

# Structure-function relationship of atrial fibrillation waves in goat and man

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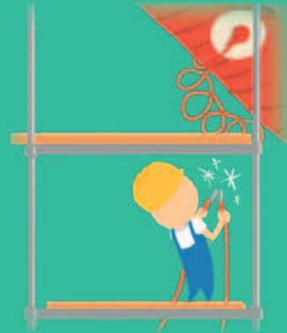
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# Valorization



## Valorization

## 1. Social relevance and need for further research

Atrial fibrillation (AF) is the most common arrhythmia with an estimated prevalence in the developed world of approximately 1.5-2% of the general population.<sup>1</sup> The prevalence of AF increases with age, so with the ageing of the general population, AF prevalence is estimated to at least double in the next 50 years.<sup>2</sup> In a large Dutch population-based prospective cohort study among 6808 subjects aged 55 years and above, the overall AF prevalence was 5.5%, rising from 0.7% in the age group 55-59 years to 17.8% in those aged 85 years and above.<sup>3</sup> Although AF prevalence and incidence are higher in men, the absolute number of men and women with AF is about equal as women have a longer life expectancy.<sup>4</sup> In the Framingham Heart Study the lifetime risk for developing AF at the age of 40 years was 26.0% for men and 23.0% for women.<sup>5</sup>

The arrhythmia goes hand in hand with an important increase in mortality and morbidity; AF is associated with a doubled death rate (independent of other mortality predictors), an increased stroke risk (approximately every fifth stroke is due to AF), frequent hospitalizations, a reduced quality of life and exercise capacity and left ventricular dysfunction.<sup>2, 6-9</sup> As a consequence, AF attributes to an extensive economic and public health burden.<sup>10, 11</sup> Also, screening for AF might reduce the economic burden as patients with undiagnosed AF have greater medical costs than patients with similar observable characteristics without AF.<sup>12</sup>

It is clear that the medical and socio-economic impact of AF on the health system worldwide is huge and warrants further research. First, research on methods enabling prediction of AF or prevention of AF by treating risk factors is important. For example, recently it has been shown that sustained weight loss can reduce AF burden and even maintain sinus rhythm.<sup>13, 14</sup> Secondly, we need optimization and individualization of new and current AF treatment options. To do so, algorithms to rapidly identify AF complexity and further understanding of underlying mechanisms driving AF are necessary.

## 2. Target groups and innovation

This thesis presents information that might not only be interesting for researchers in the field of AF, but also for clinicians treating patients with AF

## Valorization

(e.g. cardiologists, electrophysiologists, cardiac surgeons, etc.), for mathematicians in the field of AF modeling and even for (treatment) of AF patients. The data and findings presented in this thesis contribute to the understanding of AF and might help to improve AF therapy in different ways.

### *AF complexity analysis*

The novel algorithm presented in chapter 6 provides rapid and automated analysis of AF electrograms. It can not only be used to study AF mechanisms in different settings, but also to identify AF complexity using non-invasive diagnostic tools to facilitate the development of patient-tailored treatment.

### *Atrial Anatomy*

The correlation – presented in chapter 3 – between the atrial bundle anatomy and AF conduction patterns helps to understand the occurrence of endo-epicardial dissociation of electrical activity and transmural conduction during AF, both mechanisms that are believed to be important in AF perpetuation. Furthermore, based on the findings in chapter 3, we hypothesize that observed inter-individual differences in atrial fibrillation substrates in humans can partly be attributed to differences in the individual atrial anatomy. Research on and identification of the underlying atrial anatomy in AF patients has been underexplored so far.

### *Human Paroxysmal AF*

Based on detailed analysis of AF conduction patterns in chapter 4, we show that AF complexity is comparable between patients with paroxysmal AF and patients without a history of AF. As such, the increase of AF complexity identified in patients with persistent AF occurs primarily *after AF has become persistent*. This helps to explain why AF treatment is much more successful in paroxysmal than in persistent AF and might validate aggressive AF treatment in paroxysmal AF patients to prevent deterioration to persistent AF. In this context the large variability in AF complexity in patients with paroxysmal AF is important, as these patients would benefit most of real-time identification of the underlying AF substrate complexity.

### *Endomysial fibrosis*

The occurrence of endomysial fibrosis has already been correlated to AF complexity in the goat model of AF by our group.<sup>15</sup> In chapter 4, endomysial fibrosis, not overall fibrosis, is also identified in human AF as the only structural marker correlating with AF complexity. Of course reproducing these find-

ings in further studies is needed, but the relevance of imaging overall atrial fibrosis as a predictor of conduction disturbances can be questioned.

### *Complex Fractionated Electrograms*

The importance of targeting complex fractionated electrograms in AF ablation is still not fully understood. However, the inconsistency in bipolar complex fractionated atrial electrogram (CFAE) algorithms and the poor correlation of these algorithms with underlying AF complexity and unipolar fractionation might explain the limited success rates of CFAE ablation. Based on the findings in chapter 5, we can postulate that ablation guided by currently available algorithms might lead to erroneous targeting of AF substrate sites.

## **3. What is next?**

Early detection and treatment of AF can possibly help to reduce the AF burden in the general population. Development of non-invasive diagnostic tools to identify AF complexity is needed to enable patient-tailored, and thus substrate-based, treatment of AF. Also, identification of patients how will but also will not benefit from a specific AF treatment can help us to optimize AF treatment. Next to animal models, direct contact mapping studies in humans are still needed to further study mechanisms underlying AF, as no animal model can mimic the plethora of different pathological processes active in the ageing human heart. Finally, the continued development of relevant AF computer models that enable us to test the efficacy of antiarrhythmic drug therapy or AF ablation strategies is needed so that research in animal models can be maximally minimized.