Relations between monophasic action potential duration and refractoriness after cardioversion of persistent atrial fibrillation: results in wash-out and amiodarone-treated patients

Claudio Pandozi, Giuseppe Gentilucci, Leonardo Calò, Antonio Castro, Filippo Lamberti, Maria Luisa Loricchio, Luca Santini, Barbara Magris, Alan Bulava, Petr Peichl, Massimo Santini

Department of Cardiovascular Diseases, San Filippo Neri Hospital, Rome, Italy

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Action potentials; Atrial fibrillation; Electrophysiology.

Background. **The relation between repolarization and refractoriness has been clinically evaluated both in the atrium and ventricle. However, this relation has not been carefully investigated in the atria of patients with persistent atrial fibrillation after cardioversion.**

Methods. **We determined the refractoriness and monophasic action potential duration at 90% of repolarization (MAP90), at 5 pacing cycle lengths (300 to 700 ms) and in 5 right atrial sites after internal cardioversion of persistent atrial fibrillation in 27 patients.**

Results. **The effective refractory periods (ERPs) were longer in amiodarone-treated patients (group 1) than in wash-out patients (group 2) (211.3 ± 26.4 vs 199.1 ± 24.3 ms, $p < 0.002$) as well as the MAP90 (243.6 ± 36.8 vs 223.1 ± 29.2 ms, $p < 0.001$). Linear regression analysis showed a direct relation between the MAP90 and ERP changes induced by different pacing cycle lengths ($r = 0.77$ and $r = 0.92$ in the amiodarone and wash-out patients, respectively). The ERP/MAP90 ratio was similar at all pacing cycle lengths in both wash-out and amiodarone groups and was always < 1. The mean ERP and MAP90 were shorter in the lateral right atrial sites than in the atrial roof and septum in both group 1 and group 2 patients ($p < 0.001$).**

Conclusions. **A linear correlation was found between ERP and MAP90 in response to changes in pacing cycle lengths. Postrepolarization refractoriness was not observed after cardioversion of persistent atrial fibrillation. Pretreatment with oral amiodarone does not affect these electrophysiological features or the dispersion of ERP and MAP90 in the right atrium after sinus rhythm restoration.**

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Address:
Dr. Claudio Pandozi
Via Madonna di Fatima, 22
00147 Roma
E-mail:
pandozi@micanet.net

Introduction

Several studies have utilized monophasic action potential (MAP) recordings to assess some electrophysiological features of the atrium and ventricle such as repolarization and restitution[1-4]. 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[5]. Only recently have corresponding data from the human atrium been reported[6]. These data showed that the action potential duration at 90% of repolarization (APD90) and the effective refractory period (ERP) are very closely correlated. Therefore, the ERP/APD90 ratio remains almost constant during different steady state pacing 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[7,8], may variably modify ERPs and MAP duration at 90% of repolarization (MAP90) and hence alter the ERP/MAP90 relationship. On the other hand, the effect of sustained arrhythmias on these parameters, especially in the context of the electrical remodeling process, has not been evaluated in detail. For example, the parallel changes of ERP and MAP90 duration induced by persistent atrial fibrillation (AF) have not been carefully investigated, although three studies[9-11] have evaluated the modification in refractoriness and MAP duration after cardioversion of persistent AF. A full understanding of the parallel modifications in refractoriness and action potential duration and hence in the ERP/MAP90 ratio is extremely important.

In fact, the postrepolarization refractoriness, that consists in an ERP/MAP90 ratio > 1, could be a protective mechanism against AF recurrences and is actually considered as one of the main electrophysiological effects induced by some antiarrhythmic drugs[12]. For example, amiodarone was shown to determine a significant prolongation of the ERP/MAP90 ratio in the ventricle at cycle lengths ranging between 400 and 600 ms[8]. However, the possible presence of this effect in the right atrium after cardioversion of persistent AF has not been fully investigated.

The aim of the present study was to assess in patients with persistent AF after cardioversion: a) the effect of pretreatment with oral amiodarone before cardioversion on ADP90, ERP and the ERP/MAP90 ratio, and b) the value of ADP90, ERP and the ERP/MAP90 ratio at different cycle lengths and at several right atrial sites.

Methods

Patient selection. The study was carried out on 27 consecutive patients with persistent AF (duration between 30 days and 30 months), enrolled from July 1999 to April 2000, 5 min after low-energy internal cardioversion. The study was approved by our Institutional Ethics Committee and all the patients gave their written informed consent.

The diagnosis of AF was based on the surface ECG with the following criteria: replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in size, shape and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular conduction was intact[13]. These criteria had to be validated by an endocardial recording showing irregular atrial activation not separated by an isoelectric line or discrete atrial complexes separated by an isoelectric line but with irregular atrial intervals. Moreover, the atrial intervals were not to be characterized by a periodic pattern[14]. Thyroid dysfunction was ruled out in all patients. Twelve patients were on amiodarone treatment (group 1) and the remaining 15 in therapeutic wash-out (no antiarrhythmic drugs, verapamil or digoxin included) (group 2). As a rule, the patients in wash-out were treated with intravenous propafenone (2 mg/kg body weight) after the completion of the protocol, followed by oral administration of the drug (600-750 mg/die). The mean age, AF duration, presence and type of heart disease, and left atrial diameter were similar in the two groups (Table I).

Table I. Baseline characteristics of the two study groups.

	Group 1 (n=12)	Group 2 (n=15)	p
Age (years)	60.8 ± 12	63 ± 8	NS
AF duration (days)	210 ± 269	206 ± 300	NS
LA diameter (mm)	46.4 ± 3.8	44.7 ± 5.3	NS
Cardiomyopathy			
Hypertensive	4 (33.3%)	5 (33.3%)	NS
Valvular	2 (16.6%)	2 (13.3%)	NS
Dilated	1 (8%)	2 (13.3%)	NS
Hypertrophic	0	1 (6.6%)	NS
CAD	2 (16.6%)	4 (26.6%)	NS
Lone AF	2 (16.6%)	2 (13.3%)	NS

AF = atrial fibrillation; CAD = coronary artery disease; LA = left atrial.

Electrophysiological study. Two catheters were used in each patient. They were introduced in the same sheaths used for the leads necessary for internal cardioversion. A standard quadripolar lead with 2 mm spacing (Bard-USCI Inc., Tewksbury, MA, USA) was positioned in the right atrium, allowing contemporary recording of bipolar electrograms from the distal and proximal pairs. A second catheter for MAP recordings (Franz catheter, EP Technologies, Sunnyvale, CA, USA) was also positioned in the right atrium.

In each patient, up to 5 right atrial sites, depending on the quality of MAP recording at the different sites, were mapped in the 30° left and right anterior oblique views. The mapped sites were the following: mid lateral wall, low lateral wall, high lateral wall, atrial roof and septum.

Stimulation protocol. The Franz catheter was used for pacing, delivering a square wave of 2 ms pulse duration at twice the diastolic stimulation threshold. The stimulation protocol was performed after both an adequate MAP recording and a pacing threshold < 1 mA were achieved in each specific site; the atrial pacing threshold at each site was then verified at the end of the stimulation protocol. In cases where a significant difference in the pacing threshold was found (> 0.5 mA), the datum was not considered for analysis, the catheter was repositioned, and the stimulation protocol was repeated. The sites where a good MAP was not recorded were excluded. At each site the ERP was measured at basic cycle lengths of 300, 400, 500 and 600 ms and when possible (with respect to the sinus rate) 700 ms, by the extrastimulus method. A train of 8 stimuli (S1) was followed by a late extrastimulus (S2) beginning from 300 ms, except for the 300 ms cycle length during which the first extrastimulus (S2) was delivered beginning from 290 ms. The coupling interval was then shortened by 10 ms steps until the S2 failed to produce the atrial response. Thereafter, this last S1-S2 interval was increased by 10 ms and shortened by 2 ms decrements until S2 capture failure. The ERP was defined as the longest S1-S2 coupling interval that failed to result in atrial capture on two consecutive attempts.

The MAP90 was manually calculated at the seventh and eighth beat of the last train of 8 stimuli of each pacing cycle length, when atrial refractoriness was reached. The mean of these two beats was used for cal-

culations. The maximum MAP height (crest of the MAP plateau during varying MAP recording conditions or waveforms) was determined using the Franz criteria that distinguish a "plateau height equal to the MAP upstroke height", a "receding MAP" and a "spike-and-dome" configuration[15]. The MAP90 duration was calculated as shown in figure 1. Two electrophysiologists calculated the MAP90 to evaluate the interobserver variability.

The stimulation protocol was performed in a random order, using a simple randomization, in a clockwise (from the low lateral atrial wall to the septum) or counter-clockwise (from the septum to the low lateral atrial wall) manner to avoid bias in the determination of the local refractoriness related to the different time elapsing from sinus rhythm restoration to the stimulation of the different atrial sites. According to our protocol, the study was stopped if pacing or programmed stimulation reinduced AF or other sustained atrial arrhythmias requiring electrical cardioversion. Patients were considered for data analysis only when the protocol was completed at least at two sites.

Statistical analysis. All data, unless otherwise noted, are expressed as mean ± SD. Differences in continuous variables were analyzed using the Student's t-test. Differences in categorical variables were analyzed using the χ^2 test. Results were considered to be statistically significant when $p < 0.05$. The linear correlation between ERPs and MAP90 was calculated using single linear regression analysis.

Results

Patients and paced sites. Twenty patients were male and 7 female. The mean age was 62.4 ± 7.4 years. All patients had a history of AF lasting > 30 days (mean 209 ± 328 days, range 30-900 days). Twelve patients had a history of paroxysmal AF in the preceding years. The mean left atrial size was 45.8 ± 5.4 mm (range 38-59 mm). The underlying heart diseases were as follows: valvular heart disease (4 patients), hypertension (9 patients), dilated cardiomyopathy (3 patients), hypertrophic cardiomyopathy (1 patient), and coronary artery disease (6 patients) (Table I). Four patients had lone AF. In 9 of the 27 patients the study was stopped because of AF induction during the first or second stimulation sequence in the first paced site. Seven of these patients were in wash-out and 2 were on amiodarone. Therefore, the stimulation protocol was completed in 18 patients, 10 on amiodarone and 8 in wash-out. It was performed in all the 5 sites in 15 patients (7 in wash-out and 8 on amiodarone), in 4 sites in 1 patient (on amiodarone) and in 3 sites in 2 patients (1 in wash-out and 1 on amiodarone). In one group 1 patient the sequence at the 700 ms cycle length was not performed because of the higher sinus rate.

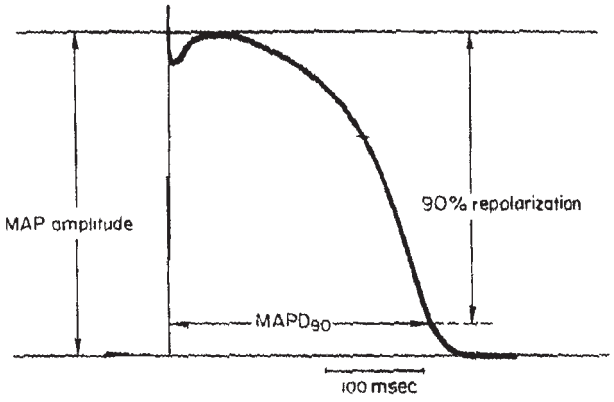

Figure 1. *Method of calculation of the monophasic action potential (MAP) duration at 90% of repolarization: in this "spike-and-dome" configuration of MAP, the MAP duration at 90% of repolarization is calculated by determining the duration of the MAP at 90% of the distance between the horizontal lines respectively indicating the baseline and the crest of the MAP plateau (MAPD90).*

Interobserver variability. There were no significant interobserver differences in the calculation of the MAP90 (1 to 5%).

ERPs in group 1 and group 2 patients. The mean ERP at the different stimulation cycle lengths in group 1 and group 2 patients are reported in table II and take into account all the paced sites. As expected, the mean ERP was significantly longer in group 1 than in group 2 patients (211.3 ± 24.3 vs 199.1 ± 24.3 ms, $p < 0.002$); this difference was significant at all the cycle lengths except for the 400 ms pacing cycle.

MAP90 in group 1 and group 2 patients. The mean MAP90s at the different stimulation cycle lengths in group 1 and group 2 patients are reported in table II. As for the mean ERP, the mean MAP90 was globally significantly longer in group 1 than in group 2 patients (243.6 ± 36.8 vs 223.1 ± 29.2 ms, $p < 0.001$); this difference was significant at all the cycle lengths except for the 400 ms pacing cycle.

ERP/MAP90 ratio in group 1 and group 2 patients. Linear regression analysis showed a direct relation between MAP90 and ERP in response to changes in the pacing cycle length ($r = 0.92$ and $r = 0.77$ in group 2 and group 1 patients respectively) (Fig. 2). The values of the mean ERP/MAP90 ratio of group 1 and group 2 patients are reported in table II. The mean ERP/MAP90 ratio was similar at all the cycle lengths in both groups and was always < 1, indicating that no postrepolarization refractoriness was present in basal conditions or was induced by the drug.

Regional variations of the ERP and MAP90. The ERP and MAP90 were significantly shorter in the lateral atrial sites compared to the atrial roof and to the

Table II. Effective refractory period (ERP), monophasic action potential duration at 90% of repolarization (MAP90) and the ERP/MAP90 ratio at each pacing cycle length in wash-out and amiodarone-treated patients.

	Wash-out group (n=14)	Amiodarone group (n=11)	p
ERP			
Basic cycle length (ms)			
300	183.7 ± 20.6	197.8 ± 26.5	0.02
400	194.9 ± 23.3	204.2 ± 24.3	0.08
500	200.1 ± 23.4	213.3 ± 28.6	0.03
600	208.0 ± 27.4	216.0 ± 24.5	0.01
700	208.6 ± 23.4	225.1 ± 24.0	0.008
MAP90			
Basic cycle length (ms)			
300	207.7 ± 24.4	221.7 ± 25.4	0.02
400	222.5 ± 31.0	235.9 ± 28.1	0.08
500	221.8 ± 31.3	248.8 ± 42.5	0.007
600	229.2 ± 26.5	250.8 ± 36.1	0.01
700	234.2 ± 25.0	260.7 ± 35.4	0.003
ERP/MAP90			
Basic cycle length (ms)			
300	0.89 ± 0.1	0.89 ± 0.1	NS
400	0.87 ± 0.1	0.89 ± 0.2	NS
500	0.92 ± 0.2	0.86 ± 0.1	NS
600	0.91 ± 0.1	0.87 ± 0.1	NS
700	0.89 ± 0.1	0.87 ± 0.1	NS

Data are expressed as mean ± SD.

septum ($p < 0.001$) in both groups (Fig. 3), implying dispersion in ERP and MAP90 duration within the right atrium. The ERP/MAP90 ratio was similar in all the atrial sites both in group 1 and group 2 patients.

Discussion

The main finding of the study was that after cardioversion of patients with persistent AF: 1) a linear correlation exists between ERP and MAP90 in response to changes in the pacing cycle lengths, 2) postrepolarization refractoriness is not present, 3) pretreatment with oral amiodarone does not affect these electrophysiological features, and 4) dispersion of ERP and MAP90 is present in the right atrium after sinus rhythm restoration.

ERP/MAP90 relationship in the ventricle. Initial findings showed a poor correlation between the duration of the right ventricular action potential and ERP measurements[16]. However, in that study the action potential duration and ERP were measured at disparate right ventricular endocardial sites and the lack of a close correlation between the two variables may have been due to site-specific variability of either the action potential duration or ERP. In fact, a later study[5] showed that, when the pacing and MAP recording sites are the same, the action potential duration and ERP in the human ventricle have a close relation that remains fixed over a wide range of cycle lengths. Both the action potential duration and ERP shortened linearly with the cycle length, maintaining a parallel relation. Moreover, the action potential duration was always greater than ERP at each cycle length.

ERP/MAP90 relationship in the atria. Corresponding data about the relationship between the action potential duration and refractoriness in the human atria have been reported only recently. In one study[9], MAP90 and ERP were measured simultaneously in 7 patients at multiple right atrial sites and during different steady state cycle lengths. The results of this work showed a very close correlation between MAP90 and ERP, which was nearly constant among different patients and among different right atrial sites in the same patient. Likewise, cycle length changes ranging from 800 to 300 ms did not alter the correlation.

Another study, limited to only two atrial sites, evaluated the MAP90 and ERP behavior in control subjects and in patients after AF cardioversion[11]. The results of this paper showed that after AF cardioversion no postrepolarization refractoriness was present in the two right atrial sites paced at two different cycle lengths. Surprisingly and interestingly, a period of postrepolarization refractoriness confined to the right atrial appendage was found in the control population. The authors concluded that the postrepolarization refractoriness at the right atrial appendage observed in the normal atria could be a protective mechanism against the recurrence of atrial tachyarrhythmias, by preventing the propagation of early atrial ectopic beats and in-

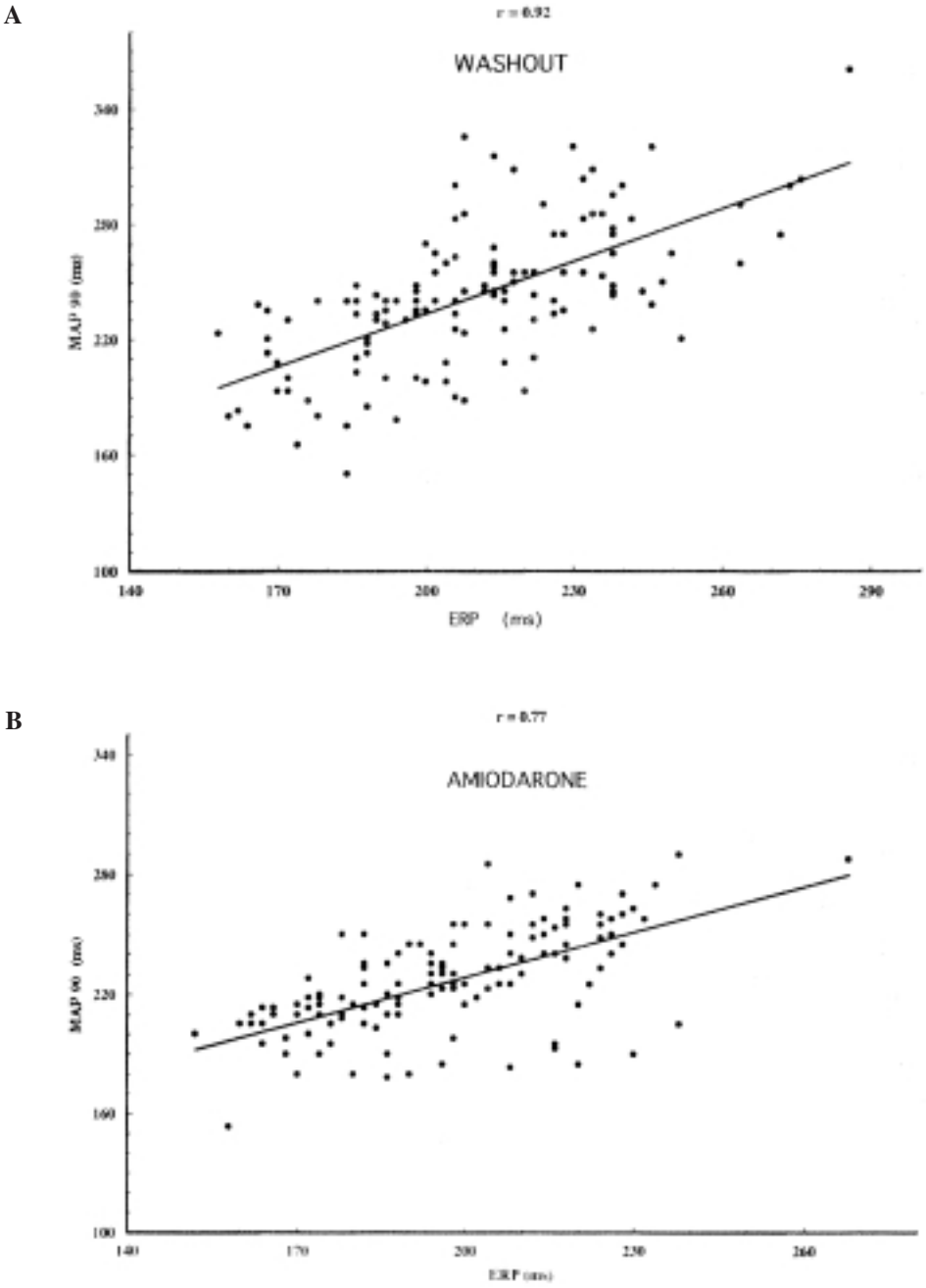

Figure 2. *Linear regression analysis shows the presence of a direct relationship between the effective refractory period (ERP) and the monophasic action potential duration at 90% of repolarization (MAP90) in response to different pacing cycle lengths in wash-out patients* (A) *and in amiodarone-treated patients* (B).

creasing the wavelength of possible reentrant circuits. It is important to stress that not only the presence of an evident postrepolarization refractoriness but also any change of the ERP/MAP90 ratio towards unity may exert protective antiarrhythmic effects.

Results of the present study. Our study is the first to determine both the MAP90 duration and refractoriness at several right atrial sites during pacing at 5 different cycle lengths.

The results of the study showed the presence of a close correlation between MAP90 and ERP in all the atrial sites and at all the pacing cycle lengths after cardioversion of persistent AF; that is, a decrease in the MAP90 duration is accompanied by a similar decrease in refractoriness. This led to the maintenance of a fixed ERP/MAP90 ratio constantly < 1, indicating the complete absence of any tendency to postrepolarization refractoriness.

These results imply, as reported by other studies[11], that after cardioversion of persistent AF the atria lack the protective mechanism of postrepolarization refractoriness. The importance of postrepolarization refractoriness, as an antiarrhythmic mechanism, is well

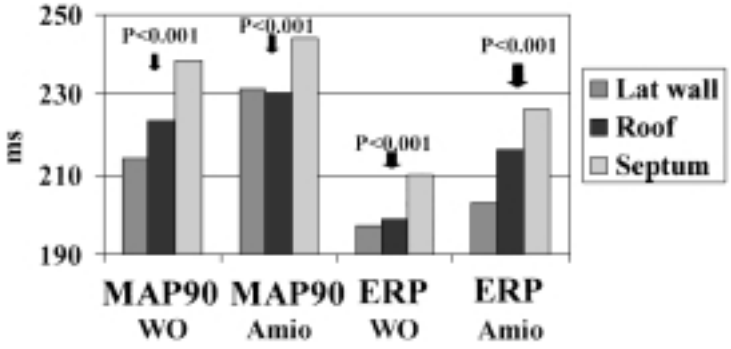

Figure 3. *Mean value of the effective refractory period (ERP) and monophasic action potential duration at 90% of repolarization (MAP90) in the lateral wall, roof and septum of the right atrium. Dispersion in the ERP and MAP90 within the right atrium is clearly shown. See text for further discussion. Amio = amiodarone group; WO = wash-out group.*

demonstrated by the action of certain antiarrhythmic drugs, such as propafenone, that may be effective in the treatment of AF at least in part by inducing postrepolarization refractoriness at higher atrial rates[17].

Unfortunately, our study cannot confirm whether the protective effect of postrepolarization refractoriness is present in normal subjects, as suggested by Kamalvand et al.[11], or whether it reappears sooner or later after cardioversion. In fact, the loss of postrepolarization refractoriness could be the expression of a certain type of not yet well-known AF-induced remodeling facilitating early recurrences of the arrhythmia[18,19].

The effect of pretreatment with amiodarone. Studies in the human ventricle have shown that the ERP/MAP90 ratio was significantly increased in amiodarone-treated patients compared with untreated subjects[8]. Moreover in amiodarone-treated patients the ratio increased towards unity that is towards the presence of postrepolarization refractoriness.

Similar results for the human ventricle have been reported with procainamide[5]. This drug prolonged the action potential duration and refractoriness, but the increase in ERP was greater than that in the action potential duration particularly at pacing cycle lengths < 400 ms, when an ERP/MAP90 ratio > 1 was achieved.

In our study, pretreatment with amiodarone produced a similar degree of prolongation in both the atrial ERP and atrial MAP90 and did not induce any change in the ERP/MAP90 ratio, i.e. just as for wash-out patients, it remained unchanged in all studied sites and at all pacing cycle lengths. Then, in patients treated with amiodarone, as in those in wash-out, the ERP/MAP90 ratio remained well distant from unity and from the achievement of postrepolarization refractoriness.

These differences in the response to amiodarone between ventricular and atrial tissues may be the consequence of several factors. It may reflect a different effect of the drug at the ventricular and atrial levels either in the time-dependent recovery of sodium channel blockade at the end of phase 3 of the action potential or after complete repolarization. A second explanation may be related to the presence of ionic remodeling in patients with persistent AF that could allow a more rapid time-dependent recovery of the sodium channel from inactivation.

Another result of this study is that the antiarrhythmic effect of amiodarone is not related to a decreased dispersion of the atrial electrophysiological properties since the drug did not reduce the dispersion of refractoriness and the MAP90 duration between different atrial sites.

Atrial electrical instability after cardioversion of atrial fibrillation. In 9 of 27 patients the study was stopped because of AF induction during the first or the second stimulation sequence in the first paced site. This reflects the high electrical instability of the atria immediately after cardioversion. Electrophysiological remodeling[10,11,18] (decreased refractoriness, dispersion of refractoriness, repolarization and activation time) as well as structural remodeling[19] could be the cause of the high vulnerability to AF. In the clinical setting, this could be at least one of the electrophysiological explanations for the immediate and early recurrences of AF after cardioversion.

Study limitations. The calculation of MAP90 after 2 min of regular pacing to allow for the achievement of a new MAP90 steady state for each cycle length was not performed for the following reasons:
- pacing for 2 min at each cycle length at each pacing site would have further prolonged the already relatively long study protocol;
- several drive trains occur prior to reaching refractoriness during scanning of diastole using the decremental method; these drive trains represent *de facto* a conditioning period. As reported in a previous study[20], programmed stimulation using a pacing cycle length faster than the spontaneous cycle length and incorporating an inter-train pause of only 1 s may produce a change in the MAP duration that differs by only 8 ms from that

found after 3 min of a fixed pacing cycle at the same rate.

We used only one Franz catheter for each study, so that we could not simultaneously calculate the duration of MAP90 in more than one site. Moreover, recording and pacing by only one lead did not allow us to evaluate the dispersion of other important electrophysiological parameters such as the activation time and the total repolarization time. Therefore, our study cannot confirm the results reported by the Olsson group[21]; these authors found a dispersion not only of refractoriness, similar to the results of our study, but also of the activation time and of the total repolarization time.

No study was repeated at a distance after sinus rhythm restoration to evaluate the possible changes in the ERP/MAP90 ratio with time.

In conclusion, our study shows that after cardioversion for persistent AF, ERP and MAP duration are modified in direct relation to the changes in the pacing cycle length in all paced sites of the right atrium. This finding is similar to those reported for the human ventricle and for the atria of patients without AF. Importantly, in contrast to the effect found at the ventricular level, amiodarone does not modify the postrepolarization refractoriness in the atrium, at least in patients with persistent AF. Further studies are necessary to establish whether the absence of postrepolarization refractoriness found in our study represents a new particular expression of the electrophysiological atrial remodeling induced by long-lasting AF that could favor the early recurrence of the arrhythmia.

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