Repolarization and refractoriness in patients with persistent atrial fibrillation

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Summary. - The use of monophasic action potential (MAP) recordings has been of important value during atrial fibrillation to understand the possibility of local pacing capture during the arrhythmia, while MAP and refractoriness determination after sinus rhythm restoration have highlighted the issue of electrophysiological remodeling owing to rate. Moreover the contemporary recording of MAP and refractoriness at the same atrial sites permitted to better understand the behavior of the ERP/MAP ratio in these patients. Local atrial pacing capture has been demonstrated in humans with chronic atrial fibrillation and suggests the presence of re-entrant circuits with large excitable gaps. The studies about atrial remodeling have shown a shortening of atrial ERP or monophasic action potential duration after cardioversion of persistent AF, while discordant results have been observed for what it concerns refractoriness adaptation to rate. Finally, the recording of a mean ERP/MAP90 ratio <1 at all the pacing cycle lengths, indicates that no post-repolarization refractoriness was present after cardioversion of persistent atrial fibrillation.

Key words: atrial fibrillation, monophasic action potential, refractoriness, excitable gap, post-repolarization refractoriness.

Riassunto (Ripolarizzazione e refrattarietà in pazienti con fibrillazione atriale persistente). - La registrazione del potenziale di azione monofasico (MAP) durante fibrillazione atriale è stato di estrema importanza per valutare la possibilità di cattura locale durante l’aritmia, mentre la registrazione del MAP e la determinazione della refrattarietà dopo il ripristino del ritmo sinusale hanno permesso una migliore comprensione del fenomeno del rimodellamento elettrico. Inoltre la contemporanea registrazione del MAP e del periodo refrattario (ERP) nella stessa sede ha permesso la valutazione del rapporto ERP/MAP. La cattura locale durante fibrillazione atriale è stata chiaramente dimostrata nei pazienti con fibrillazione atriale persistente, suggerendo la presenza di circuiti di rientro con “gap” eccitabile. Gli studi sul rimodellamento elettrico hanno invece mostrato un accorciamento dell’ERP o della durata del potenziale di azione dopo cardioversione di una fibrillazione atriale persistente, mentre sono stati riportati dati discordanti a riguardo dell’adattamento della refrattarietà al ciclo di stimolazione. Infine la registrazione di un rapporto ERP/MAP <1 a tutti i cicli di stimolazione ha indicato che non è presente alcuna refrattarietà post-ripolarizzazione dopo cardioversione elettrica di una fibrillazione atriale persistente.


Introduction

Monophasic action potential duration recordings and refractoriness determination have been evaluated in recent studies in patients with persistent atrial fibrillation (AF). The use of monophasic action potential (MAP) recordings has been of important value during AF to understand the possibility of local pacing capture during the arrhythmia, while MAP and refractoriness determination after sinus rhythm restoration have highlighted the issue of electrophysiological remodeling owing to rate. Moreover the contemporary recording of MAP and refractoriness at the same atrial sites permitted to better understand the behavior of the ERP/MAP ratio in these patients.

AF is maintained by multiple wandering wavelets continuously re-entering themselves [1-3]. The number of wavelets is related to the atrial mass and to wavelength (product of refractoriness and conduction velocity) of the reentrant circuits [4, 5]. Short wavelengths allow the simultaneous presence of a greater number of wavelets, while long wavelengths reduce their number, increasing the probability of their simultaneous extinction and the termination of the arrhythmia [6].

The types of circuits identified in AF models include leading circle reentry [7], random reentry [7] and spiral wave reentry [8]. Each of these mechanisms has typical electrophysiological features, so that the actual importance of a given model of reentry in human AF can be established.

Local capture and local capture extension in human chronic atrial fibrillation

Local atrial pacing capture has been demonstrated in dogs with induced AF [9] and in humans with chronic AF [10] (in type I and type II AF according to the Wells and Waldo classification) [11] (Figs 1 and 2). The possibility
of local pacing capture in humans has important implications regarding the electrophysiologic mechanisms underlying the maintenance of chronic AF. In fact, because local capture implies the presence of an excitable gap, in at least some phases, it is clear that leading circle re-entry (in which there is no excitable gap) is not the only electrophysiological mechanism maintaining AF in humans [12]. Although the presence of random re-entry [13] cannot be excluded, it is unlikely that the very short excitable gap associated with this pattern can account for the frequency of pacing capture observed during chronic AF in humans [10]. Therefore, local pacing capture suggests the presence, at least in some moments, of re-entrant circuits with large excitable gaps [14]. An alternative explanation has been proposed in the spiral wave hypothesis [15], which states that the core of the re-entrant wavefronts remains excitable but is not excited during re-entry.

In a previous study [10], we demonstrated the possibility of local pacing capture during chronic AF, using a Franz catheter for pacing and MAP recordings, and a quadripolar standard lead with 2-mm spacing, which allowed contemporary recording of bipolar electrograms from the distal and proximal pairs, as well as unipolar recording from the distal electrode.

In another study [16], we evaluated the extension of atrial capture in the lateral wall of the right atrium. An octopolar lead (5-mm inter-electrode distance, 6 mm between pairs) was positioned, in the 30 degree left anterior oblique view, in the lateral right atrium and simultaneous recording of bipolar electrograms were obtained from the four pairs. A Franz catheter was used for MAP recording and pacing. The octopolar and MAP catheters were positioned about 10 mm apart in the mid-lateral atrial wall. Capture extended radially up to 40 mm from the pacing site in a roughly half of the capture episodes, and up to 30 mm in the other half (Figs 3 and 4). In only two of the 48 episodes, more limited capture extension (≤ 20 and ≤ 10 mm respectively) was observed. Pacing termination of AF was never observed, and the mean capture extension in patients treated with antiarrhythmic drugs was significantly greater than that seen in untreated patients.

Extensive local capture during AF has important theoretical implications for treatment of this arrhythmia. It suggests that AF might be terminated by reducing the fibrillating tissue mass below the critical value necessary for perpetuation of the arrhythmia [17]; a goal that could theoretically be achieved by simultaneous multisite...
Pacing capture might produce a more organized form of AF, thus reducing the defibrillation threshold [18]. The latter phenomenon might have important implications regarding the diffusion of low-energy intracardiac cardioversion of AF using temporary leads or automatic atrial defibrillator.

**MAP characteristics during atrial fibrillation**

MAP recordings during AF are generally very irregular, and the depolarization phase is slowed and distorted [19]. The severity of these alterations is related to the degree of synchronization of the arrhythmia at a specific site and to the recording site itself. In fact, local AF, in the right lateral wall anteriorly to the *crista terminalis*, appears to be more organized than that occurring in the septum. We have demonstrated that the degree and the changes in the severity of MAP alterations occurring during AF are not artefacts, but are related to the organization and variation in the degree of organization of the arrhythmia, respectively [20]. Bipolar electrograms were recorded simultaneously from the distal and proximal pairs of a quadripolar lead, and MAP were obtained from a Franz catheter positioned 10 mm from the latter. Using the Wells and Waldo method [11], we classified the AF as: type I AF (discrete electrograms separated by an isoelectric baseline free of perturbations); type II AF (discrete electrograms, with perturbation of the baseline) or type III AF (absence of discrete complexes and isoelectric intervals). MAP were arbitrarily classified, based on their morphology, as: type I (almost normal, similar to that recorded during atrial flutter); type II (partially altered, with depolarization and repolarization phases that were markedly slowed, distorted and of variable amplitude) and type III (totally altered, in which the normal phases were no longer discernible). We found a perfect correspondence (100%) between type I and type III AF and type II and type III MAP, respectively; type II MAP were recorded in about 70% of the sites showing type II AF. Morphological changes in bipolar electrograms occurred during recording at 23 sites. Again, perfect correspondence (100%) was found between types I and III AF and types I and III MAP respectively, while type II MAPs were observed in about 70% of the situations in which type I or III AF changed to type II.

Therefore, MAP morphology and MAP modifications are not related to recording artefacts but to the complexity of local AF and to changes in local activation.

Another aspect of MAP during chronic AF is its triangular shape, which is the result of a shorter phase 2 and the decreased slope of phase 3 [21]. It is very interesting to note how these MAP features, which were described many years ago, are in total agreement with the more recent findings regarding atrial electrical remodeling and the changes in membrane ion flux underlying the latter phenomenon [22-25]. The ionic remodeling responsible for action potential changes in a canine model of AF is predominantly due to a reduction in $I_{ca}$, although $I_{to}$ decreases have also been reported [26]. The reduction in $I_{ca}$ accounts for the shortening of the MAP and the refractory period, and for the loss of the plateau that gives the MAP its specific triangular shape. In fact, the same effects on MAP morphology are produced by nifedipine, while exposure of fibrillating atrial cells to Bay K 8644, a drug that enhances $I_{ca}$, restores the plateau and MAP duration [25].

**Advantages of MAP recording during atrial fibrillation local capture attempts**

The use of MAP recording during local capture attempts has also some practical advantages. First, calculation of the FF interval, and consequently the occurrence of capture, can sometimes be evaluated using only the distance between two consecutive MAP upstrokes [27]. Our experience confirms that, at least for type I or type II MAP, the upstroke and its notch, which corresponds to the intrinsic deflection of the unipolar recording, are always well defined. In contrast, the FF interval cannot always be evaluated using the intrinsic deflection on the unipolar recording because of the low amplitude of the signal and/or contamination by electrical activity in the neighboring area. Sometimes, the FF interval and the occurrence of capture are difficult to determine in the bipolar recording. This can occur when capture extension is limited and there is fusion between the spontaneous activation of AF and pacing activation at the bipolar recording site. Second, episodes of very local capture, missed by both unipolar and bipolar recordings, can be detected only by MAP recordings, due to the particular configuration of the Franz catheter in which the pacing and recording sites are almost identical. In these cases, if we look very carefully at the tracing, we often find that transient capture limited to the MAP recordings actually occurs before the achievement of stable capture of the unipolar and bipolar recordings. A third advantage of MAP recording is that it can be useful for clarifying the mechanism of capture failure or delay of capture after the initiation of pacing, when, for example, capture is not achieved because the spikes fall during the atrial repolarization phase.

**Electrophysiological remodeling**

MAP and refractoriness determination after sinus rhythm restoration has improved our knowledge of the electrophysiological remodeling owing to rate.
Electrophysiological remodeling has been well described in experimental studies. The seminal paper by Wijffels et al. [28], published in 1995, has demonstrated that, in goats, pacing induced AF of up 2 weeks in duration induces a shortening of the atrial refractoriness and a reverse adaptation of refractoriness to rate. The reduction of refractoriness reduces the wavelength, and then stabilizes AF and favors its recurrences after cardioversion. Reverse adaptation (atrial ERP shorter at lower rates and longer at higher rates) obviously cannot contribute to the promotion of AF maintenance, because it minimizes the ERP reduction at higher rates, such as those present during AF. Instead, it could have a great importance in AF induction and recurrences because the short ERP during sinus rhythm increases the ability of premature beats to induce AF. In the experience of Wijffels et al., artificial maintenance of AF led also to an increase in inducibility and stability of the arrhythmia with time, while it had no effect on conduction velocity and refractoriness dispersion.

The study by Morillo et al. [29] published in the same year, demonstrated that rapid atrial pacing in dogs for 42 days reduced atrial ERP and promoted the ability to maintain AF. Moreover, this Author found that atrial conduction velocity was also decreased, as shown by an increase in P wave duration and in the PA interval. This should further reduce the wavelength and stabilize AF. Finally, another experimental study by Gaspo et al. [30] showed that in dogs paced for 1 to 42 weeks, rapid atrial activation caused time-dependent decreases in ERP, in rate-dependent ERP accommodation, in conduction velocity and wavelength, along with an increase in regional heterogeneity. In conclusion, high atrial rates due to rapid atrial pacing or induced AF decreases atrial ERP, abolish or reduce accommodation to rate in almost all experimental models, while the effects on conduction velocities and refractoriness dispersion are discordant. The results of these experimental studies, showing that AF or rapid atrial pacing induced electrophysiological changes favoring maintenance and recurrences of AF, led to the concept that “AF begets AF” and seemed to provide a good explanation for the observed “domestication” of AF.

Electrophysiological remodeling in humans

Several studies have addressed the presence and the characteristics of the electrophysiological remodeling in humans. All the studies described below have shown a shortening of atrial ERP or monophasic action potential duration after cardioversion of persistent AF, while discordant results have been observed for what it concerns refractoriness adaptation to rate. No study in man has demonstrated the presence of a reverse or completely flat refractoriness adaptation to rate, as found in experimental studies in goats. Some studies have reported the presence of normal or nearly normal adaptation to rate immediately after cardioversion of persistent AF. Pandozi et al. [31] showed that a normal or nearly normal adaptation to rate was present, according to the slope values, in 77% of the paced atrial sites of patients studied immediately after cardioversion of persistent AF (Fig. 1). Four weeks later ERP were significantly longer compared to those found immediately after cardioversion.

Tieleman [32] studied the ERP behavior measured with temporary epicardial leads during cardiac surgery in patients with both paroxysmal and persistent AF. Although no data was reported on ERP adaptation to rate, the shape of the curve in the persistent AF patients group was similar to that shown in the paper by Pandozi et al. [31].

Other studies have reported a reduced adaptation to rate in subjects with persistent AF studied immediately after cardioversion. Franz [33] reported a reduction in the duration of monophasic action potential potential and a depressed adaptation of monophasic action potential to rate compared to the control group of patients with paroxysmal SVT or VT. Finally, two studies have found normal adaptation in some atrial sites and a reduced adaptation in others [34, 35] (Fig. 3).

In conclusion, taking into account all these data, we can deduce that:

- the degree of the electrical remodeling process seems to be more pronounced in animals (particularly in goats) than in humans, in whom a clear reverse or flat adaptation to rate was never seen, and a variable degree of adaptation was found to be present.
- subjects without AF should not be compared with patients with persistent AF.

Contemporary MAP recording and refractoriness determination: the ERP/MAP ratio

Several studies have utilized monophasic action potential recordings to assess some electrophysiological features of the atrium and ventricle such as repolarization and restitution [36, 37]. The relation between repolarization and refractoriness in the human ventricle has also been assessed in previous studies showing the presence of a close relation between these parameters that remains fixed over a wide range of pacing cycle lengths [38]. Only recently corresponding data from the human atrium have been reported [39]. These data showed that action potential duration at 90% repolarization (APD90) and effective refractory period (ERP) have a very close correlation (ERP/ APD90 ratio = 0.92) which remain constant during steady state cycle lengths (from 800 to 300 ms).
However, it is well known that specific situations, such as the presence of heart diseases or treatment with antiarrhythmic drugs, can change ERP and MAP90 duration in a different way altering the ERP/MAP 90 relationship. Unfortunately, the effect of sustained arrhythmias on these parameters, especially in the context of the electrical remodeling process, has not been evaluated in details. For example the parallel change of ERP and MAP90 duration induced by persistent AF have not been carefully investigated, although three studies [33, 31, 35] have evaluated the modification in refractoriness and MAP duration after cardioversion of persistent AF. In fact, the first study reported in detail only monophasic action potential, the second one only the atrial effective refractory period, while the third one reported the results of both the techniques but only in two right atrial sites and during two basic cycle lengths (600 and 400 ms). Therefore, also the last study did not give complete information about the modifications in refractoriness and APD induced by persistent AF. The full understanding of the parallel modifications in refractoriness APD duration and hence in the ERP/MAP ratio are extremely important because postrepolalarization refractoriness that consists in an ERP/MAP ratio > 1, could have relation with AF recurrences. However, a higher ERP/MAP ratio or the development post-

refractoriness refractoriness is considered as one of the main electrophysiological effect induced by some antiarrhythmic drugs. Unfortunately, not all the drugs having an effect on the ERP/MAP ratio in the ventricle have been studied to prove the same effect in the atrium of normal patients or in the atrium of patients with AF. For example, amiodarone have shown to determine a significant prolongation of the ERP/MAP ratio in the ventricle at cycle lengths between 400 and 600 ms [40]. However, the possible presence of this effect also in the atrium and particuraly in the atrium of patients after cardioversion of persistent AF has not been investigated.

Therefore, we have addressed in patients with persistent AF after cardioversion:

- the value of ADP90 duration, ERP and the ERP/

MAP ratio at different cycle lengths and at several right atrial sites;

- the effect of pretreatment with oral amiodarone before cardioversion on the same parameters. In fact, half patients were on amiodarone treatment and the remaining half in therapeutic wash-out (no antiarrhythmic drugs, verapamil or digoxin included).

Two catheters were used for each patient; a standard quadripor lar lead with 2-mm spacing (Bard-USCI Inc., MA, USA) was positioned in the right atrium, allowing contemporary recording of bipolar electrograms from the distal and proximal pairs. In the right atrium was also positioned a second catheter for MAP recording (Franz catheter, EP Technologies, CA, USA).

In each patient, up to five right atrial sites, depending on the quality of MAP recording at the different sites, were mapped in the 30 degree left and right anterior oblique views. The mapped sites were following: mid lateral wall, low lateral wall, high lateral wall, atrial roof and septum.

At each site the ERP was measured at basic cycle lengths of 300, 400, 500, 600 ms and when possible - in relation to the sinus rate - 700 ms, by the extrastimulus method.

Linear regression analysis showed a direct relation between MAP and ERP with changes after pacing cycle length (r = 0.77 and 0.92 in the amiodarone and wash-out patients respectively). The mean ERP/MAP90 ratio was similar at all the pacing cycle lengths in wash-out and amiodarone groups and was always < 1, indicating that no post-repolarization refractoriness was present in basal condition or was induced by the drug.

ERP and MAP90 were significantly shorter in the lateral atrial sites than in the atrial roof and in the septum in both groups, implying a dispersion in ERP and MAP90 duration within the right atrium. The ERP/MAP90 ratio similar in all the atrial sites in wash-out as well as in amiodarone patients. The ERP were anywhere shorter than MAP90 duration (ERP/MAP90 ratio < 1), implying the absence of post-repolarization refractoriness in all the atrial sites.

This study is the first to determine both MAP90 duration and refractoriness at several right atrial sites during pacing at five different cycles.

The result of the study showed, after cardioversion of persistent AF, the presence of a close correlation between MAP90 and ERP in all the atrial sites at all the pacing cycle length; that is, shortening in MAP90 is accompanied by a similar shortening in refractoriness. This lead to the maintenance of a fixed ERP/MAP90 relation constantly < 1, clearly far from the unity, indicating the complete absence of or any tendency to post-repolarization refractoriness.

These results mean that, as reported by other studies, after cardioversion of persistent AF the atria lack of the protective mechanism of post-repolarization refractoriness. The importance of post-repolarization refractoriness, as an antiarrhythmic mechanism, is well demonstrated by the action of certain antiarrhythmic drugs, such as propafenone, that could be effective in the treatment of AF at least in part by inducing post-repolarization refractoriness at higher atrial rates.

Unfortunately, our study cannot confirm if the protective effect of post-repolarization refractoriness is present in normal subjects, as suggested by the results obtained by Kamalvand [35], or if it reappears at distance from cardioversion. In fact, the loss of post-repolarization refractoriness could be a sort of AF induced remodeling, not yet well studied, facilitating the early recurrences of the arrhythmia.
In this study, pretreatment with amiodarone produced a similar degree of prolongation in both atrial ERP and atrial MAP90 and did not induce any change in the ERP/MAP90 ratio, that, similarly to wash-out patients remained unchanged all the studied sites and at all the pacing cycle lengths. Then, in patients treated with amiodarone, similarly to those in wash-out, the ERP/MAP90 ratio remained well far from the unity and from the achievement of post-repolarization refractoriness.

In conclusion, this study study, conducted in patients with persistent AF, showed that after cardioversion of the arrhythmia ERP and MAP90 duration have parallel modifications in relation to changes in pacing cycle length in all the paced sites of the right atrium. This findings are similar to those reported in human ventricle and in the atria of patients without AF. Importantly, in contrast to the effect showed at the ventricular level, amiodarone does not modify ERP/MAP90 relationship in the atria, at least in patients with persistent AF. Further studies are necessary to establish if the absence of post-repolarization refractoriness and/or the lack of any effect on atrial ERP/MAP90 relation by pretreatment with amiodarone found in our study, represent a particular, new expression of the electrophysiological atrial remodeling induced by long-lasting AF, that could favor the early recurrence of the arrhythmia.

Conclusions

Recording of MAP during local pacing capture of persistent AF had an important role in confirming the presence of an excitable gap during this arrhythmia.

Moreover, MAP recordings and refractoriness assessment after sinus rhythm restoration in patients with persistent AF gave important information about the electrophysiological remodeling owing to rate in humans and point out the behavior of another important electrophysiological parameter, such as the ERP/MAP ratio.

Submitted on invitation.
Accepted on 29 March 2001.

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