Electrophysiological Characteristics of the Human Atria After Cardioversion of Persistent Atrial Fibrillation

Claudio Pandozi, MD; Leopoldo Bianconi, MD; Mauro Villani, MD; Giuseppe Gentilucci, MD; Antonio Castro, MD; Giuliano Altamura, MD; Anna P. Jesi, MD; Filippo Lamberti, MD; Fabrizio Ammirati, MD; Massimo Santini, MD

Background—In animal models, induced atrial fibrillation shortens the atrial effective refractory period (ERP) and reverses its physiological adaptation to rate. It is not clear whether this process, known as “electrical remodeling,” occurs in humans.

Methods and Results—We determined the ERPs, at 5 pacing cycle lengths (300 to 700 ms) and in 5 right atrial sites, after internal cardioversion of chronic atrial fibrillation in 25 patients (14 in pharmacological washout and 11 on amiodarone). The ERPs were 195.5 ± 18.8 ms in the washout and 206.3 ± 17.9 ms in the amiodarone patients (P < 0.0001). ERPs were closely correlated with the stimulation rates (r = 0.95 in the washout and r = 0.94 in the amiodarone group), and slope values indicating a normal (≥0.07) or nearly normal (0.05 to 0.06) adaptation of ERP to rate were found in 77% of the 84 paced sites. The mean ERP was shorter in the lateral wall (198.1 ± 17.9 ms) than in the atrial roof (203.3 ± 21.5 ms) and in the septum (210.5 ± 20.0 ms) (P < 0.03). After 4 weeks of sinus rhythm, the mean ERP, determined again in 8 patients (4 in wash-out and 4 on amiodarone), was significantly increased compared with the basal study (221.4 ± 21.4 versus 197.8 ± 18.3 ms, P < 0.0001).

Conclusions—After cardioversion of chronic atrial fibrillation, (1) atrial ERP adaptation to rate was normal or nearly normal in the majority of the cases, (2) a significant dispersion of refractoriness between different right atrial sites was present, and (3) ERPs were significantly increased after 4 weeks of sinus rhythm in both washout and amiodarone patients. (Circulation. 1998;98:2860-2865.)

Key Words: fibrillation ■ remodeling ■ electrophysiology ■ atrium

Atrial fibrillation (AF) is maintained by multiple wandering wavelets continuously reentering themselves. The number of the wavelets is related to the atrial mass and to the wavelength (product of refractoriness and conduction velocity) of the reentrant circuits. Short wavelengths allow the simultaneous presence of a greater number of wavelets, whereas long wavelengths reduce their number, making the occurrence of simultaneous extinction of all the wavelets and the termination of the arrhythmia more likely. Therefore, the 2 components of the wavelength, conduction velocity and atrial refractoriness, are basic determinants of the AF onset and perpetuation. A third important factor favoring the onset of the arrhythmia is dispersion of refractoriness. In fact, after a premature impulse, it increases the likelihood of local unidirectional block, one of the prerequisites of a reentrant circuit.

Recently, Wijffels demonstrated in healthy goats that the artificial maintenance of AF by rapid atrial pacing induced a progressive shortening of the atrial effective refractory period (ERP). Moreover, the rate-related shortening of ERP was inverted, resulting in shorter refractoriness at lower rates. The loss of the normal increase in refractoriness with a decrease in rate could be another important factor favoring AF. In fact, it might facilitate the induction of the arrhythmia by a premature atrial beat during normal sinus rhythm. These changes in the refractoriness behavior have been called “electrical remodeling” and constitute the experimental basis of the concept that AF tends to perpetuate itself: “AF begets AF.”

Nevertheless, the findings observed in AF induced in healthy goats are not necessarily applicable to the patients with the same spontaneous arrhythmia, even though shortening of the atrial ERPs after as little as 7 or 8 minutes of pacing-induced AF and short ERPs after cardioversion of chronic lone AF have been demonstrated in humans. Moreover, it is not known whether other peculiar electrophysiological features, such as an abnormal response of atrial refractoriness to abrupt cycle length changes, are present after cardioversion of clinical persistent AF.

The present study was conducted in patients with spontaneous chronic AF immediately after internal electrical cardioversion and was designed to assess the following:

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From the Department of Cardiology, San Filippo Neri Hospital, Arrhythmia Control Unit (M.V.), La Sapienza University, Rome, Italy.

Correspondence to Claudio Pandozi, MD, Via Madonna di Fatima, 22, 00147, Rome, Italy. E-mail mvillani@uniroma1.it

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the atrial ERPs immediately after cardioversion and their behavior with time, the relation between stimulation rate and ERPs, the dispersion of refractoriness in the right atrium, the refractoriness response to long-short and short-long cycles, and the effects of amiodarone on the above parameters.

Methods

Patient Selection

The study was carried out in 25 consecutive patients with chronic AF (duration between 30 days and 4 years) 5 minutes after low-energy internal cardioversion. The study was approved by our Institutional Ethical Committee, and all the patients gave written informed consent.

The diagnosis of AF was based on the surface ECG, with the following criteria: presence of fluctuation of the baseline without regular P or F waves, with totally irregular RR intervals. These criteria had to be validated by endocardial recordings showing irregular atrial activation not separated by an isoelectric line or discrete atrial complexes separated by an isoelectric line but with irregular atrial intervals (FF). Moreover, no periodic pattern of the FF intervals could be present.

Thyroid dysfunction had been ruled out in all patients. Eleven patients were on amiodarone treatment; the remaining 14 were in therapeutic washout (no antiarrhythmic drugs, verapamil, or digoxin included). As a rule, the patients in washout were treated with intravenous propafenone (2 mg/kg) after the completion of the protocol, followed by oral administration of the drug (600 to 750 mg/d).

Electrophysiological Study

Two catheters were used for each patient; they were introduced in the same sheaths as used for the leads necessary for internal cardioversion. A standard quadripolar lead with 2-mm spacing (Bard-USCI Inc) was positioned in the right atrium, allowing simultaneous recording of bipolar electrograms from the distal and proximal pairs. A second catheter was also positioned in the right atrium for monophasic action potential recording. This lead (Franz catheter, EP Technologies) was preferred for its low stimulation threshold.

In each patient, up to 5 right atrial sites, depending on the time needed for the procedure, were mapped in the 30° left anterior oblique view. The mapped sites were the mid lateral wall, low lateral wall, high lateral wall, atrial roof, and septum.

Stimulation Protocol

The Franz catheter was used for pacing by delivering a square wave of 2-ms pulse duration at twice the stimulation threshold. The stimulation protocol was performed after a pacing threshold <1 mA was achieved in each specific site; the atrial pacing threshold at each site was then verified at the end of the stimulation protocol. When a significant difference in the pacing threshold was found (>0.5 mA), the data were not considered for analysis, the catheter was repositioned, and the stimulation protocol was repeated. At each site, the ERP was measured at basic cycle lengths of 300, 400, 500, 600, and (when possible in relation 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. The coupling interval was then shortened in steps of 10 ms until S2 failed to produce an atrial response. Then, this last S1-S2 interval was increased by 10 ms and shortened by 2-ms decrements until S1 capture failure. The pause between pacing trains was 1 second. The ERP was defined as the longest S1-S2 coupling interval that failed to result in atrial capture on 2 consecutive attempts. The bipolar electrograms were used to confirm atrial capture at shorter coupling intervals or when the monophasic action potential recording was of low amplitude. In the majority of our patients, the ERP was then calculated after a short-long (8 basic drive beats at 300 ms followed by a 600-ms premature beat) and a long-short (8 basic drive beats at 600 ms followed by a 300-ms premature beat) sequence and compared with the ERP at basic cycle lengths of 600 and 300 ms, respectively. The stimulation protocol was performed in random order in a clockwise (from the low lateral atrial wall to the septum) or counterclockwise (from the septum to the low lateral atrial wall) direction. This was done to avoid bias in determination of local refractoriness related to the different time elapsed from restoration of sinus rhythm and the stimulation of the different atrial sites.

According to our protocol, the study was stopped if pacing or programmed stimulation induced AF or other sustained atrial arrhythmias, requiring cardioversion. Patients were considered for data analysis only when the protocol was completed in ≥2 sites; otherwise, the patient was considered a dropout.

In 10 of the 12 patients considered for data analysis who remained in sinus rhythm 4 weeks later, the electrophysiological study was repeated at that time using the same protocol except for the short-long and long-short sequences. Five of these patients were on amiodarone and 5 in washout. In these latter patients, propafenone had been discontinued 3 days before the control electrophysiological study.

Statistical Analysis

For each paced site, the linear correlation between the ERPs and the corresponding pacing rates was calculated by the single linear regression analysis. The presence of normal or abnormal refractoriness adaptation to rate and its degree were also established by evaluation of the slope values. According to the slope figures, the adaptation of the ERP to rate was considered absent when the slope value was zero and inverted if its value was negative. For positive values between 0.01 and 0.04, the adaptation was considered poor; between 0.05 and 0.06, it was considered nearly normal; and for values ≥0.07, it was classified as normal.

Data are presented as mean±SD. Differences in continuous variables were analyzed by paired or unpaired Student’s t test or ANOVA as appropriate, and comparisons between groups were performed by multiple Bonferroni test. Differences in categorical variables were analyzed by χ² test, with Yates' correction if needed. A value of P<0.05 was considered statistically significant.

Results

Patients and Paced Sites

Seventeen patients were men and 8 women, with a mean age of 61.6±8.8 years; AF duration was ≥30 days in all the patients (mean, 220.8±366.1 days; median, 90.0 days; range, 30 to 1440 days). Ten patients had a history of paroxysmal AF in the preceding years. The mean left atrial size was 46.0±5.7 mm (median, 45.0 mm; range, 38 to 59 mm). The underlying heart diseases were as follows: valvular heart disease (4 patients), hypertension (8), dilated cardiomyopathy (3), hypertrophic cardiomyopathy (1), and coronary heart disease (5). Four patients had lone AF. In 7 of the 25 patients, the study was stopped because of AF induction during the first or the second stimulation sequence in the first paced site. Six of these patients were in washout, and 1 was on amiodarone. Therefore, the stimulation protocol was carried out in 18 patients, 10 on amiodarone and 8 in washout. It was performed in all the 5 sites in 14 patients (7 in washout and 7 on amiodarone), in 4 sites in 1 patient (on amiodarone), and in 3 sites in 3 patients (1 in washout and 2 on amiodarone), for a total of 84 sites. In 2 patients (1 in washout and 1 on amiodarone), the sequence at 700-ms cycle length was not performed because of the higher sinus rate.

In 2 of the 10 patients who underwent the second electrophysiological study 4 weeks after the first one (1 in washout and 1 on amiodarone), AF was reinduced during determina-
tion of refractoriness at the first selected site during the first or second cycle length. Therefore, the second electrophysiological study was carried out in 8 patients (4 in washout and 4 on amiodarone).

The pertinent clinical and electrophysiological features of the patients initially recruited, both those who underwent the full set of initial tests and those who underwent the second study, are reported in Table 1. Table 2 shows the sites at which the stimulation was performed in both the initial and the second study.

Adaptation of ERPs to Rate
Taking into account all the paced sites, the mean ERPs at the different stimulation cycle lengths in both groups of washout and amiodarone patients are reported in Table 3. At all stimulation cycles, the ERPs were significantly shorter in the washout than in the amiodarone patients.

As graphically shown in Figure 1, there was a linear correlation between the mean atrial ERPs and the stimulation rate (r=0.95 in the washout group and r=0.94 in the amiodarone group). The mean slope value was 0.07±0.03 in the washout group and 0.07±0.04 in the amiodarone group.

Considering the individual stimulation sites, slope values ≥0.07 were present in 47 sites (60%), slope values between 0.05 and 0.06 in 18 sites (21%), slope values between 0.01 and 0.04 in 16 sites (19%), and a slope value of 0 in 1 site (1%). No negative slope values were found in any site. Therefore, a normal or nearly normal adaptation to the rate was present in 65 sites (77%): 31 (82%) in the washout patients and 34 (74%) in the amiodarone patients.

Dispersion of Refractoriness
As illustrated in Figure 2, the ERPs were significantly shorter in the lateral right atrial sites (198.1±17.9 ms) than in the atrial roof (203.3±21.5 ms) and in the septum (210.5±20.0 ms) (P<0.03). These results demonstrate the presence of a significant dispersion of refractoriness within the right atrium after cardioversion of chronic AF.

Effect of the Long-Short and Short-Long Sequences
The determination of refractoriness after a long-short and a short-long sequence was performed in 14 patients, 7 in washout and 7 on amiodarone. The results are shown in Table 4.

The mean ERP after the long-short sequence (basic cycle length, 600 ms, followed by a beat at 300 ms) was significantly shorter than the ERP found during constant pacing at 300 ms (170.9±12.1 versus 181.8±17.0 ms, P<0.001) (Figure 3), implying an overshoot of the adaptation of refractoriness to the preceding premature beat. The overshoot was not bidirectional, that is, no difference was found between the atrial ERP during the short-long sequence (basic cycle length, 300 ms, followed by a beat at 600 ms) and the ERP during constant pacing at 600 ms (211.6±23.3 versus 204.2±19.1 ms, P=NS) (Figure 3).

Changes of Refractoriness With Time
In the 8 patients who completed the second electrophysiological study (4 in washout and 4 on amiodarone), the mean atrial ERPs were found to be significantly increased at all the basic stimulation cycles with respect to the basal study in both the washout and the amiodarone patients (Table 5). For each stimulation cycle length, the ERPs were shorter in washout than in amiodarone patients.

The determination of the refractoriness to the rate was found to be normal or nearly normal in both the washout and amiodarone groups and was similar to that observed immediately after cardioversion (r=0.95 in the washout group and r=0.96 in the amiodarone group). The mean slope values were 0.08 in the washout patients and 0.07 in the amiodarone patients.

| TABLE 1. Clinical Data of the Studied Patients |
|--------|--------|--------|--------|--------|
|         | Whole Group | Study Completed | Follow-Up Study | Follow-Up Completed |
|         | (n=25)      | (n=18)        | (n=10)        | (n=8)        |
| Age, y  | 61.6±8.8    | 62.2±9.1      | 61.2±9.4      | 61.8±9.9      |
| Sex, M/F, n | 17/8 | 13/5 | 9/1 | 7/1 |
| AF duration, d | 220.8±366.1 | 231.1±353.1 | 262.7±214.2 | 250.6±225.7 |
| Left atrial diameter, mm | 46.0±5.7 | 45.8±5.6 | 48.5±4.8 | 49.6±3.8 |
| Washout, n | 14 | 8 | 5 | 4 |
| Amiodarone, n | 11 | 10 | 5 | 4 |

| TABLE 2. No. of Sites at Which the Stimulation Protocol Was Performed in Washout and Amiodarone Patients |
|--------|--------|--------|--------|
|         | Lateral |        |        |
|         | Low     | Mid    | High   |
| Washout | 8       | 8      | 7      |
| Amiodarone | 10 | 10 | 10 |

| TABLE 3. Refractory Periods (Mean±SD of All Paced Sites) at Each Basic Cycle Length in Washout and Amiodarone Patients |
|--------|--------|--------|--------|
| Basic Cycle Length | Washout | Amiodarone | P |
| 300 | 180.2±14.6 | 192.3±15.9 | 0.0006 |
| 400 | 190.8±16.8 | 200.9±15.8 | 0.006 |
| 500 | 197.5±17.4 | 207.5±16.2 | 0.007 |
| 600 | 203.0±17.5 | 214.4±17.0 | 0.003 |
| 700 | 207.4±18.8 | 217.8±16.5 | 0.01 |
| All | 195.5±18.8 | 206.3±17.9 | 0.0001 |

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The ERPs were still different in the various right atrial sites: 217.5±21.3 ms in the lateral wall, 226.3±20.1 ms in the roof, and 234.0±19.0 ms in the septum (P<0.003).

**Discussion**

Sinus rhythm can be restored by pharmacological or electrical cardioversion in the great majority of the patients with chronic AF, but frequently the arrhythmia recurs despite antiarrhythmic drug treatment. The recurrence rate is higher in patients with a longer duration of the arrhythmia, and the arrhythmia relapse usually occurs in the first days or weeks after cardioversion. These findings are in agreement with the concept of atrial “electrical remodeling” considered to be induced by sustained rapid rates, suggesting that some electrophysiological features found in patients with AF and favoring the arrhythmia recurrence could be the consequence, and not the cause, of the arrhythmia itself.

**Previous Studies on Atrial Electrophysiological Features Associated With AF**

In goats, the artificial maintenance of AF or longstanding high-rate atrial pacing was found to produce a marked shortening of refractoriness with a reversion of its physiological adaptation to rate. Shortening of the ERPs after 7 hours of constant atrial pacing was also demonstrated in dogs. In humans, a significant reduction in atrial refractoriness after several minutes of induced AF has been described, and after cardioversion of chronic lone AF, ERPs were shorter than in a control group of patients without atrial arrhythmias. Failure in the rate adaptation of the atrial ERP has been found in patients with either increased atrial vulnerability or atrial arrhythmias at Holter monitoring. Finally, shorter ERPs and a reverse adaptation to rate were found in the atrial appendages of patients with chronic AF and rheumatic heart disease undergoing corrective cardiac surgery.

Two other factors recognized as favoring the arrhythmia are dispersion of refractoriness and decreased conduction velocity. The first one does not appear to be the consequence of rapid atrial rates, but it seems to be related to local vagal influence, atrial fibrosis, and age. Conduction velocity also appears to be related to cellular fibrosis and uncoupling present in ill or aged atria, but it was prolonged even in healthy dogs with induced chronic AF. In goats, however, conduction velocity was not found to be affected by sustained rapid atrial rates.

**Atrial Refractoriness and Its Adaptation to Rate**

In our study, atrial ERPs were found to be shorter immediately after cardioversion than 4 weeks after sinus rhythm restoration. This is in agreement with the previous finding that long-lasting AF causes shortening of refractoriness. As expected, patients in washout had shorter ERPs than patients on amiodarone, both at baseline and 4 weeks later.

Contrary to what was previously reported in both animals and humans, we found a normal or nearly normal adaptation of the ERPs to the stimulation rate after cardioversion of persistent AF in the great majority of the right atrial sites of our patients. It can be argued that, in animal models, the pacing-induced AF may be an arrhythmia that is somehow different from the chronic AF in humans in terms of arrhythmia duration and presence of atrial disease. Moreover, species-specific differences in modulation of ion channel gene expression might play a role in determining a different behavior.

Other human studies have been conducted on patients who are different from ours. In fact, Attuel et al studied subjects with atrial vulnerability at electrophysiological study or with paroxysmal atrial tachyarrhythmias by Holter monitoring and not patients with chronic AF. Indeed, the results of Le Heuzey et al in an ex vivo study are only apparently different from ours. In fact, they did find a reverse rate-related adaptation of the refractoriness, but only for very long cycle lengths (from 1200 to 1600 ms). Until these very low rates, usually not achievable in the electrophysiological laboratory because of the higher sinus rate, the adaptation of refractoriness to rate was conserved. Our study does not exclude the possibility that at lower sinus rates, which may be present only in patients with sick sinus syndrome, a reverse adaptation to rate could be possible.

Our finding that a normal or nearly normal adaptation of ERPs to rate is present after cardioversion of chronic AF means that this is probably not a cause of maintenance of the arrhythmia or of the recurrence of arrhythmia after cardioversion in humans. Nevertheless, our data showing...
an increase in refractoriness at distance confirm the previous finding that ERPs after cardioversion are short.\textsuperscript{10} In our opinion, even this finding is not sufficient to completely explain the tendency of AF to maintain itself and to recur. In fact, despite major shortening of refractoriness obtained by short periods of pacing, sustained AF did not develop in either the animal or clinical studies.\textsuperscript{9,18} Moreover, it is a common clinical observation that recent-onset AF subsides spontaneously within 24 hours\textsuperscript{29} in the majority of cases. Then, as recently suggested by Zipes,\textsuperscript{30} other electrophysiological and perhaps structural changes, such as atrial dilation and changes in mitochondria, connexin-43 expression, connexin-40 distribution, and cell size, are required for AF to be sustained and to recur.

**Refractoriness Dispersion**

In our patients, the ERPs were significantly shorter in the lateral wall than in the atrial roof and septum, demonstrating a nonuniform recovery of excitability within the right atrium. This phenomenon was persistent after 4 weeks of sinus rhythm, meaning that according to previous studies,\textsuperscript{23,24} it is not related to the electrical remodeling caused by the arrhythmia. Dispersion of refractoriness may indeed be considered the consequence of the nonuniform state and fibrosis of the diseased atrial cells and the related electrical uncoupling present in at least some areas of the atrium.\textsuperscript{25} This hypothesis is indirectly confirmed by the fact that the pacing-induced AF in healthy goats did not cause dispersion of refractoriness, at least when determined at the 2 atrial appendages.\textsuperscript{5}

**Effect of Abrupt Cycle Length Changes on Refractoriness**

In normal subjects, the ERP of atrial myocardium abruptly and appropriately adjusts to the duration of the last cycle, whereas adaptation of ventricular myocardium reflects the cumulative effect of the preceding cycles, and His-Purkinje refractoriness overshoots in the direction of the preceding cycle length change.\textsuperscript{31,32} The behavior of the response of atrial refractoriness to an abrupt change of cycle length in patients with persistent AF after cardioversion is unknown at this time, although an abnormal response could affect the likelihood of AF relapse.

In our study, atrial refractoriness showed an abnormal overshoot in adaptation after a long-short sequence. This phenomenon may have clinical relevance, because it could contribute to the frequent recurrence of the arrhythmia in the first days after cardioversion. In fact, a marked reduction of atrial refractoriness, and thus a shortening of the cycle length caused by a premature beat could favor the reinduction of AF by a second short-coupled premature beat.

**Study Limitations**

First, our findings about the refractoriness behavior are limited to the right atrium, because the left atrium was not considered in our study.

Second, in patients with reinduced AF, the protocol was discontinued, leading to the exclusion of the subjects with the higher atrial vulnerability. We cannot exclude the possibility that these patients might have had a different behavior in the adaptation of refractoriness to rate and/or to the response to the long-short sequence. Nevertheless, our observations are applicable to the majority of patients with AF, because the protocol was completed in 70\% of the patients studied.

**Conclusions**

Our study, conducted in patients with spontaneous chronic AF, confirms that after cardioversion of the arrhythmia, atrial ERPs are short and tend to increase with time. Moreover, a significant dispersion of refractoriness was present in the right atrium, as well as an abnormal response of the ERPs to an abrupt shortening of the stimulation cycle. All these findings can concur to explain the tendency of AF to be sustained and to recur. However, we did not find failure of the adaptation of refractoriness to rate. This phenomenon, observed experimentally in animals, thus cannot be considered a cause of the early recurrence of the arrhythmia after cardioversion in humans. This also means that caution has to
be exerted in automatically extending to humans the results achieved in animal models.

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