Editorial

A paradigm shift in treatment for atrial fibrillation: from electrical to structural therapy?

Hein Heidbüchel*

University Hospital Gasthuisberg, Leuven, Belgium

Received 16 June 2003; accepted 30 June 2003

See doi:10.1016/j.ehj.2003.08.014, for the article to which this editorial refers

Atrial fibrillation (AF) is associated with increased morbidity and mortality, most notably due to stroke and heart failure. Maintaining sinus rhythm in AF patients is not an easy task, and eventually it will even fail in most leading to permanent AF. Therefore, the therapeutic goal often lies in postponing permanent AF as long as possible. Except from the surgical correction of mitral valve disease, almost all therapeutic approaches have been focused on the electrical problem that is AF. The tools to maintain sinus rhythm, however, are suboptimal, leading to frustration at both the side of the patient and the doctor. Anti-arrhythmic drugs prevent multiple electrical wavelets by interfering with electrical excitation (class-1 drugs) or repolarization (class-3 drugs). Although amiodarone has emerged as the most potent of the pack, its performance is less than stellar and its potential side-effects are well known. Since abundant atrial ectopy may be a dominant trigger of AF, ablation techniques have evolved to eliminate them. Elaborate ablation schemes are deployed now, targeting all four pulmonary veins, but maintenance of sinus rhythm is achieved in only ±70% in the best series. Moreover, only a fraction of the AF population may be ideal candidates for ablation and the procedure carries a definitive risk for veno-occlusive pulmonary hypertension due to pulmonary vein (PV) stenosis or occlusion, a complication without general effective therapy. Autonomic factors definitely play a role in the genesis of AF, but also beta-blockers are weak to prevent the arrhythmia while there is no specific treatment for the rare patients with vagally-induced AF.

After the foregoing decades with focus on the electrical aspects of AF, attention is turning back towards the underlying atrial substrate. It is known for long that age, structural heart disease and hypertension are strongly associated with AF development, and that enlarged atria are the predominant clinical risk factor for its recurrence. Recent research is focusing increasingly on the atrial structural remodelling, which underlies the development of AF in different pathological conditions. This had led to concepts about how interfering with the substrate might prevent AF development and recurrence. The article by Ueng et al. in this issue of the Journal exemplifies this trend. The authors showed that in patients with long-lasting persistent AF (≥3 m, mean 38 m), 4 weeks pre-treatment with an ACE-inhibitor (ACEi; enalapril ≥20 mg/day) and continuation of the drug after cardioversion resulted in a significantly lower recurrence rate of AF (hazard ratio 0.37). The effect of enalapril was studied on top of that of amiodarone, which was started concomitantly. Also the time to first recurrence of AF (electrocardiographically evaluated by daily heart rhythm recordings) was significantly increased in the enalapril-group. The rate of spontaneous conversion to sinus rhythm was not different, but the study was not powered to detect such effects. DC (Direct Current) cardioversion showed a trend to higher success in the ACEi arm, with less immediate recurrences of AF within the first 2 min. Complication rate was not higher than expected from a sum of those by amiodarone and enalapril respectively.

The findings of Ueng et al. fully confirm earlier findings by Madrid et al., who showed that irbesartan (a type-1 angiotensin-II receptor blocker) resulted in a lower AF recurrence rate after cardioversion of persistent AF. They also corroborate other reports of a protective effect of ACEi on AF development and recurrence: ACEi reduced the incidence of AF after acute myocardial infarction (in patients with left ventricular dysfunction) and in a single centre cohort of patients in the Studies Of LV Dysfunction (SOLVD), both in the treatment and prevention arms. We also observed a correlation between ACEi and risk for development of AF after radiofrequency catheter ablation of atrial flutter, even though ACEi was more often used in patients with underlying heart disease or hypertension.
The mechanisms for this preventive effect of ACEi or AT-II receptor blockers are probably multiple. They may comprise general haemodynamic changes leading to lower intra-atrial pressure and wall-stress, although this direct haemodynamic effect may be of limited importance. Systolic pressure at the end of follow-up was comparable in both groups of the study by Ueng et al., but unfortunately no data on diastolic pressures are provided. Therefore, they do not allow critical evaluation of this aspect. More importantly, angiotensin-II is a potent stimulus for atrial fibrogenesis, leading to an atrial substrate for AF. Ventricular dysfunction will lead to higher levels of circulating AT-II and will promote activation of local atrial AT-II production. Prevention of fibrosis by ACEi may be an important long-term effect, but it is unknown in how far it contributes to reversed structural remodelling within a time frame of weeks (as in the studies by Ueng et al. and Madrid et al.). Although ACEi do not reverse long-term electrical remodelling induced by AF itself, direct electrical effects may contribute to decreased atrial electrical heterogeneity and automaticity after cardioversion. Interestingly, patients receiving enalapril had significantly fewer atrial premature beats immediately after cardioversion and 1 m later. The lower frequency of atrial ectopy may be due to such direct electrical effects, but it could also be an expression of an altered substrate (e.g. decreased wall stress may lead to less distention of the PV, and hence less ectopy). Less atrial premature beats means less triggers for AF. However, since ACEi pre-treatment presumably did not lead to reverse electrical remodelling, there still is a window of increased vulnerability early after cardioversion. This may explain why the effect of ACEi on immediate recurrences of AF was lower than that observed after 4 weeks.

Available evidence shows that ACEi definitely has a role in AF prevention in patients that have signs of atrial structural remodelling (like increased size, persistent AF, etc.) or risk factors for it (myocardial infarction, heart failure, etc.). It is not known yet whether ACEi may also prevent AF progression in patients with lone AF, i.e. having normal-sized left atria and/or normal left ventricular function. Its potential for prevention of AF development in other clinical situations like after cardiac surgery, during thyrotoxicosis, and in patients with hypertension has not been studied. It is intriguing to know whether ACEi could attenuate the relation between age and AF. The therapeutic effect of ACEi in mono-therapy (vs in association with amiodarone) has not been studied. Conversely, it is also not clear whether there is a ‘point of no-return’ beyond which measures to revert structural remodelling do not make sense anymore, like in patients with very enlarged atria (left atrial >60 mm were excluded from the present study and the one by Madrid et al.) or long-lasting AF.

The promising value of ACEi or AT-II receptor antagonists may herald a whole new era of AF treatment, where AF is prevented and treated by modifying its substrate rather than fighting it electrically. It is conceivable that interference with other stimuli or signalling pathways of structural remodelling may also yield therapeutic benefit. Some subforms of matrix metalloproteinases seem to be involved in atrial dilation and remodelling, and may be targets for future treatment. Together, all these new developments of today definitely provide hope that we can do better tomorrow in maintaining sinus rhythm and postponing the acceptance of permanent AF.

References