Quantification of electrical remodeling in human atrial fibrillation

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Received 18 May 2000; accepted 19 May 2000

See article by Manios et al. [10] (pages 244–253) in this issue.

Mapping of the atrial electrical activation pattern during human Atrial Fibrillation (AF) has provided evidence supporting Moe’s hypothesis that AF is based on the continuous propagation of multiple wavelets wandering throughout the atria in the majority of cases [1]. Since the average size of reentry pathways during AF is dependent on atrial wavelength (conduction velocity×refractory period) it is not surprising that different complex atrial activation patterns with different numbers and dimensions of the reentry circuits were found. While long wavelengths are associated with larger and fewer wavefronts, short wavelengths result in a greater number of smaller circuits. A numerical index for quantification of spatial AF organisation was proposed and applied to different AF patterns by Botteron and Smith [2]. These authors, by calculating a so-called activation space constant from five bipolar right atrial recordings illustrated that the spatial organisation was smaller in patients with chronic AF, whereas a group of patients with induced AF and no AF history exhibited the highest degree of AF organisation. An intermediate value was observed in patients with paroxysmal AF. From a pathophysiological point of view it can therefore be concluded that AF is not a homogenous arrhythmia.

From animal models it is known that atrial effective refractory period (AERP) shortening and the loss of its normal rate adaptation are associated with an increase in AF stability and duration of AF paroxysms leading to the concept that ‘AF begets AF’ [3]. In humans, these findings of this so-called electrical remodeling process were replicated in induced AF [4,5] and confirmed in chronic AF [6,7]. Daoud et al. have investigated AERP changes in pacing-induced AF in 20 patients. They found a significant AERP shortening (up to 20%) already after a few minutes of AF. Similar observations have been reported by Yu and co-workers [5]. These authors additionally showed that ERP shortening is a rate-dependent process with shorter cycle length leading to a greater decrease in AERP.

Franz and co-workers [7] found shorter monophasic action potentials (MAP) at two right atrial sites in 7 patients with chronic AF (>3 weeks) 15–30 min after electrical cardioversion compared with 9 control subjects. This change showed a preponderance at longer pacing cycle lengths confirming the observation in animals [3] that AERP loses its ability to adapt to rate. Similarly, Kumagai and associates [6] studied several atrial electrophysiological properties in 12 patients with chronic (more than 1 year) lone AF 24 h after successful electrical cardioversion. In their study, mean AERP measured at the high right atrium was significantly shorter in AF patients than in 12 controls. Furthermore, these authors showed that P wave duration was significantly longer in AF patients. When one takes a closer look at their individual data one must, however, recognize that there is some considerable overlap in the atrial electrical properties when comparing patients and normals, even if the arrhythmia had persisted for a mean of 3.6 years. For instance, in AF patients P wave duration and AERP ranged between 80 and 140 ms and 190 and 260 ms, respectively, while it was between 50 and 110 ms and 200 and 300 ms, respectively, in controls.

Progressive atrial electrical remodeling seems to be responsible for the transition from paroxysmal to chronic AF. Atrial electrophysiology was studied in paroxysmal and chronic human AF and compared with control subjects by Tse et al. [8]. The authors observed heterogenous changes in different atrial parts with the normal spatial distribution of AERPs totally reversed in chronic AF, but preserved in paroxysmal AF. Furthermore, P wave duration was longer in chronic AF as compared with paroxysmal AF and controls. However, it was similar between paroxysmal AF and the controls. These findings in turn are further support for the heterogenous nature of AF.

From previous investigations it can be assumed that restoration and maintenance of sinus rhythm could fully
reverse these electrophysiological changes observed after experimental [3], induced [4] or chronic AF [9]. At this point in time, the resolution course of these changes and its relation with arrhythmia recurrence were unknown.

In this issue of Cardiovascular Research Manios and colleagues [10] present results on changes in atrial electrical properties following cardioversion of chronic AF (>3 months) in 28 patients. They confirmed that chronic AF leads to a shortening of both AERP and MAP duration, an abnormal adaptation of repolarisation to rate and slowing of conduction as expressed by prolongation of the P wave on the surface ECG. The reversibility of the atrial electrical remodeling process was analyzed in detail. This study represents the largest analysis of this kind with observations obtained from three serial stimulation procedures. While AERP and MAP duration returned to values comparable to those obtained from normals within 24 h following restoration of sinus rhythm, P wave duration exhibited a slower resolution course. Finally, the authors identified MAP duration at short pacing cycle lengths to be a predictor for early AF recurrence following cardioversion.

There is substantial interindividual variability in the atrial electrophysiological state. AF treatment is, however, based on trial and error, since no test is able to predict the natural history of this arrhythmia or its response to treatment. The most common parameter used to guide therapy is left atrial size even though its role for prediction of outcome following cardioversion is controversial. While some investigators have found higher AF recurrence rates in patients with left atrial enlargement [11,12] others have not [13–15].

As the number of therapeutic options including new antiarrhythmic drugs or non-pharmacologically approaches (ablation, implantable atrial defibrillator, pacing) increases, there is a clear need for tests that quantify the atrial electrical remodeling and subsequently guide AF management.

Only few studies, so far, have investigated the relation between atrial electrophysiological properties and outcome in human AF. In studies analyzing induced AF [16–18], patients with sustained AF had shorter mean atrial cycle lengths compared to patients with non-sustained AF. These data are in close agreement with observations from our group in spontaneous paroxysmal AF [19]. AF episodes that persisted for longer than 15 min had a baseline fibrillatory frequency obtained from the surface ECG of 5.3 Hz (189 ms), significantly higher than the 4.8 Hz (208 ms) found in shorter episodes. As early as 1971, Olsson and colleagues found a shorter MAP duration in patients with AF recurrence following cardioversion compared with patients who maintained sinus rhythm for over 3 months [20]. Two preliminary studies reported shorter atrial cycle length in relapsed patients immediately prior internal [21] or external cardioversion [22] when compared with non-relapsed patients. It was also shown that atrial cycle length, which closely corresponds with AERP, may contain prognostic information in patients undergoing cardioversion with ibutilide, a selective class III antiarrhythmic agent that prolongs MAP and AERP. Two independent studies identified an atrial cycle length of 160 ms obtained from the high right atrium [23] and 166 ms obtained from the surface ECG [18], respectively, as valuable cut-off points for a successful cardioversion. Patients with short cycle lengths had a low chance of drug-induced conversion while longer cycle lengths were associated with a higher success rate.

While the latter studies assessed fibrillatory cycle length prior to the intervention Manios et al., similar to the Olsson study, determined atrial electrical parameters immediately after cardioversion. They found that patients who failed to shorten the MAP to values less then 195 ms at a pacing cycle length of 350 ms were more likely to have AF recurrence. This finding was explained by a more abnormal rate adaptation curve, which is in agreement to an early study performed by Attuel and colleagues showing that poor or absent rate adaptation of AERP is related with vulnerability to AF [24].

Since there is a strong intercorrelation between MAP duration, AERP as well as atrial fibrillatory cycle length, and subsequently AF organisation and complexity it may be possible to quantify the individual AF-induced electrical changes by one or more of these measures.

The major contribution of Manios’ study is that it strengthens our knowledge of the atrial electrical remodeling process and especially its reversibility in chronic AF. It demonstrates the relation between atrial electrical properties on a patient-by-patient basis and outcome which may be of great importance to select among the various therapeutic approaches.

References


