Chapter 7

General Discussion
In the present study we investigated the role of the rapid atrial rate on one hand and the influence of a concurrent rapid ventricular rate, resulting in the development of tachycardiomyopathy, on the other, on atrial electrical, (ultra)structural and neurohormonal remodeling during chronic experimental atrial tachycardia. We demonstrated that part of the atrial remodeling process depends on the high atrial rate (i.e. rate dependent remodeling) and part depends on the development of tachycardiomyopathy (i.e. CHF dependent remodeling). The separate parts of atrial remodeling investigated in this study and their relationship to the high atrial or ventricular rate are depicted in figure 1.

**Atrial electrical remodeling**

We have shown that changes in atrial refractoriness during atrial tachycardia with a concurrent high ventricular rate were influenced by both the high atrial rate and the development of tachycardiomyopathy. The high atrial rate was responsible for shortening of the atrial effective refractory period (AERP) with a reversal of the physiological adaptation of AERP to rate. This has been previously extensively demonstrated in other experimental\(^1\) as well as clinical\(^2\) studies and is a process that has been shown to be completely reversible after cessation of the atrial arrhythmia.\(^1\)

However, when tachycardiomyopathy developed, AERP started prolonging and partly recovered towards its baseline values. This phenomenon has been described less extensively\(^3\).
and at present it is unclear whether this AERP prolongation is reversible with the recovery of tachycardiomyopathy. To our knowledge, only one study has shown a recovery of CHF induced AERP prolongation when neither the AERP prolongation nor its recovery were statistically significant.\textsuperscript{4}

The rate dependent shortening of AERP is considered to be of importance in the progressive nature of clinical AF since a shorter AERP will result in a shorter atrial wavelength allowing more wavelets in the fibrillating atria. However, evidence supporting a pivotal role of atrial electrical remodeling in patients with AF is lacking. In our experiments, shortening of AERP in the absence of atrial dilatation or changes in atrial ultrastructure was not accompanied by an increased inducibility of AF. Furthermore, other investigators have demonstrated complete recovery of atrial electrical remodeling with sustained susceptibility to AF which indicates that other atrial remodeling processes must play an important role in the enhanced propensity to sustain AF.\textsuperscript{5}

Finally, we demonstrated that the ventricles, unlike the atria, do not show rate dependent electrical remodeling.

**Atrial dilatation**

We demonstrated that atrial dilatation during chronic atrial tachycardia only occurs in the presence of a concurrent high ventricular rate and the subsequent development of tachycardiomyopathy. Clinical AF is associated with progressive atrial enlargement\textsuperscript{6} which has been shown to be at least partly reversible after restoration of sinus rhythm.\textsuperscript{7,8} The relationship between the level of the ventricular rate and the progression of atrial dilatation during clinical AF, however, has never been investigated.

**Changes in atrial ultrastructure and extracellular matrix**

In the absence of a high ventricular rate, a chronic high atrial rate did not result in predominant changes in atrial (ultra)structure. Only an increased number of mitochondria and a homogeneous distribution of nuclear chromatin were observed, indicating an enhanced atrial metabolism due to the high rate. In contrast, when tachycardiomyopathy develops, severe damage to the atrial extracellular matrix as well to the individual atrial myocytes occurs, including the loss of contractile material and sarcoplasmic reticulum, the accumulation of glycogen and changes in shape and size of the mitochondria. Furthermore, these subcellular changes were accompanied by an increase of perimysial and endomysial connective tissue, including the development of severe fibrosis.

Similar subcellular changes have been previously described in a goat model of sustained AF (with an uncontrolled ventricular rate) and were shown to be largely irreversible even 4 months after cessation of the arrhythmia. This was associated with an increased duration of AF.\textsuperscript{9} In dogs, recovery of pacing induced heart failure was not accompanied by a reduction of CHF induced atrial fibrosis.\textsuperscript{4}
Atrial natriuretic peptides
During chronic experimental atrial tachycardia, a concurrent high ventricular rate was responsible for elevated plasma atrial natriuretic peptide (ANP) levels rather than the high atrial rate. Although rapid atrial pacing both in the presence and absence of a high ventricular rate resulted in an acute rise of circulating ANP, this increase was transient when the ventricular rate was normal. Furthermore, there was a relation between atrial dilatation and ANP levels, indicating that either atrial stretch or increased atrial pressure is the trigger for the release of ANP rather than a high atrial rate.

In conclusion, the results of the present study suggest that a high atrial rate itself does not result in irreversible damage to the atria. It is merely the high ventricular rate, resulting in tachycardiomyopathy that causes an array of partly irreversible changes in atrial function and structure. These changes potentially form a substrate for AF and may be responsible for the intractability of this arrhythmia.

Can we prevent atrial remodeling during atrial fibrillation/tachycardia?
The treatment of clinical atrial fibrillation remains a disappointing endeavor. Despite repeated (electrical) cardioversion and treatment with antiarrhythmic drugs, maintenance of sinus rhythm in an individual patient tends to become more and more difficult in time. Finally, permanent AF may develop. Apart of progression of underlying heart disease, atrial remodeling may play an important part in this process. Therefore, therapy aiming at reduction of development of (irreversible) damage to the atria during AF potentially may improve treatment of this arrhythmia.

Rate control during AF
The results of the present study indicate that rate control during AF does not only prevent damage to the ventricles but also to the atria. Possibly, during sufficient rate control, atrial remodeling is attenuated which might prevent further deterioration of the substrate vulnerable to AF. Thus, in order to eventually carry out successful rhythm control, one should first aim to obtain adequate rate control as soon as possible. However, it is currently unknown what the ideal rate control strategy is. This will be investigated in RACE II, a Dutch multicenter study in which 500 patients with permanent AF (>3 months duration) will be randomized to rigid (resting heart rate <80 bpm, during minor exercise <110 bpm) or lenient (resting heart rate <110 bpm) rate control during a period of 2-3 years (with a minimum of 2 years). Primary endpoints will be the composite of heart failure, ischemic stroke, major bleeding, systemic and pulmonary emboli, myocardial infarction, unstable angina pectoris, syncope, ventricular tachycardia, cardiac arrest, life-threatening adverse effects of rate control drugs.
The role of the Renin-Angiotensin system

The role of the renin-angiotensin system in the clinical course of AF has gained a lot of interest. Angiotensin II is a potent promoter of fibrosis, leading to cardiac fibroblast proliferation and reduced collagenase activity and thus may play an important role in the formation of a substrate vulnerable to AF.

Shortening of atrial refractoriness after 3 hours of rapid atrial pacing was shown to completely blocked by the ACE inhibitor captopril and the angiotensin II type 1 receptor antagonist candesartan. In contrast, atrial electrical remodeling after long term (7 days) atrial pacing in dogs could not be attenuated by administration of enalapril.

In experimental CHF, ACE inhibition with enalapril attenuated the development of atrial fibrosis and impairment of atrial contractility.

Administration of the ACE inhibitor trandolapril reduced the incidence of AF in patients with systolic dysfunction after myocardial infarction. Recently, data from a prominent heart failure trial indicated that treatment with enalapril reduces the risk of developing AF in patients with left ventricular dysfunction. Furthermore, preliminary data have demonstrated an enhanced cardioversion outcome in patients with AF treated with ACE-inhibitors when these were instituted before arrhythmia onset. Madrid et al. demonstrated a lower recurrence rate of AF after electrical cardioversion in patients that were treated with amiodarone in combination with the angiotensin II type 1 receptor antagonist irbesartan when compared to patients treated with amiodarone alone.

The mechanism by which inhibition of the renin angiotensin system may reduce the vulnerability to AF is unclear. First, progression of CHF is attenuated by ACE inhibition which will result in decreased atrial pressures. Second, ACE inhibition may directly diminish the profibrotic effects of angiotensin II on the atrial myocardium.

FUTURE PERSPECTIVES

The feasibility of atrial remodeling as a target in the treatment of AF has yet to be established. An important limitation is that, in most patients, the substrate for AF develops during sinus rhythm, preceding the eventual development of AF. Ageing, for instance, is associated with the development of cardiac fibrosis. This implicates that “the damage is already done” when a patient presents him/herself with AF. Therefore, aggressive treatment of conditions which predispose to AF such as hypertension and CHF are warranted.

References


