Reversal of Atrial Electrical Remodeling After Cardioversion of Persistent Atrial Fibrillation in Humans

W. Julian C. Hobbs, MB; Simon Fynn, MB; Derick M. Todd, MB; Peter Wolfson, MB; Mike Galloway, BS; Clifford J. Garratt, DM

Background—Although atrial electrical remodeling has been studied extensively in animal models, the reversibility of this phenomenon after termination of clinical atrial fibrillation (AF) has not been demonstrated. We aimed to examine this important question of reversibility by using AF cycle length (AFCL) and coupling intervals of atrial premature beats after cardioversion as measures of atrial refractoriness.

Methods and Results—We measured AFCL at the right atrial appendage and distal coronary sinus before attempting internal cardioversion in 39 patients with persistent AF. Patients were monitored by daily transtelephonic recordings after discharge and admitted rapidly for repeat internal cardioversion if there was spontaneous AF recurrence. Measurements of AFCL were repeated immediately before repeat cardioversions in the 17 patients who had recurrence of AF. There was an increase in AFCL from the initial cardioversion to that measured at the time of first AF recurrence at both the right atrial appendage (161±22 vs 167±26 ms, P=0.05) and distal coronary sinus (162±20 vs 168±22 ms, P=0.01) sites. The magnitude of increase in AFCL was positively correlated with duration of sinus rhythm before AF recurrence (r=0.524, P=0.001). Other measures of refractoriness (shortest coupling interval of atrial premature beats and directly measured refractory periods after cardioversion) also increased from initial to subsequent cardioversions.

Conclusions—These findings demonstrate that changes in atrial electrophysiology associated with chronic AF in humans are reversible after cardioversion and that the extent of this reversal is dependent on the duration of sinus rhythm after cardioversion. (Circulation. 2000;101:1145-1151.)

Key Words: fibrillation remodeling cardioversion

Atrial fibrillation (AF) has a tendency to become more persistent with time. A large percentage of patients with paroxysmal AF eventually develop chronic AF.1 Recently Wijffels and coworkers2 have demonstrated, in a chronically instrumented conscious goat model, that episodes of AF may be self-perpetuating (“AF begets AF”) and have suggested that there may be a purely electrophysiological explanation for the increased persistence of AF with time. The self-perpetuating process in this animal model is associated with a marked shortening of atrial refractoriness and loss of the normal adaptation of atrial refractoriness to heart rate (termed atrial electrical remodeling) that is reproducible in other animal models.3-5 These authors suggested that the refractoriness changes would stabilize episodes of AF by decreasing atrial wavelength (wavelength=refractory period×conduction velocity), leading to an increase in the potential number of electrical reentrant wavelets in the atria and thereby increase AF stability as predicted by Moe’s multiple wavelet hypothesis.6

In the animal model described above, the remodeling process is reversible and atrial refractoriness returns completely to normal within 1 week of cessation of burst pacing (or DC cardioversion) and resumption of sinus rhythm. During this “remodeling reversal” phase the atria are in a state of increased vulnerability, which has been suggested as the mechanism for the markedly increased risk of AF recurrence seen in patients with chronic AF in the first week after cardioversion.7 A logical extension of this suggestion is that if such a patient could be kept in sinus rhythm over this short period, then subsequent likelihood of recurrence would be dramatically lowered. This possibility forms an attractive theoretical basis for the use of repeated early cardioversions in such patients. Alternatively, if atrial remodeling were found to be irreversible in humans, then it would be difficult to support such a strategy in this patient group, at least on the basis of the atrial remodeling hypothesis.

The aim of this study was to examine the hypothesis that atrial electrical remodeling is reversible after DC cardioversion in patients with persistent AF. We compared AF cycle length (AFCL) (as a measure of atrial refractoriness)6 recorded at the time of cardioversion of persistent AF with that recorded at the time of subsequent spontaneous AF recurrences in the same patient group. In addition, we compared the shortest coupling interval of atrial premature beats (as a separate measure of atrial refractoriness) after initial and...
subsequent cardioversions. Finally, in a subset of patients, atrial effective refractory periods were measured directly after both initial and subsequent cardioversions.

Methods

Patient Selection
Consecutive patients with persistent AF (minimum duration of 3 months) documented by serial ECGs were considered for the study. Written informed consent was obtained through the use of an information sheet and consent form approved by the Central Manchester Research Ethics Committee, which also approved the protocol. Planned exclusion criteria for the study were a contraindication to anticoagulation, pregnancy, and a lack of willingness to undergo repeated cardioversion at short notice in the event of spontaneous AF recurrence. Only 2 patients under consideration were actually excluded from entry into the study, both because of difficulties in traveling rapidly from their homes to the hospital.

Study Protocol
Patients were admitted to the hospital for internal cardioversion of persistent AF (CV1) after at least 4 weeks of adequate anticoagulation. Blood was sampled for measurement of International Normalized Ratio weekly and on the day before the planned procedure. Transesophageal echocardiography was performed immediately before cardioversion in any patients with a measured International Normalized Ratio <2.0 at any time in the 4 weeks before the procedure. Anticoagulation was not stopped before cardioversion. Antiarrhythmic medication was stopped 3 full days before the procedure in all patients except those taking amiodarone, which was continued.

Initial Cardioversion
A TADcath model 8010 temporary transvenous defibrillation catheter (110 cm, Courand Curve, ProCath Corp) was inserted into the coronary sinus through the right internal jugular vein. This is an 11-electrode catheter, 2 electrodes being used for bipolar pacing/sensing and 9 comprising the defibrillation electrode. A second defibrillation catheter was placed in the right atrium through the right femoral vein, with the tip in the right atrial appendage and positioned so that the majority of the catheter electrodes had contact with the right atrial free wall. Before delivery of shock energy, bipolar electrogram recordings of 1-minute duration were made at the right atrial appendage by use of the distal electrode pair (2-mm interelectrode distance) of a quadrupolar catheter (Duig) and one at the most distal coronary sinus position possible by use of the sensing electrode pair of the defibrillation catheter. A quadrupolar catheter was positioned at the right ventricular apex to allow synchronization of the defibrillation shock, appropriate synchronization being confirmed with a Defibrillation Systems Analyser (DSA, InControl). Immediately before shock delivery, 2 to 12 mg of midazolam was administered intravenously to ensure adequate sedation. Defibrillation DC shocks were delivered between the right atrial and coronary sinus electrodes at an output of 400 V with a 6/6 ms biphasic truncated exponential waveform. If the first shock was unsuccessful, the right atrial defibrillation catheter was repositioned and the procedure repeated.

Postcardioversion Measurements
After successful cardioversion, bipolar recordings of spontaneous atrial activity were made from the right atrial and distal coronary sinus electrodes already in place. The coupling intervals of all atrial premature beats (APBs) occurring in the immediate postcardioversion period (2 minutes) were measured (shortest A-A interval in either endocardial signal) with the use of on-screen calipers at a screen speed of 100 mm/s. Fifteen minutes after successful cardioversion, right atrial effective refractory periods were measured (twice diastolic threshold, pacing cycle lengths 250, 300, 400, 500, 600, and 700 ms) in the subset of patients who agreed to this part of the protocol.

Patient Follow-Up and Repeat Cardioversions
Patients were discharged the day after the procedure. Antiarrhythmic therapy was not reinstited after cardioversion (except for amiodarone, which, if present before cardioversion was continued throughout), but anticoagulation was continued for ≥6 weeks. Patients made transthoracic recordings of their cardiac rhythm to a central monitoring station on a daily basis for 35 days after the procedure. Transthoracic recordings also were made in the event of symptoms suggestive of return of atrial fibrillation during this period. In the event of a confirmed recurrence of AF, patients were readmitted as rapidly as possible for repeat internal cardioversion (CV2). Immediately before the repeat cardioversion, patients underwent intracardiac recordings as described for the initial procedure. The complete protocol was repeated for up to a maximum of 2 recurrences.

Data Analysis
The endocardial signals were acquired with the use of a multichannel Cardiobath system (Pruka Engineering Inc) and stored on optical disk. Individual atrial electrograms were identified with the use of predefined criteria and marked manually with the use of a mouse-driven program. Atrial electrograms with an apparent separation of ≤90 ms were considered to be double potentials from a single atrial activation. AFCLs were calculated automatically with the use of commercially available software (Pruka Inc). AFCL (mean±SD of recordings taken over a period of 1 minute) at the initial cardioversion of persistent AF was compared with that at the time of AF recurrence in the same patients. The relation between duration of sinus rhythm after cardioversion and change in AFCL between initial and subsequent cardioversions was examined for the whole group. Comparisons also were made between initial and subsequent cardioversions in terms of postcardioversion measurements, in particular, (1) shortest APB coupling intervals immediately after cardioversion and (2) right atrial refractory periods after cardioversion. Statistical comparisons between the 2 groups were performed by Student’s t test (2-tailed) or the Mann-Whitney rank sum test when a normal distribution could not be assumed. ANOVA (for parametric data) or a Kruskal-Wallis rank sum test was used for multiple group comparisons, followed by a Bonferroni corrected t test or a corrected Mann-Whitney rank sum test. Continuous data were expressed as mean±SD, and a value of P<0.05 was considered statistically significant.

Results

Clinical Characteristics
Thirty-nine patients were entered into the study and underwent attempted internal cardioversion of persistent AF. Mean duration of AF before attempted cardioversion was 38 months (range 3 to 384), and 7 patients had previously failed ≥1 external cardioversion. Of these 39 patients, sinus rhythm could not be achieved in 5 patients, and in a further 5 there was repeated recurrence of AF in the electrophysiology laboratory. Twenty-nine patients left the electrophysiology laboratory in sinus rhythm. Of these 29, 17 patients (the study group) had a recurrence of AF within the following 35 days (mean time in sinus rhythm 129 hours, range 1 to 740). Mean time from AF recurrence to measurement of AFCL and repeat cardioversion was 17±13.9 hours. The clinical characteristics of the total patient group, the 29 patients who left the laboratory in sinus rhythm and the 17 patients who had ≥1 recurrence of AF, are detailed in the Table. Patients leaving the electrophysiology laboratory in sinus rhythm had a trend toward a shorter arrhythmia history than those who remained in AF (26±32 vs 38±66 months, NS), but there were no differences in clinical characteristics between those patients.
who had subsequent arrhythmia recurrence (the study population) and those who did not.

Change in AF Cycle Length

Figure 1 shows the change in AFCL measured at the time of the initial cardioversion (CV1) from that recorded at the time of first recurrence of AF (CV2) for all 17 patients with AF recurrence. There is a significant increase in cycle length at both the right atrial appendage (RAA) (161±22 vs 167±26 ms, \( P=0.05 \)) and distal coronary sinus (DCS) (162±20 vs 168±22 ms, \( P=0.01 \)) sites. In 7 patients with measurements at the time of a second recurrence (third cardioversion, CV3) there was a progressive increase in AFCL with each recurrence. AFCL at the RAA increased from 156±26 (CV1) to 161±20 (CV2) and then 174±27 (CV3) (\( P=0.02 \), ANOVA) in this group. Corresponding values for the DCS were 164±24 (CV1) to 167±20 (CV2) and then 180±27 (CV3) (\( P=0.03 \)). A representative example of electrograms recorded from both sites at the time of 3 successive cardioversions is shown in Figure 2. In Figure 3, histograms derived from measurement of individual AFCLs at the time of each of 3 cardioversions in a single patient are shown.

Effect of Duration of Sinus Rhythm Before AF Recurrence

Figure 4 shows the relation between change in AFCL (between CV1 and CV2) and time in sinus rhythm between cardioversions in all 17 patients with AF recurrence. There is a significant increase in cycle length at both the right atrial appendage (RAA) (161±22 vs 167±26 ms, \( P=0.05 \)) and distal coronary sinus (DCS) (162±20 vs 168±22 ms, \( P=0.01 \)) sites. In 7 patients with measurements at the time of a second recurrence (third cardioversion, CV3) there was a progressive increase in AFCL with each recurrence. AFCL at the RAA increased from 156±26 (CV1) to 161±20 (CV2) and then 174±27 (CV3) (\( P=0.02 \), ANOVA) in this group. Corresponding values for the DCS were 164±24 (CV1) to 167±20 (CV2) and then 180±27 (CV3) (\( P=0.03 \)). A representative example of electrograms recorded from both sites at the time of 3 successive cardioversions is shown in Figure 2. In Figure 3, histograms derived from measurement of individual AFCLs at the time of each of 3 cardioversions in a single patient are shown.

Effect of Duration of Sinus Rhythm Before AF Recurrence

Figure 4 shows the relation between change in AFCL (between CV1 and CV2) and time in sinus rhythm between cardioversions in all 17 patients with AF recurrence. The longer the duration of sinus rhythm before recurrence of AF, the greater the difference in AFCL between chronic AF and recurrence. The relation is exponential rather than linear, with time in sinus rhythm plotted on a logarithmic scale (\( r=0.524, \ P=0.001 \)).

Ventricular Rates During AF

There were no significant differences in mean ventricular rate measured (at the same time as AFCL measurement) immediately before CV1, CV2, or CV3 (87±10, 94±25, and 86±16 per minute, respectively).

Clinical and Echocardiographic Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=39)</th>
<th>Patients Leaving Laboratory in SR (n=29)</th>
<th>Patients With a Recurrence (n=17)</th>
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</thead>
<tbody>
<tr>
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<td>23/6</td>
<td>11/6</td>
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<tr>
<td>Cause of AF</td>
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<td>3</td>
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<tr>
<td>Alcohol</td>
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</tr>
<tr>
<td>Lone</td>
<td>17</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Amiodarone therapy</td>
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<td>LA diameter, cm</td>
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<td>Mean±SD</td>
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SR indicates sinus rhythm; AF, atrial fibrillation; LA, left atrial; LV, left ventricular; and EF, ejection fraction.
Coupling Intervals of Atrial Premature Beats After Cardioversion

Of the 17 patients undergoing repeated internal cardioversion after a relapse of AF, 12 had atrial premature beats (APBs) present in the immediate postcardioversion period. In these patients, the shortest APB coupling interval increased from a mean of 325±59 ms after cardioversion of persistent AF to 395±124 ms after cardioversion of the first recurrence ($P<0.05$). The mean cycle length of sinus beats immediately before the shortest coupled atrial premature beat did not change from one cardioversion to the next (951±232 ms for CV1, 923±232 ms for CV2, 959±193 ms for CV3, difference not significant), and there was no difference in mean R-R interval during sinus rhythm after the respective cardioversions. Figure 5 shows a representative example of the shortest coupled atrial premature beats after 3 successive cardioversions in a single patient.

Atrial Refractory Periods After Cardioversion

Refractory period measurements at the right atrium were obtained at both initial and second cardioversions in a subset of 5 patients (Figure 6). There was a significant increase in refractory periods at the longer pacing cycle lengths (500, 600, and 700 ms) from CV1 to CV2.

Conclusions

Main Findings

This study has demonstrated for the first time that the electrophysiological characteristics of acute recurrences of AF differ from those of the corresponding chronic arrhythmia in the same patient group. Mean cycle length of AF was significantly longer, when measured at the RAA and DCS, shortly after the onset of acute AF recurrence than immediately before the initial cardioversion of chronic AF. This
increase is progressive with repeated spontaneous recurrences of AF. These findings support the hypothesis that AF-induced changes in atrial electrophysiology (atrial electrical remodeling) are reversible after cardioversion of persistent AF in humans. Previous work has shown that (1) chronic AF in humans is associated with a reduction in refractoriness and (2) there is a strong correlation between measures of atrial refractoriness and AFCL at any particular atrial site, which suggests that a reversal of refractoriness change is the most likely underlying mechanism. Further support for this conclusion is the finding that other measures of refractoriness examined in this study (shortest coupling interval of APBs and directly measured refractory periods) also showed an increase from the initial cardioversion to that of an acute recurrence.

Correlation Between Change in AFCL and Duration of Sinus Rhythm
The demonstration of a positive correlation between the magnitude of increase in AFCL and duration of sinus rhythm between cardioversions provides strong support for the suggestion that this change is related to a reversal of AF-induced changes in atrial electrophysiology and argues against any artifactual change occurring as a result of repeated sedation or catheterization. Although it could be argued that patients may be more familiar with the procedure at the time of the second...
cardioversion (and that this might have an influence on refactoriness through autonomic changes), any such effect would be expected to decrease rather than increase with increasing separation of the 2 procedures in time. Other arguments against a possible change in autonomic tone from one cardioversion to another are (1) the lack of difference in ventricular rate during AF and (2) the lack of difference in sinus rate after cardioversion from one procedure to the next observed in this study. The positive correlation between AFCL change and time in sinus rhythm is evident despite the confounding factor of differences in durations of AF recurrence before measurement of AFCL (as a result of differences in proximity of the patients to the hospital and availability of the electrophysiology laboratory), which emphasizes the influence of sinus rhythm on atrial electrophysiology. The logarithmic nature of the relation between changes in atrial electrophysiology and time in sinus rhythm is consistent with what has been described previously in animal models of AF.10

Other Measures of Refractoriness Change
The principal evidence for reversal of refactoriness after cardioversion in this study relies on indirect measures of refractoriness such as AFCL and APB coupling interval. Capucci and coworkers8 have shown that there is a strong correlation between mean AFCL and the atrial effective or functional effective refractory period at the same atrial site in patients with lone paroxysmal AF. Animal studies confirm a strong correlation between refractoriness and AFCL.11 The use of AFCL as a measure of atrial refractoriness allowed us to examine reversibility of remodeling specifically in patients with AF recurrences rather than those who maintained sinus rhythm in the long term after cardioversion (see clinical relevance below).

Tieleman and coworkers7 have demonstrated previously that there is a correlation between the shortest coupling interval of APBs after cardioversion of persistent AF and likelihood of early relapse of arrhythmia. They suggest that this is due to the presence of atrial remodeling and shortened refractoriness after cardioversion, that is, shortened refractoriness leads to both shortened APB coupling interval and arrhythmia relapse. In the current study we used the shortest APB coupling interval as a measure of refractoriness and showed that this parameter increased between CV1 and CV2, consistent with the changes in AFCL discussed above.

Direct measurements of atrial effective refractory period after cardioversion were made in only a subset of patients at the time of acute AF recurrence: A number of patients were unwilling to take the risk of reinduction of AF and requirement for further shocks at this time. Nevertheless, the results of these measurements were entirely consistent with those of AFCL and shortest APB coupling interval.

Previous Evidence for Atrial Electrical Remodeling and Its Reversibility in Humans
Franz and coworkers9 have demonstrated that in patients after cardioversion of persistent AF or atrial flutter, there is a marked decrease in the right atrial monophasic action potential duration during steady-state pacing and extrastimulation relative to control patients without atrial arrhythmias. In addition, these workers showed a “flat” response of atrial monophasic action potential duration to changes in heart rate, similar to the flattened rate adaptation curve seen in the goat model.2 They interpreted these findings as demonstrating atrial electrical remodeling occurring in humans as a consequence of persistent clinical AF. Previous studies had shown that a flat rate adaptation curve is associated with an increased susceptibility to atrial arrhythmias in humans.12 The only previous clinical study that has examined reversibility of remodeling is that of Daoud and coworkers,13 in which the atrial refractory period response to very short episodes of induced AF was measured. Short bursts of AF resulted in reduction of atrial refractory periods (measured at 350- and 500-ms pacing cycle length) and then, within a few minutes of sinus rhythm, returned to normal. The current study extends the findings of these authors in that it demonstrates reversibility in patients with spontaneously occurring, persistent clinical AF rather than in subjects with induced, short-lasting, “nonclinical” episodes. The time courses of increase in refractoriness after AF termination in these 2 studies are very different (being much slower in the current study), which suggests that 2 distinct physiological or pathophysiological processes are involved. The fact that in the current study these changes are still demonstrable several hours after onset of AF recurrence indicates that they have a time course similar to that described in the goat model (ie, lasting hours rather than minutes).10

Limitations of the Study
It is possible that a number of electrophysiological variables other than atrial refractoriness are “remodeled” during persistent AF. Studies in dog models of atrial fibrillation have shown decreasing conduction velocity in the atria14 and prolonged surface P-wave duration4 after prolonged periods of high-rate atrial pacing. Gaspo and coworkers14,15 have demonstrated that this atrial pacing–induced conduction slowing in dogs has a slower time course than that of atrial refractoriness change and suggest that this effect may constitute an important additional factor in the self-perpetuation of AF. No attempt was made to assess changes in conduction velocity in the current study, and further studies are necessary to address this question.

This study was not designed to address the issue of whether the likelihood of AF recurrence is related to the degree or rate of reversal of remodeling in any particular patient.

Clinical Relevance
The demonstration of reversibility of atrial electrical remodeling in the current study has important clinical implications.16,17 It is perhaps the most convincing evidence to date for the existence of remodeling in humans and provides a mechanism whereby focal15 or reentrant19 “origins” of AF may degenerate to the typical complex arrhythmia seen in most patients. It supports the hypothesis that the persistence of remodeling in the first few days after cardioversion of persistent AF is the mechanism of the increased rate of AF recurrence during this period.7 This finding highlights the potential role of therapies that target the remodeling process in the management of AF. In addition, it suggests that if these patients can be kept in sinus rhythm for sufficient time for
remodeling to reverse, the subsequent likelihood of recurrence should be significantly lowered, forming an attractive theoretical basis for the use of repeat “acute” cardioversions in the event of early AF recurrences in such patients. The current study was not designed to examine the clinical benefit of reversal of remodeling in patients with AF (repeat cardioversions were limited to 2 recurrences), but preliminary studies of patients with implanted atrial defibrillators suggest that AF recurrence rate may be reduced after implantation of these devices.

The electrophysiological differences between chronic AF and acute recurrences in this study suggests that the latter might be more likely to terminate with antiarrhythmic drug therapy. In the study of Capucci and coworkers, a progressive increase in mean AFCL interval with time was associated with early termination of AF, and several studies have shown an increase in mean AFCL before termination of AF by drugs. Further clinical studies are required to test this hypothesis formally.

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References

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