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Electrical remodeling and management of atrial fibrillation : experimental studies in the chronically instrumented goat

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Summary

In the present thesis, we studied in the caprine model of AF, the role of AF-induced electrical remodeling in the management of atrial fibrillation.

In **Chapter 1** the background to the present study is given. In recent years the interest in AF has increased explosively. Especially the increased awareness of the considerable prevalence, morbidity and mortality associated with AF has shifted the attention of cardiologists to the oldest arrhythmia (atrial fibrillation: the oldest arrhythmia-the newest disease). The renewed interest in AF has boosted the development of both pharmacological and non-pharmacological therapies for treatment of atrial fibrillation. However, despite all these efforts, present-day treatment of AF can still be characterized as 'doing our best without knowing what is wrong'. To develop a more effective strategy for treatment of AF, one needs to study the underlying pathophysiological mechanisms of AF. Or, as Thomas Lewis laconically suggested in 1902, *"The notion of a patient continuing to live with an auricle incapable of contraction is a somewhat novel idea...it seems necessary to devote a little study to the condition."*

In **Chapter 2** we described the cumulative effect of repeated paroxysms of AF on inducibility and stability of AF in the goat. Two days of sinus rhythm were found to be enough to recover completely from AF-induced electrical remodeling by 5 days of atrial fibrillation. Also we observed no cumulative effect of repeated 5 day paroxysms of AF on inducibility and stability. These findings highlight the importance of atrial refractoriness as a potential target for antiarrhythmic strategies aimed at inhibiting the self-perpetuation of AF.

In **Chapter 3** we studied the effect of AF-induced electrical remodeling on atrial vulnerability by single atrial premature beats. In the goat, 2 days of atrial fibrillation was associated with a marked widening of the window of inducibility of AF by single premature beats. Enhanced vulnerability in remodeled atria was due to a higher likelihood of reentry in the presence of critical conduction at Bachmann's bundle. These findings suggest that, during the first days of after cardioversion of human AF, both early and late premature beats can initiate early recurrences of AF. In patients, measurement of the window of inducibility might be useful to predict likelihood of recurrence of AF and to evaluate the efficacy of new treatment strategies.

In **Chapter 4** we described the transient changes in atrial electrophysiology immedi-

ately after spontaneous termination of atrial fibrillation. In the goat, during the first 2 minutes of sinus rhythm after spontaneous termination of AF there was a transient decrease in both atrial refractory period and conduction velocity. In remodeled atria, the cumulative effect of electrical remodeling and this short-term changes created an ultra-short atrial wavelength after termination of AF. In patients, immediate re-initiation of AF (IRAF) can be explained by this transient supervulnerable phase. However for immediate re-initiation of AF, the spontaneous occurrence of atrial triggers is at least as important as a vulnerable substrate for reentry.

In **Chapter 5** we determined the effects of different atrial pacing sites on the inducibility of AF by both right and left single atrial premature beats. It was found that, in remodeled atria, preventive atrial pacing markedly could reduce the window of inducibility of AF by single premature beats. The optimal site for preventive pacing was found to be at Bachmann's bundle, close to the area of critical conduction delay. Also in patients, the inter-atrial septum (Bachmann's bundle) might play a critical role in the genesis of AF. Pacing at Bachmann's bundle might be optimal pacing to prevent AF by both right and left atrial premature beats. Multi-site pacing seems of limited additional value.

In **Chapter 6** the effects of both digoxin and verapamil were evaluated on the duration and electrophysiological properties of paroxysmal atrial fibrillation. In the goat, verapamil but not digoxin exerted a direct pro-fibrillatory effect on paroxysmal AF. Especially in remodeled atria, intravenous administration of verapamil converted paroxysmal into persistent AF. This pro-fibrillatory effect of verapamil was due to shortening of atrial refractoriness at high AF rates (rate-dependent shortening of AERP). These findings suggest that in patients with paroxysmal AF, administration of verapamil might reduce the likelihood of spontaneous termination of the atrial arrhythmia. In contrast, digoxin is expected to reduce ventricular rate during AF without any effect on atrial electrophysiology during AF.

In **Chapter 7** we described five methods to determine the refractory and excitable period during chronic AF. During persistent AF with an AFCL of 98±14ms, the RP_{AF} determined by mapping of synchronized premature stimuli (gold standard) was 70±12ms, with an excitable period of 28±8ms. Although the indirect methods to measure RP_{AF} all correlated well with the gold standard, slow fixed-rate pacing seemed the most attractive technique because of the ease of acquiring the data and the clear graphic result.

Finally, in the last chapter of this thesis (**Chapter 8**) the possible implications were discussed. To develop a more effective strategy for treatment of AF one needs to know the underlying pathophysiological mechanisms of AF. Three different "players" are involved in the electropathology of AF: triggers, initiators and perpetuators. Although in many cases the underlying pathophysiology will be multifactorial (e.g. elderly), in some patients a dominant pathophysiological mechanism might prevail. It is quite feasible that different underlying mechanisms of AF require different therapies (differential treatment of AF).