to clinical practice as both vernakalant and mapping, as a tool for AF ablation, are applicable strategies in the treatment of AF. Moreover, new algorithms that are presented in this thesis may contribute to more robust analysis of conduction patterns during AF. The work in this thesis is of interest for basic scientists, engineers and clinicians. The work on both, the antiarrhythmic drug vernakalant and mapping of AF, was presented on several congresses and network meetings in the Netherlands, Europe and US in the years 2014 to 2018. Scientific congresses (e.g. ESC, HRS, Europace, EHRA and CINC) that target a large audience with a broad range of backgrounds (e.g. basic, engineering and clinical sciences) were selected to maximize the impact of our work. Four out of five chapters are published in peer-reviewed journals relevant to our field of research: Heart rhythm, Europace, Frontiers in Physiology and IEEE. The other chapter is in preparation for submission in the near future.

Antiarrhythmic drugs

The first main topic of this thesis is the antiarrhythmic drug vernakalant. Vernakalant was approved for the clinical practice not long before the studies for chapter 2 and 3 were started. At that time, the majority of mechanistic knowledge about vernakalant was obtained in *in vitro* and in small animal models. The studies suggested an atrial-specific effect of vernakalant. The novelty of our work was that the effects were characterized during AF, the condition that is treated. Vernakalant was investigated in a large animal model that closely resembles the human electrophysiology. Therefore, the results in chapter 2-4 are expected to be well transferable to patients. The critical finding of the studies in chapter 2-4 was that the actual antiarrhythmic mechanism of vernakalant is dependent on the inhibition of sodium current that is present in the ventricle as well as the atrium. This insight is supported by investigations from two other independent laboratories.^{7,8} This finding is relevant because sodium current inhibition may increase the risk of lethal arrhythmias. It is therefore likely that our findings will contribute to a cautious use of vernakalant.

Another interesting observation is that the multi-ion-channel approach of vernakalant tended to be more efficacious compared to single ion-channel strategies. This finding is in line with numerical and experimental studies that suggest that the block of different currents may lead to synergistic electrophysiological effects.^{9,10} We have therefore setup a project that addresses the potential synergistic effects of combining different drugs. Our aim in this study is to achieve improved AF cardioversion efficacy without the cost of ventricular arrhythmias. Improved cardioversion efficacy will be achieved by the combination of the inhibition of atrial-specific currents and conventional antiarrhythmic drugs. The first results of this study are expected in spring 2019. In case of promising findings (a) phase I trials will be required before a combination approach can enter phase II and III trials to assess efficacy and safety in AF patients. We estimate that the entire trajectory will be at least ten years before it can be applied in standard clinical care.

Mapping and ablation of AF

The second main topic of this thesis is the analysis of propagation patterns during AF. We believe that insights of propagation patterns are fundamental to understand why, where and when AF requires an intervention (drugs, electrical shock, catheter ablation or surgical intervention) to terminate. This understanding may help the scientific community to design new therapies that affect specific mechanisms by for instance ablation.

An ablation approach is designed to eliminate atrial tissue to exclude the local tissue from the atrial activity. When an ablation procedure is performed successfully the patient is free of AF, at least for a longer period compared to pharmacological or electrical AF termination. However, there still is a large group of patients, about 40%, who does

develop recurrent AF in the first year after the procedure. It is therefore of interest for patients and physicians to develop a technology that identifies critical sites for AF maintenance. Moreover, the large group of AF patients represents a large economic value for biotech companies. This is well illustrated by the \$250 million investment of Abbott® in 2014 to acquire FIRM (Focal Impulse and Rotor Modulation) procedure developed by Topera Inc. FIRM requires extensive processing of the atrial signals. The risk of such processing signals is that the technology may lead to false detections of critical sites that will be irreversibly damaged. The work in chapter 6 focuses on the pitfalls of signal processing steps required for the detections of putative AF maintaining sites. Based on these results the concerns were addressed about the probability of false detections and proposed an additional step for improvement. This work is important to make scientists, physicians and engineers aware of the limitations of the technology when it is applied in an AF patient.

A novel analytical approach for the analysis of conduction patterns is presented in chapter 5. This approach is designed to identify patterns that occur repeatedly. The basic principle of this approach is a tool that can be applied to a chaotic system to describe the dynamical behavior of it. A particular pattern reoccurred in some animals of the study. Interestingly, some recurrent patterns matched to AF termination patterns, as discussed in the general discussion. It is therefore of high interest to study the mechanisms that disrupt such recurrent patterns as they might be critical for AF maintenance. If a particular mechanism can be identified, it might serve as an ablation target. Recurrent pattern analysis can be applied to signals obtained in preclinical models and from patient data sets. Moreover, recurrent pattern analysis may also be applied to noninvasive electrical mapping of the heart. Hence, we foresee that recurrent pattern analysis might have a great potential to identify AF maintaining mechanisms. However, further evaluation and validation needs to be applied before it can be used in the clinic. Whether and how frequently recurrent propagation patterns occur in patients remains to be investigated. It would be of potential interest to focus identification of ablation targets on the mechanisms that disrupt recurrent propagation patterns. The time window that is required that recurrent pattern analysis that will be applied in clinics are dependent on the outcome of our preclinical explorations, manpower for algorithm development and analysis, financial opportunities and cannot be estimated at this moment of time.

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