Electrophysiological Properties in Chronic Lone Atrial Fibrillation

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Background. Although the electrophysiological mechanisms underlying self-sustaining atrial fibrillation (AF) are unclear, recent studies suggest that one requirement for reentry, slow conduction, is frequently present in patients with AF. However, these observations limited to paroxysmal AF may not necessarily apply to chronic AF. Therefore, electrophysiological properties of the atrium and sinus nodal function in chronic lone AF were evaluated.

Methods and Results. Electrophysiological studies were performed after electrocardioversion in 12 patients with chronic lone AF. Atrial enlargement was absent in the patients with AF. Twelve patients without atrial arrhythmias served as the control group. The patients with AF had a higher incidence of sinus nodal dysfunction, a shorter atrial effective refractory period (215±19 msec versus 238±23 msec, p<0.02), and a longer P wave duration than control patients (115±16 msec versus 86±16 msec, p<0.01). The conduction delay zone was significantly greater in patients with AF (60±12 msec) than that in the control patients (8±13 msec, p<0.01), and the maximal conduction delay was also greater in the study patients than those in the control group, both to the His bundle region (31±12 msec versus 10±15 msec, p<0.01) and to the coronary sinus (41±15 msec versus 15±11 msec, p<0.01). The fragmented atrial activity zone was wider in the study group (23±25 msec) than in control subjects (1.7±4 msec, p<0.02). Repetitive atrial firing was observed in four patients with AF but it was not seen in the control group.

Conclusions. These electrophysiological features, which are manifestations of the abnormal atrial electrophysiology, would favor production of atrial reentry in chronic lone AF. (Circulation 1991;84:1662–1668)

Atrial fibrillation (AF) may not only occur in the presence of a variety of cardiovascular diseases but also in the absence of any other clinical evidence to suggest a primary cardiac disorder, and in the latter case it is known as lone AF.1 In the past, chronic AF without any valvular heart disease has been considered an innocuous condition. However, recently, chronic AF even in the absence of valvular disease has been demonstrated to be associated with an increased stroke incidence.2–6

Although the electrophysiological mechanisms underlying self-sustaining AF are unclear, recent evidence from human and experimental studies suggests that one requirement for reentry, slow conduction, is frequently present in patients with transient AF both in sinus rhythm7–9 and in response to premature stimuli.10–12 However, these observations limited to paroxysmal AF may not necessarily apply to chronic sustained lone AF. Moreover, the electrophysiological mechanisms in chronic AF are unclear because of technical difficulties such as atrial stimulation.

The purpose of this study is to evaluate the electrophysiological properties of the atrium and sinus nodal function in patients with chronic sustained lone AF by electrophysiological studies performed after electrocardioversion.

Methods

Patients. The study group consisted of 12 patients with chronic (more than 1 year) lone AF who were referred for external direct current cardioversion. A diagnosis of chronic lone AF in the present study was made by excluding the following diseases: coronary artery disease, valvular heart disease, congestive heart failure, cardiomyopathy, hypertension, chronic
obstructive pulmonary disease, apparent cardiomegaly on chest radiograph, and hyperthyroidism. Ages ranged from 51 to 67 years (mean, 55±8.9 years). Previous conventional ECG and Holter ECG recordings that were available showed that in all 12 patients the persistent AF had been established for more than 1 year (range, 1–6 years; mean, 3.6±1.7 years). Patients who appeared to have sick sinus syndrome demonstrated by the evidence of AF with a slow ventricular response (less than 35 beats/min) and a max RR interval of greater than two seconds in duration were excluded. In all AF patients, the left atrial dimension was measured by echocardiography and ranged from 36 to 44 mm (mean, 39±2.5 mm). It was confirmed that antiarrhythmic agents were ineffective in achieving conversion to sinus rhythm. All the AF patients received such agents, including dipryramide in nine, procainamide in two, and verapamil in one.

The control group consisted of 12 patients with associated arrhythmias except for atrial flutter or fibrillation, sick sinus syndrome, and organic heart disease. Associated rhythm abnormalities included atrioventricular nodal reentrant tachycardia in six and manifest or concealed Wolff-Parkinson-White syndrome in six. Their ages ranged from 20 to 70 years (mean, 45±18 years), and the left atrial dimension ranged from 33 to 41 mm (mean, 38±2.5 mm). Informed consent was obtained from the patients for performance of the studies.

Electrocardioversion. The patients with AF were anticoagulated for 3 weeks prior to cardioversion. Anesthesia was induced by single slow bolus intravenous injection of a sleep-inducing dose (50–75 mg) of 2.5% thiamylal sodium. Electrical energy was delivered starting with the energy level setting of 100 J and increasing in 100-J increments until successful electroversion occurred or until 400 J had been delivered.

Electrophysiological studies. The electrophysiological studies were performed on the day after electroversion. All cardioactive medications were discontinued at least 3 days before the procedure. Patients were studied in the fasting and nonedated state. Quadripolar catheter electrodes with a 1-cm interelectrode distance were advanced to the high right atrium (HRA) through a femoral vein and to the coronary sinus (CS) from a left anterior cubital vein. Stimulation of the right atrium was performed through the distal pair of electrodes of the same catheter. Bipolar recordings were obtained from the HRA through the proximal pair of electrodes of the same catheter and from the left atrium through the distal pair of the CS catheter. A His bundle electrogram was recorded with the two distal electrodes of a tripolar catheter electrode. Stimulation was performed with square impulses 2 msec in duration and an intensity of twice threshold delivered by a programmable stimulator (SEC-3102, Nippon Koden, Ltd.). The intracardiac signals were filtered to record frequencies of 50–700 Hz. Recordings were made on a recorder (WS-641G, Nippon Koden, Ltd.) at a paper speed of 100 mm per second. Intervals to and from the intracardiac potentials were measured from their onsets, defined as the first sharp deflection taking off from the baseline.

Measurements and terms. Sinus nodal recovery time was measured after 30 seconds of atrial overdrive pacing at a pacing rate up to 190 beats per minute, the longest value being reported. A corrected recovery time longer than 525 msec was considered abnormal. Sinoatrial conduction time was estimated using Narula’s method. The P wave duration was measured from the lead II ECG recorded at 100 mm per second. The duration of the atrial activity was measured from the high right atrial electrogram. After every eight-pace beat (S1=cycle length of 600 msec), a premature beat (S2) was introduced. The S1-S2 interval was decreased in 10 msec steps until the effective refractory period of the right atrium was reached.

Atrial conduction delay was defined as prolongation of the S2-A2 interval to longer than the S1-A1 interval by 20 msec at any recording site. Conduction delay zone was the range of extrastimuli producing atrial conduction delay in the CS recording site explored (Figure 1).

Fragmented activity was defined according to Ohe et al as the occurrence of disorganized atrial activity more than 150% of the duration of the local atrial activity of the basic beats recorded on the right atrial electrogram. The zone of fragmented activity was defined as the range of S1-S2 intervals that resulted in atrial fragmented activity (Figure 1).

Repetitive atrial firing (RAF) was defined, according to Wyndham et al as the occurrence of two or more early atrial responses with a return cycle (A2-A3) of 250 msec or less and a subsequent cycle length (A3-A4 and subsequent cycles) of 300 msec or less. The zone of RAF was defined as a zone of S1-S2 intervals between the longest and shortest intervals giving rise to RAF (Figure 1).

Results

There were no significant differences between the two groups in age and in the left atrial dimension. Electrophysiological findings are summarized in Table 1.

Intra-atrial conduction. P wave duration was significantly longer (p<0.01) in the study group than in the control group. The duration of atrial activity was also significantly prolonged (p<0.01) in the study group.

Sinus nodal function. Corrected sinus recovery time was over 525 msec in nine patients with AF and significantly longer (p<0.01) than that in the control group. Sinoatrial conduction time was over 150 msec in 11 patients and significantly longer (p<0.01) than that in the control group.


**Atrial effective refractory period.** At the same paced cycle length of 600 msec, the atrial effective refractory period was shorter \((p<0.02)\) in the study group than in the control patients.

**Conduction delay zone.** With increasing prematurity of the extrastimuli, progressive delay was observed in the intra-atrial conduction time, expressed as a conduction delay zone. The conduction delay zone was significantly larger \((p<0.01)\) in the patients with AF than in the control patients.

**Fragmented atrial activity zone.** The fragmented atrial activity zone was wider \((p<0.02)\) in the study group than in the control group. In all patients, the outer margin of the fragmented activity zone was the longest S1-S2 interval that resulted in fragmented atrial activity and the inner margin was the atrial effective refractory period.

**Repetitive atrial firing zone.** Repetitive atrial firing was observed in four of 12 patients in the study group but it was not seen in the control subjects. Repetitive atrial firing led to AF in only one patient (Patient 6 of the study group). This patient showed widening of both the conduction delay zone and the fragmented atrial activity zone.

**Intra-atrial conduction delay.** As shown in Table 2, there was no significant difference in the intra-atrial conduction time of nonpremature stimuli \((S1-A1\) interval) to the high right atrium, the His bundle region or the CS between the two groups. The degree of atrial conduction delay to the various recording sites was quite different. The maximal conduction delay was greater \((p<0.01)\) in the study group than in the control group, both to the His bundle region and to the CS. In the study group, the maximal conduction delay to the CS was significantly greater \((p<0.01)\) than that to the His bundle region. In contrast, in the control group there was no significant difference in the conduction delay to either distant recording site.

**Discussion**

The self-sustaining character of atrial fibrillation has been explained primarily through a reentrant mechanism,\(^{17,18}\) although a role of abnormal automaticity in its precipitation and maintenance has been suggested.\(^{19,21}\) Animal experiments have demonstrated that a conduction disturbance was essential for a reentrant mechanism.\(^{22–24}\) AF has also been explained as an alteration of impulse conduction. A dispersion of the recovery of excitability, creating more marked desynchronization of adjacent areas of myocardium, would break the activation fronts into multiple wavelets that could perpetuate themselves as continuous irregular atrial activation, given a large enough mass of tissue and a short enough refractory period.\(^{17,18,24}\) Both Moe’s multiple wavelet hypothesis

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**FIGURE 1.** Electrocardiographic lead II, the high right atrial electrogram (HRA), His bundle electrogram (HBE), and left atrial electrogram recorded from the coronary sinus (CS) are shown. Basic atrial driven cycle length (BCL) was 600 msec. There is disorganized fragmented activity of the atrium at the HRA after S2 (arrow). An extrastimulus with a 220-msec S1-S2 interval prolongs intra-atrial conduction from 70 to 110 msec in the CS. S2 produces repetitive atrial firings that result in atrial fibrillation.
using a computer model of AF and Allessie's experimental evaluation of Moe's study using dogs indicated that multiple wandering wavelets of different sizes and traveling in various directions were present during AF.\textsuperscript{18,25}

A recent study showed that AF per se leads to atrial enlargement and that atrial dilation can be attributed to the presence of AF.\textsuperscript{26} However, there was no difference in atrial dimensions of the AF group and the control group in the present study.

The present study showed that the prevalence of sinus nodal dysfunction was high in the patients with chronic lone AF. Kirchhof and Allessie's\textsuperscript{27} observation that AF causes minor overdrive suppression of sinus automaticity may be one explanation for this result. Nadeau et al\textsuperscript{28} reported that experimental AF was more readily initiated and sustained for a longer period of time in the presence of an intact sinus node than after its suppression. Kirchhof and Allessie\textsuperscript{29} described that the presence of normal automaticity in the SA node during AF may contribute to the perpetuation of AF. On the other hand, some investigators have reported that bradycardia may induce an increase in the dispersion of excitability recovery and facilitate reentrant arrhythmias.\textsuperscript{30,31} Thus, the role of normal sinus function in the induction and maintenance of AF is probably complex.

Recently, Spach et al\textsuperscript{32} found that early premature impulses originating in the sinus nodal area were propagated throughout right atrial preparations without conduction block or reentry. Conversely, when the premature impulses originated at sites distal to the sinus node, conduction block and reentry occurred frequently. This protective effect was related to the duration of the longest atrial action potentials occurring in the sinus nodal area, with a continued decrease in action potential duration occurring as the distance from the sinus node increased.\textsuperscript{33} Thus, sinus dysfunction may predispose to ectopic premature atrial activity producing conduc-

\begin{table}
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\caption{Summary of Electrophysiological Findings}
\begin{tabular}{cccccccc}
\hline
Case & PWD & AWD & SNRT & SACT & ERP & CDZ & FAAZ & RAFZ \\
\hline
1 & 120 & 120 & 746 & 165 & 200 & 70 & 10 & 0 \\
2 & 115 & 100 & 468 & 157 & 260 & 70 & 10 & 0 \\
3 & 100 & 100 & 320 & 152 & 240 & 40 & 0 & 0 \\
4 & 140 & 140 & 840 & 200 & 220 & 40 & 0 & 0 \\
5 & 80 & 70 & 460 & 185 & 210 & 50 & 10 & 0 \\
6 & 100 & 80 & 840 & 148 & 210 & 70 & 90 & 30 \\
7 & 130 & 130 & 644 & 250 & 190 & 70 & 0 & 10 \\
8 & 120 & 120 & 680 & 184 & 200 & 50 & 10 & 0 \\
9 & 110 & 105 & 546 & 197 & 210 & 60 & 30 & 10 \\
10 & 110 & 110 & 590 & 162 & 220 & 70 & 10 & 0 \\
11 & 130 & 125 & 723 & 179 & 200 & 60 & 30 & 0 \\
12 & 125 & 120 & 820 & 210 & 220 & 70 & 40 & 0 \\
\hline
Mean±SD & 115±16* & 110±20* & 640±167* & 182±29* & 215±19† & 60±12* & 23±25† & 5.8±10 \\
\hline
Case & PWD & AWD & SNRT & SACT & ERP & CDZ & FAAZ & RAFZ \\
\hline
1 & 90 & 70 & 280 & 90 & 230 & 0 & 0 & 0 \\
2 & 50 & 50 & 290 & 60 & 240 & 0 & 0 & 0 \\
3 & 90 & 70 & 220 & 80 & 220 & 0 & 0 & 0 \\
4 & 80 & 80 & 300 & 93 & 240 & 0 & 0 & 0 \\
5 & 80 & 80 & 390 & 97 & 300 & 0 & 0 & 0 \\
6 & 80 & 70 & 340 & 138 & 220 & 0 & 0 & 0 \\
7 & 100 & 50 & 270 & 116 & 240 & 0 & 0 & 0 \\
8 & 90 & 90 & 354 & 82 & 240 & 10 & 0 & 0 \\
9 & 110 & 90 & 460 & 134 & 240 & 20 & 10 & 0 \\
10 & 90 & 80 & 280 & 90 & 200 & 10 & 0 & 0 \\
11 & 70 & 70 & 290 & 97 & 240 & 20 & 0 & 0 \\
12 & 100 & 85 & 290 & 45 & 240 & 40 & 10 & 0 \\
\hline
Mean±SD & 86±16 & 74±13 & 314±64 & 94±27 & 238±23 & 8.3±13 & 1.7±4 & 0 \\
\hline
\end{tabular}
\end{table}

PWD, P wave duration; AWD, A wave duration; SNRT, corrected sinus nodal recovery time; SACT, sinoatrial conduction time; ERP, effective refractory period of atrium; CDZ, conduction delay zone; FAAZ, fragmented atrial activity zone; RAFZ, repetitive atrial firing zone.

\textsuperscript{*}p<0.01 vs. control group.

\textsuperscript{†}p<0.02 vs. control group.
tion block and reentry and thus facilitate the initiation and continuation of AF.

Our patients with chronic lone AF also had a shorter atrial effective refractory period. This should also favor reentry and may be essential for the maintenance of fibrillation. Similar findings were reported by Luck34 and Cosio11 but could not be confirmed by Bauernfeind35 and Buxton.12 Different selected groups of patients may be one explanation for this discrepancy.

Simpson et al10 reported that slow conduction of premature impulses in patients with prolonged P wave duration may be related to the pathogenesis of AF, but a direct relation was not shown in their results. Cosio et al11 demonstrated that patients with AF had a greater tendency to develop slow intra-atrial conduction than patients without atrial arrhythmias. However, they did not find a greater increase in conduction delay to the coronary sinus than to the His bundle region recording site during right atrial stimulation. Our study demonstrated that marked intra-atrial conduction delay in response to premature stimuli was observed much more commonly in patients with chronic lone AF than in the control subjects. Moreover, the patients with AF had a greater conduction delay to the coronary sinus than to the His bundle region recording site compared with the control patients. These results coincide with the observations of Buxton et al12 suggesting that this delay was not just a manifestation of local conduction delay but that patients with AF had diffuse abnormalities of atrial conduction.

Recent studies at both the microscopic and macroscopic levels have demonstrated that the occurrence of conduction disturbances leading to reentry depends on a combination of mechanisms involving both spatial differences in membrane properties and the anatomical complexities of the atrial muscle, including anisotropic cellular coupling and the geometric arrangement of muscle bundles.36 Discrete
anatomical structures and muscle bundle junctions appear to be important in creating localized conduction delays in a reentrant circuit. Regional differences in the conduction velocity are thus determined by interactions between the kinetics of the depolarizing currents and the passive anisotropic properties of the atrial bundles.\(^{32,36,37}\)

Ohe et al\(^ {15}\) reported that widening of the fragmented atrial activity zone was characteristic of AF and may be a good index of a tendency to develop spontaneous AF. We also found that the fragmented atrial activity zone was wider in the patients with AF than in the control subjects. It is, therefore, conceivable that the fragmented atrial activity represents local continuous activity in response to premature beats, and the widening of the fragmented atrial activity zone might imply the ease with which a premature beat resulted in local continuous activity in response to atrial extrastimulation.\(^ {15}\) It seems possible that the nonuniform structural anisotropy of atrial muscle may contribute to the genesis of fragmented activity, that is, propagation transverse to the long axis of the cells may be interrupted so that adjacent fascicles become excited in a markedly irregular sequence and the extracellular waveforms show multiple small deflections.\(^ {36}\)

Repetitive atrial firing was observed in four patients with AF, whereas this was not found in one of the control patients. Repetitive atrial responses have been used by some as an index of atrial vulnerability. Our results are similar to previous observations\(^ {16,38}\) in that atrial repetitive responses are a nonspecific finding. Animal studies demonstrated that a mechanism of these responses was local reentry around a point of stimulation, different in pattern from fibrillation circuits.\(^ {24,39,40}\) However, only one patient in the present study in whom the repetitive atrial firing led to AF showed widening of both the conduction delay zone and the fragmented atrial activity zone. Accordingly, we suppose that when both the conduction delay zone and the fragmented atrial activity zone are wide, repetitive atrial firing may tend to be induced.

Thus, sinus nodal dysfunction, a shorter atrial effective refractory period, and widening of the conduction delay zone and the fragmented atrial activity zone were observed in our patients with chronic lone AF. Because these findings are important indexes of abnormal atrial electrophysiology, it is apparent that these abnormalities in disease states may help understand the pathogenesis of chronic lone AF.

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