Global Distribution of Atrial Ectopic Foci Triggering Recurrence of Atrial Tachyarrhythmia After Electrical Cardioversion of Long-Standing Atrial Fibrillation: A Bi-Atrial Basket Mapping Study

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OBJECTIVES
The objective of this study was to assess the spatial distribution of atrial ectopic foci potentially triggering recurrent atrial tachyarrhythmias after electrical cardioversion of long-standing atrial fibrillation (AF).

BACKGROUND
It remains unknown whether targeted ablation of atrial ectopic foci concentrated in the pulmonary veins is feasible in patients with long-standing AF as it is in patients with paroxysmal AF.

METHODS
Two basket electrodes (32 bipoles on each eight splines) were positioned in the right and left atrium to identify the earliest endocardial activation sites of atrial ectopic foci emerging immediately after external electrical cardioversion of long-standing AF, before and after intravenous administration of dl-sotalol (16 patients) and propafenone (16 patients).

RESULTS
Before the use of antiarrhythmics, 91 distinct atrial ectopic foci were recognized after cardioversion. In 69 of the 91 foci, the earliest sites of presystolic atrial activation could be identified. Left atrial posterior (16 foci), left atrial anterior (11 foci) and right atrial posterior regions (13 foci) appeared to be prevalent. However, atrial ectopies from the remaining atrial regions (29 foci) were not uncommon. After adding dl-sotalol or propafenone, only 64 atrial ectopic foci were recognized after cardioversion; 50 of those were identifiable at the earliest activation sites. The scattered pattern of spatial distribution of the atrial ectopic foci was virtually unchanged.

CONCLUSIONS
Atrial ectopic foci potentially triggering the recurrence of atrial tachyarrhythmias after successful electrical cardioversion of long-standing AF were scattered in spatial distribution and multiple in production, possibly rendering difficult the targeted ablation approach. (J Am Coll Cardiol 2001;37:904–10) © 2001 by the American College of Cardiology

Atrial fibrillation (AF) is a self-perpetuating dysrhythmia characterized by progressive electrical and anatomical remodelings (1,2). Timely interventions targeting elimination of the arrhythmogenic substrate or the arrhythmia triggers are crucial for long-term maintenance of sinus rhythm. Nevertheless, at present, most therapeutic approaches to AF, either by antiarrhythmic drug modification (3) or by atrial compartmentalization surgery (4,5), have been focused on the arrhythmogenic substrate. The yield is partial and often confronted with significant morbidity.

Recently, Haissaguerre et al. (6) first reported that radiofrequency catheter ablation of atrial ectopic beats initiating paroxysmal AF is effective for long-term elimination of the arrhythmia. They found that these atrial triggers, highly clustered around the orifices of the pulmonary veins, are susceptible to total eradication by radiofrequency energy. However, it is unknown whether a similar observation can be made in patients with long-standing AF, in whom AF is often reinitiated by premature atrial ectopies after successful electrical cardioversion (7,8). The spatial distribution of atrial ectopic foci in patients with long-standing AF may be different and more complex than it is in patients with paroxysmal AF. Thus, this study attempted to delineate by bi-atrial basket electrode mapping the spatial distribution of potential atrial ectopic triggers responsible for reinitiation of atrial tachyarrhythmia after successful electrical cardioversion of long-standing AF (i.e., lasting >3 months) as well as to evaluate the influence of antiarrhythmic drugs on production of the atrial ectopic triggers.

METHODS

Patients. Between June 1997 and May 1999, 32 consecutive patients with long-standing AF (>3 months) who were referred for elective electrical cardioversion were included in the study. Patients with untreated hyperthyroidism, severe congestive heart failure with a left ventricular ejection fraction <30% or with intra-atrial thrombus demonstrated...
by transthoracic or transesophageal echocardiography were excluded. There were 20 men and 12 women. The mean age was 63 ± 12 years, ranging from 31 to 82 years. All patients had failed to maintain sinus rhythm by use of at least three antiarrhythmic agents of different categories. Combined medical conditions underlying the chronic AF included hypertension in 11 patients, rheumatic mitral valve disease in 6 patients, chronic obstructive pulmonary disease in 3 patients, coronary artery disease in 5 patients and tachycardia-bradycardia syndrome in 1 patient. Nine patients had no detectable medical cause. Seven patients had experienced transient or reversible cerebrovascular events.

**Electrophysiology study and electrical cardioversion.** Every patient was studied in the fasting state under intravenous propofol anesthesia after informed consent was obtained. All antiarrhythmic agents were withheld for at least five half-lives. Amiodarone, if any, was stopped for at least three months. All patients had been taking warfarin to keep an international normalized ratio of 2.0 to 3.0 for at least three months. All patients had been taking warfarin to keep an international normalized ratio of 2.0 to 3.0 for at least four weeks before the study. Transthoracic and transesophageal echocardiography were performed to evaluate the presence or absence of intracardiac thrombus and the atrial and ventricular chamber size and performance.

Two basket electrodes (Mercator, Cardiac Pathways, Sunnyvale, California or Constellation, Boston Scientific EP Technologies, Watertown, Massachusetts) were used for global bi-atrial mapping of AF and atrial ectopic beats, which occurred after external electrical cardioversion by direct current (DC) shock (PhysioControl, Seattle, Washington). Each basket electrode has eight equidistant splines that are labeled clockwise “A” through “H” in cephalad view. The spatial orientation of the splines in the atrium was identified by additional radiopaque markers positioned on splines “A,” “B” (Constellation) and “C” (Mercator). Each spline has four pairs of bipole electrodes numbered one through four from the distal end. The intra-bipole distance is 2 mm, and the inter-bipole distance is 8 mm in Mercator baskets; whereas the intra- and inter-bipole distances were 4 to 5 mm in Constellation baskets. The volume of the basket can be chosen according to the atrial size. One basket was deployed first in the left atrium by standard trans-septal technique, and the other was deployed in the right atrium (Fig. 1). Care was taken to expand the basket splines evenly over the whole atrial wall. Before the trans-septal approach, intravenous heparin was first given as 5,000 U in bolus followed by continuous infusion of 100 U/h throughout the procedure. Local atrial electrograms from 32 recording sites of one basket electrode together with a 12-lead surface electrocardiogram (ECG) were monitored and recorded simultaneously by a computerized multi-channel oscilloscope system (CardioLab 4.02, Prucka Engineering Inc., Houston, Texas). The data were sampled at 1 KHz and stored in a compact disc for immediate and off-line analysis.

Electrical cardioversion by transthoracic DC shock was started from 100 J and increased by 100 J until termination of AF or a maximum of 400 J was reached. After each successful cardioversion, simultaneous 12-lead ECG and local electrograms from 32 atrial sites of each of the basket electrodes were continuously recorded, each for 2 min in sequence to document any occurrence of atrial ectopic beats or the early reinitiation of atrial tachyarrhythmias including atrial tachycardia, atrial flutter and AF. Observation was then extended for a total of 30 min to monitor and capture any further recurrence in the later phase. The order of mapping in either the right or left atrium was at random.

**Antiarrhythmic drug effect.** To evaluate the effect of antiarrhythmic drugs on the occurrence of atrial ectopic beats after successful cardioversion, the 32 patients were divided randomly into two groups (16 patients in each) receiving either intravenous dl-sotalol (1.5 mg/kg) (Bristol-Myers Squibb GmbH, Munich, Germany) or intravenous propafenone (2 mg/kg) (Knoll AG, Ludwigshafen, Germany) before repeated electrical cardioversion for previously failed or spontaneously reinitiated AF. If previous cardioversion terminated AF and reinitiation did not occur within 30 min, it would be re-induced by rapid atrial pacing before pharmacologic intervention.

**Figure 1.** The positioning of two basket electrodes in the right and left atrium in patients with chronic atrial fibrillation. Each basket electrode has eight splines and 32 bipoles (four bipoles on each spline). The basket electrode in the left atrium was deployed via trans-septal technique. The radiodense markers (A, B, C) indicate the spline “A,” “B” (Constellation basket, **right panel**) and “C” (Mercator basket, **left panel**).
Data analysis. Successful cardioversion of AF was defined as the resumption of sinus rhythm for at least three beats after external DC shock (8).

Distinct atrial ectopic beats appearing after successful cardioversion were identified by P-wave morphology on the 12-lead ECG and by the atrial activation sequence. The earliest endocardial activation site of each distinct atrial ectopic beat was localized by recording the earliest site of presystolic local activation ≥10 ms before the onset of P wave by atrial basket electrodes. To describe the anatomical locations of the atrial ectopic beats mapped by the basket electrodes, each atrium was arbitrarily divided into four regions (anterior, posterior, septal and lateral) by orthogonal fluoroscopic views. The left atrial posterior region represented the area containing the sinus node and the crista terminalis. The anterior regions of both atria represented mainly the atrial appendages.

Statistics. Continuous data were expressed as mean ± standard deviation and compared by unpaired or paired Student t test. Variance (SD^2) of local atrial electrogram intervals (local A-A intervals) was calculated to represent the dispersion of atrial refractory periods. To evaluate the potential within-patient effects, the presence or absence of the clustering of atrial ectopic foci after electrical cardioversion was analyzed by comparing the frequencies of ectopic foci among different atrial regions using generalized estimating equation (GEE) with the Poisson model and an exchangeable working correlation matrix. By choosing the most common region of atrial ectopic foci as the reference level, the relative frequencies of atrial ectopic foci in other atrial regions were presented at 95% confidence level and statistically tested by robust standard error of GEE (SAS 6.12 for Windows). The effect of antiarrhythmics was likewise tested before and after the drug. A two-side p value <0.05 was considered to be statistically significant. Also, the occurrence of atrial ectopies after cardioversion was correlated with underlying medical diseases, cardiac chamber dimensions and local A-A intervals in AF by Pearson correlation analysis.

RESULTS

Clinical characteristics and electrical cardioversion. The mean duration of long-standing AF in the 32 patients was 3.2 ± 2.5 years, ranging 3 months to 11 years. Left atrial dimension measured by echocardiography was 45.5 ± 4.2 mm (range 37 to 63 mm). The mean local A-A intervals determined by bi-atrial basket electrodes were 142 ± 6 ms in the left atrium and 149 ± 8 ms in the right (p < 0.001, paired t), whereas the variance of local A-A intervals was 48 ± 72 ms^2 in the left atrium and 85 ± 83 ms^2 in the right (p > 0.05, paired t).

Twenty-nine (90.6%) of the 32 patients could be converted to normal sinus rhythm by DC shock before phar-

macological intervention at 247 ± 98 J (range 100 to 400 J). After addition of dl-sotalol (16 patients) or propafenone (16 patients), all 32 patients (100%) could be converted to sinus rhythm. The energy requirement for the dl-sotalol group was 206 ± 85 J (range 100 to 400 J) (p < 0.05 vs. 250 ± 94 J before dl-sotalol), while that for the propafenone group was 244 ± 89 J (range 100 to 400 J) (p > 0.05 vs. 242 ± 82 J before propafenone).

Spatial distribution of the earliest activation sites of atrial ectopic beats appearing after electrical cardioversion. Before antiarrhythmic drugs were given, 91 distinct atrial ectopic beats were identified in 28 (87.5%) of the 32 patients by bi-atrial basket electrode mapping. The number of distinct atrial ectopic beats in each patient ranged from one to eight. In four patients, no atrial ectopic beat appeared after cardioversion. The emergence of atrial ectopic beats usually clustered within the initial 5 min after successful electrical cardioversion. The mean duration of the appearance of atrial ectopic beats before vanishing or reinitiating atrial tachyarrhythmias was 4.8 ± 1.4 min (range 2.5 to 10 min). The spatial locations of the earliest presystolic activation sites were verifiable in 69 of the 91 distinct atrial ectopic beats, among which 40 were located in the left atrium and 29 in the right atrium. Detailed spatial distribution of the 69 atrial ectopic foci is shown in Table 1. Atrial ectopic foci emerged more frequently from the left atrial posterior (16 foci), left atrial anterior (11 foci) and right atrial posterior (13 foci) regions; this represented the convergence area of pulmonary vein orifices, the left atrial appendage and the area containing the sinus node and the crista terminalis. However, atrial ectopies originating from the remaining regions (29 foci) were not uncommon. Indeed, relative to the most common region of atrial ectopic

| Table 1. Global Distribution of Atrial Ectopic Foci Appearing Successful Electrical Cardioversion of Persistent AF With and Without Antiarrhythmic Drugs |
|-----------------------------|----------------|----------------|----------------|----------------|----------------|
| Atrial Regions | S. | L. | A. | P. | Total |
| Pre-AAD (n = 32) | 9 (1) | 4 (1) | 11 (7) | 16 (7) | 40 (16) |
| RA | 7 (1) | 3 (0) | 6* (0) | 13 (5) | 29 (6) |
| Post-AAD (n = 32) | 4 (0) | 3 (1) | 8 (3) | 12 (5) | 27 (9) |
| RA | 4 (0) | 1 (0) | 3 (1) | 15 (4) | 23 (5) |
| STL group (n = 16) | 0 (0) | 2 (1) | 4 (1) | 7 (3) | 13 (5) |
| LA | 1 (0) | 0 (0) | 2 (0) | 10 (2) | 13 (2) |
| RA | 4 (1) | 0 (0) | 4 (2) | 5 (2) | 14 (4) |
| PPF group (n = 16) | 3 (0) | 1 (0) | 1 (1) | 5 (2) | 10 (3) |

*p = 0.044 vs. left atrial posterior region (pre-AAD) by GEE. None of the atrial regions revealed clustering of the atrial ectopic foci in either the PPF or STL group (a. p > 0.05 by GEE). See text for details. The numbers in the table represent the number of distinct atrial ectopic foci located in each anatomical region; in parenthesis, the total number of atrial ectopic foci initiating atrial tachyarrhythmias early after electrical cardioversion. AAD = antiarrhythmic drugs, i.e., dl-sotalol (STL) and propafenone (PPF); A, L, S, P regions: the four anatomical regions (anterior, lateral, septal, posterior) of each atrium mapped by basket electrodes; LA = left atrium; n = number of patients; RA = right atrium.
foci (i.e., the left atrial posterior region), only the right atrial anterior region, but not the others, appeared to be less in the ectopic frequency (p = 0.044, by GEE, Table 1). The spatial distribution of the earliest activation sites of atrial ectopic foci after successful electrical cardioversion was more scattered than concentrated in the atria. The mean local activation time relative to the onset of P-wave on surface ECG was 50 ± 29 ms (range: 10 to 143 ms) for left atrial ectopic foci and 39 ± 23 ms (range: 10 to 105 ms) for right atrial ectopic foci. The number of atrial ectopies after successful cardioversion did not correlate with the underlying medical diseases or the atrial or ventricular dimensions, nor did the local A-A interval in either the right or left atrium during AF correlate with these variables (each p > 0.05, Pearson correlation).

During the immediate post-cardioversion period, 16 (i.e., septal, 1; lateral, 1; anterior, 7; posterior, 7) of the 40 left atrial ectopic foci and 6 (i.e., septal, 1; posterior, 5) of the 29 right atrial foci (p > 0.05, chi-square, left vs. right atrium, Table 1) were noted to reinitiate nonsustained or sustained atrial tachycardia (5 foci), atrial flutter (2 foci) or AF (15 foci) (Fig. 2). The local activation time relative to the onset of P wave was 61 ± 32 ms (range: 20 to 143 ms) for these vulnerable left atrial ectopic foci and 48 ± 31 ms (range 16 to 98 ms) for right atrial ectopic foci.

**The influence of antiarrhythmic drugs on atrial ectopic triggers.** After the addition of antiarrhythmic drugs, 34 distinct atrial ectopic beats were recognized in 11 (69%) of the 16 patients in the dl-sotalol group, while 30 distinct beats were recognized in 13 (81%) of the 16 patients in the propafenone group. The number of atrial ectopic beats in each patient ranged from one to seven. Eight patients had no atrial ectopic beat after successful cardioversion.

After cardioversion, 9 (i.e., lateral, 1; anterior, 3; posterior, 5) of the 27 verifiable left atrial ectopic foci and 5 (i.e., anterior, 1; posterior, 4) of the 23 right atrial foci (p > 0.05, chi-square, left vs. right atrium, Table 1) were noted to reinitiate nonsustained or sustained atrial tachycardia (8 foci) (Fig. 3) or AF (6 foci). The mean local activation relative to the onset of P-wave was 65 ± 38 ms (range: 18 to 115 ms) for these vulnerable left atrial ectopic foci and 30 ± 8 ms (range: 20 to 40 ms) for right atrial foci. Despite the decrease of the number of atrial ectopies (p = 0.018 for propafenone group, p = 0.09 for sotalol group, relative to that before drugs, by GEE), there was no apparent change in the scattered distribution of earliest activation sites of atrial ectopic foci after intravenous administration of dl-sotalol (p > 0.05, GEE) or propafenone (p > 0.05, GEE) (Table 1). There were 15 atrial ectopic foci located at the right atrial posterior region, 12 foci at the left atrial posterior region, 8 foci at the left atrial anterior region and 15 foci at the remaining region (Table 1).

**DISCUSSION**

**Main findings.** With bi-atrial basket electrode mapping, this study demonstrated that the earliest activation sites of atrial ectopic beats emerging after successful electrical cardioversion of long-standing AF (>3 months) were scattered, rather than concentrated, over both atria. Nevertheless, the posterior and anterior regions of the left atrium, as well as the posterior region of the right atrium—representing the convergence area of pulmonary vein orifices, the left atrial appendage and the area containing the sinus node and the crista terminalis—appeared to be the regions where atrial ectopies were more frequent. The administration of intravenous dl-sotalol and propafenone enhanced the efficacy of electrical cardioversion of long-standing AF but did not change the spatial distribution pattern of earliest activation sites of the atrial ectopic foci.

**Atrial ectopic beats and spontaneous AF.** Atrial fibrillation has been shown to be self-perpetuating. The more frequent and prolonged the episodes of AF, the worse the electrical and anatomical milieu of the atria becomes. These changes include the shortening of the atrial refractory period (1,2), the heterogeneity of atrial refractoriness (9), the dilation of the atria (10) and the degeneration of myofibrils and fibrosis (11–13). Early elimination or modification of the atrial arrhythmogenic substrate and the atrial triggers is crucial in the prevention of progressive electrical and anatomical remodellings and in the recovery of stable sinus rhythm (14).

Previous clinical studies, although few (15–17), have reported that critically-timed atrial premature beats, usually with coupling intervals of 415 to 420 ms, often precede the onset of spontaneous AF. Likewise, premature atrial ectopic beats are prone to trigger the early or late recurrence of AF after successful electrical cardioversion in patients with long-standing AF (18,19). However, it is not until the recent report from Haissaguerre et al. (6) that the efficacy of elimination of atrial ectopic triggers in the control of paroxysmal AF was confirmed. They reported that precise ablation of focal atrial ectopic triggers is effective in the elimination of clinical recurrence (62%) of paroxysmal AF. Sixty-five (94%) of the 69 atrial ectopic foci detected in 45 patients with paroxysmal AF were located inside the pulmonary veins. This intriguing result nevertheless may not be applicable in patients with long-standing AF. Recently, Lau et al. (20) reported that a consistent atrial focus is responsible for reinitiation of AF in only 13% (4 of 32) of the patients with persistent lone AF (>1 month) after internal electrical cardioversion. Saksena et al. (21) further reported...
Figure 2. Early reinitiation of two episodes of atrial fibrillation (AF) in a patient after successful cardioversion of chronic AF. The recurrent episodes of AF were initiated by atrial ectopic triggers from either the right atrium (Panel A) or the left atrium (Panel B). The intra-cardiac tracings in panel A and panel B were obtained from the basket electrodes in the right atrium and the left atrium, respectively. The 32 intra-atrial local electrogram channels represent the 32 bipolar recording sites from the eight splines of the basket electrode (from spline “A” to spline “H”) and the four sites on each spline (from site 1 to site 4). The earliest activation sites for the right atrial trigger (Panel A) were identified simultaneously at F3 and F4, corresponding to the right atrial septal-inferior region (i.e., the coronary sinus ostium region) and were 36 ms preceding the onset of the P-wave on the surface electrocardiogram, while the left atrial trigger was found earliest at the E4, corresponding to the left atrial posterior-inferior region (i.e., the left lower pulmonary vein orifice region) and was 35 ms preceding the P wave. Arrowheads indicate the earliest activation sites of the atrial ectopic triggers for the recurrent AF.
that the atrial premature complexes initiating spontaneous AF after electrical cardioversion in 17 patients with ischemic or hypertensive heart disease and refractory AF were multi-located over the lateral right atrium (31%), superior left atrium (25%), inferior left atrium (25%), right atrioventricular junction (13%) and atrial septum (6%). According to results here, several distinct atrial ectopic foci would emerge after successful electrical cardioversion without antiarrhythmic drugs. The distribution of the atrial ectopic foci, with or without triggering atrial tachyarrhythmias, was scattered over both atria. The area of pulmonary vein convergence was, at best, one of the three frequent locations (i.e., the anterior-inferior region of the right atrium (i.e., the lower crista terminalis region).

Study limitations. First, the endocardial activation sequence of the atrial ectopic beats was not mapped simultaneously from both atria, because of limited recording capacity; this contributed, in part, to the lack of determina-
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Conclusions. With bi-atrial basket electrode mapping, this study showed that the earliest activation sites of atrial ectopic triggers emerging early after successful electrical cardioversion of long-standing AF were multiple and scattered over both atria. Antiarrhythmic drugs including dl-sotalol and propafenone enhanced the efficacy of electrical cardioversion and reduced the occurrence of atrial ectopic foci after cardioversion, but these drugs did not appear to change the spatial distribution of the atrial ectopies.

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REFERENCES


