SPONTANEOUS INITIATION OF ATRIAL FIBRILLATION BY ECTOPIC BEATS ORIGINATING IN THE PULMONARY VEINS

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ABSTRACT

Background Atrial fibrillation, the most common sustained cardiac arrhythmia and a major cause of stroke, results from simultaneous reentrant wavelets. Its spontaneous initiation has not been studied.

Methods We studied 45 patients with frequent episodes of atrial fibrillation (mean ± SD duration, 344 ± 326 minutes per 24 hours) refractory to drug therapy. The spontaneous initiation of atrial fibrillation was mapped with the use of multielectrode catheters designed to record the earliest electrical activity preceding the onset of atrial fibrillation and associated atrial ectopic beats. The accuracy of the mapping was confirmed by the abrupt disappearance of triggering atrial ectopic beats after ablation with local radio-frequency energy.

Results A single point of origin of atrial ectopic beats was identified in 29 patients, two points of origin were identified in 9 patients, and three or four points of origin were identified in 7 patients, for a total of 69 ectopic foci. Three foci were in the right atrium, 1 in the posterior left atrium, and 65 (94 percent) in the pulmonary veins (31 in the left superior, 17 in the right superior, 11 in the left inferior, and 6 in the right inferior pulmonary vein). The earliest activation was found to have occurred 2 to 4 cm inside the veins, marked by a local depolarization preceding the atrial ectopic beats on the surface electrocardiogram by 106 ± 24 msec. Atrial fibrillation was initiated by a sudden burst of rapid depolarizations (340 per minute). A local depolarization could also be recognized during sinus rhythm and abolished by radiofrequency ablation. During a follow-up period of 8 ± 6 months after ablation, 28 patients (62 percent) had no recurrence of atrial fibrillation.

Conclusions The pulmonary veins are an important source of ectopic beats, initiating frequent paroxysms of atrial fibrillation. These foci respond to treatment with radio-frequency ablation. (N Engl J Med 1998;339:659-66.)

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Localization of Arrhythmogenic Triggers (Atrial Ectopic Beats)

The preliminary study involved intracardiac mapping of isolated ectopic beats. The ectopic focus was localized according to the earliest atrial activity relative to the reference electrogram or the onset of the ectopic P wave. Mechanically produced beats were prevented by avoiding manipulation of the catheters during the recordings, and such beats were excluded from the analysis by comparing the electrocardiographic pattern and intracardiac sequence with the confirmed spontaneous ectopic beats. If no sharp bipolar activity was recorded in the right atrium earlier than 10 msec before the onset of the ectopic P wave, the ectopic beats were considered to have originated in the left atrium. Pacing mapping of the left atrium and pulmonary veins was performed through a patent foramen ovale (in six patients) or by means of transseptal catheterization. In the anteroposterior view, the pulmonary-vein ostia are situated on both sides of the spine and can be engaged by applying clockwise torque to the shaft of the catheter. The role of ectopic beats in the initiation of atrial fibrillation was confirmed by on-site recording of a paroxysm of fibrillation.

Ablation Procedure

No heparin was administered for ablation in the right atrium. For the left atrium, an intravenous dose of 0.5 mg of heparin per kilogram of body weight was administered during ablation, followed by an infusion to maintain a partial-thromboplastin time of 60 to 90 seconds. The sedatives midazolam and nalbuphine were administered intravenously to control pain.

Ablation was performed at the site with the earliest recorded ectopic activity. To minimize the risk of clot formation, temperature-controlled radio-frequency energy was delivered at a target temperature of 70°C in the right atrium or 55 to 60°C in the left atrium between the catheter electrode and a patch electrode measuring 575 cm² for 60 to 120 seconds, except when there was a rise in impedance. Subcutaneous heparin was administered after ablation to maintain the partial-thromboplastin time. Successful ablation was defined as the elimination of atrial triggers during the 60 minutes after ablation and the absence of the morphologic features of the targeted ectopic beats during the subsequent eight days without a need for antiarrhythmic drugs.

Telemetry and 24-hour Holter monitoring were performed continuously, and the data were monitored by nurses to identify the cumulative duration of atrial fibrillation and the duration of fibrillation during each hour. The patients were discharged and given oral anticoagulants for at least three months but no antiarrhythmic drugs. Late follow-up consisted of visits to the hospital and Holter recordings every three months. Any undocumented but suggestive symptoms were attributed to atrial fibrillation.

Statistical Analysis

Continuous variables were expressed as group means ±SD and were compared with the use of the Kruskal–Wallis test. Statistical significance was considered to be demonstrated by a two-tailed P value of less than 0.05.
RESULTS

Origin of Atrial Triggers (Ectopic Beats)

A single point of origin of ectopic beats was identified in 29 patients, two were identified in 9 patients, three were identified in 6 patients, and four in 1 patient, for a total of 69 ectopic foci. Ectopic beats originated in atrial muscle (“atrial foci”) in 4 patients (in the right atrium in 3 and the posterior left atrium in 1) and in the pulmonary veins (“venous foci”) in 41 patients (a total of 65 foci [94 percent]): 31 foci in the left superior, 17 in the right superior, 11 in the left inferior, and 6 in the right inferior pulmonary vein (Fig. 1). The venous origin of the earliest ectopic activity was demonstrated in 23 patients by the radiographic position of the mapping catheter, which was superimposed on the lungs and was outside the cardiac silhouette, and by confirmatory angiographic visualization.

Characteristics of Triggering Ectopic Beats Arising in the Pulmonary Veins

The effective mapping of venous foci required multiple procedures because of two major problems. First, the spontaneous occurrence of ectopic beats and paroxysms of atrial fibrillation was unpredictable, and provocative procedures were not consistently effective. Second, sustained atrial fibrillation lasting for minutes or hours required either waiting periods for spontaneous interruption or cardioversion. In five patients, there were no isolated ectopic beats during mapping, because each ectopic beat set off atrial fibrillation. Venous foci exhibited the characteristic electrophysiologic patterns described below.

Activity during Ectopy

The earliest local activity was traced to a point 2 to 4 cm within the main pulmonary vein or one of its proximal branches, and depolarization was marked by a “spike” (activity of sharp onset and short duration as measured electrographically) preceding the onset of the ectopic P wave by 106±24 msec (range, 40 to 160) (Fig. 2). The P wave was not distinct in six patients in whom only the reference electrogram was used for mapping. The spike was localized, and its amplitude rapidly decreased, when the catheter tip was turned or moved a few millimeters. Bystander or far-field activity from contiguous branches could be distinguished by temporal delay or lower amplitude (<0.1 mV). The spike occurred earliest deep in the vein and progressively later toward the ostium and the left atrial exit, resulting in distal-to-proximal venous activation during multipolar recordings (Fig. 2). The amplitude of the unipolar electrograms of the spikes (<0.5 mV) was too low for morphologic analysis.

A second electrographic component with a slow deflection (depolarization rate [dv/dt], <0.5 mV per msec) reflecting later left atrial activation was temporally distinct from the spike inside the vein and then approached and became continuous with the...
spike at the ostium. The conduction time from the venous spike to the activation of the left atrium increased progressively as the coupling interval of the spike spontaneously shortened and when there were repetitive spike discharges. Nonconducted spikes (those confined within the vein) were recorded in 21 patients. They were more closely coupled with the previous beat than the conducted spikes (183±29 msec vs. 207±29 msec, P=0.03), and a threshold coupling interval below which the spike was isolated could be identified in 19 patients.

**Initiation of Atrial Fibrillation**

Between one and eight instances of spontaneous initiation of atrial fibrillation were recorded in 36 patients. Two patients with atrial foci had atrial fibrillation induced after irregular atrial tachycardia, one with a mean cycle length of 230 msec and the other with a mean cycle length of 250 msec. In 34 patients with venous foci, the initiation of atrial fibrillation was documented for 45 of 58 foci with the use of a catheter in the appropriate vein. Atrial fibrillation was initiated by a single focal discharge in 3 patients (including 2 with structural heart disease), a short burst of two or more repetitive focal discharges in 40, and both mechanisms in 2 (Fig. 3). Repetitive focal discharges had irregular cycle lengths, ranging from 110 to 270 msec, with a mean of 175±30 msec (340 per minute). Five foci discharged only in bursts, with each burst producing atrial fibrillation. The coupling interval from the last sinus beat to the initial spike did not differ significantly between ectopic beats that led to atrial fibrillation and those that were isolated (212±34 msec vs. 216±34 msec). Continuous electrical activity could be recorded in the pulmonary vein during the interval between successive spikes but not during the period preceding the first spike.

In nine patients, no spontaneous initiation of atrial fibrillation could be documented during mapping. However, all nine had frequent isolated ectopic beats originating from a single focus (atrial in two patients and venous in seven, all with similar characteristics) and previous electrocardiographic documentation of the role of these beats in initiating atrial fibrillation.

Figure 2. Angiogram of a Left Inferior Pulmonary Vein Depicting the Source and Exit of Ectopic Activity.

The electrogram showed characteristic changes in timing depending on the position of the recording catheter in the specific pulmonary vein. With an increasingly distal catheter position (toward the source), the spike was recorded progressively later during sinus rhythm (left-hand panel, arrows) and correspondingly earlier during ectopic activity (arrowhead). Conversely, in a proximal position at its exit into the left atrium (right-hand panel), the spike was not as delayed during sinus rhythm (arrows) nor as precocious during ectopic activity (arrowhead). The application of radio-frequency energy at the source of ectopic activity eliminated the local spike during sinus rhythm and ectopic beats and atrial fibrillation on a short-term basis. The dotted lines mark the onset of the ectopic P wave, and 1–2 and 3–4 are bipolar recordings from the distal and proximal poles of the mapping catheter. A indicates near-field atrial activity. The radiograph (center panel) shows the position of electrographic recordings inside the pulmonary vein at the source and exit.
Activity during Sinus Rhythm

The spike could also be recognized during sinus rhythm in the terminal portions of local potentials after left atrial activity, and it occurred progressively later inside the vein, which is the opposite of the sequence during ectopy (Fig. 2). Multiple spikes were recorded at the ostia, particularly those of the superior veins. Similar (though less complex) electrograms could also be recorded in other nonarrhythmic pulmonary veins (those not giving rise to ectopic beats), indicating physiologic activation of muscular left atrial tissue extending into the veins.26,27

Radio-Frequency Ablation

The four ectopic foci mapped to atrial muscle outside the pulmonary veins exhibited the earliest activity — 35 to 45 msec before the onset of the ectopic P wave — implying a short conduction time to the rest of the atrium. They were ablated with a median of 3 and a mean of $4.5 \pm 2$ applications of radio-frequency energy in one session.

The ablation of venous foci was performed at the earliest site of the maximal amplitude of the spike during conducted or nonconducted ectopic beats. As shown in Table 2, two sessions were required for 25 patients and three sessions were required for 6 because of a recurrence after ablation or the detection of new foci. All but one recurrence occurred within three days of the initial procedure. A mean of $5 \pm 5$ and a median of 4 applications of radio-frequency energy were required for each focus.

No serious side effects were observed during these procedures. Cough was induced in some patients by applications of radio-frequency energy in the left superior veins near the bronchi and required the cessation of the delivery of radio-frequency energy or a
Follow-up

Successful ablation of ectopic foci in the hospital was achieved in 38 patients. The Holter recordings of these patients showed a decrease from 4377±3629 to 98±91 ectopic beats per 24 hours. Two patients had a recurrence of atrial fibrillation, whereas 36 patients had no recurrences during hospitalization, including the 9 patients without initiation of atrial fibrillation during the ablation procedure. Ablation of the focus was unsuccessful in seven patients, and all had recurrences of atrial fibrillation in the hospital.

During a mean follow-up period of 8±6 months (median, 7), atrial fibrillation was eliminated completely in 28 patients (62 percent) without the use of drug therapy. Seventeen patients had recurrences of atrial fibrillation, including those who had early failures, and recurrences of ectopy were documented in 12 of these patients during hospitalization or follow-up.

Reduction in power. Pain was sometimes severe, requiring additional doses of nalbuphine.

Electrograms recorded at the sites of successful ablation of 57 venous foci showed the disappearance of the local spike during sinus rhythm in 44 of the foci, an intermittent spike (every two or three beats) in 3, and dissociation from atrial activity as a slow automatic rhythm in 2 (Fig. 4). At eight sites, the spike persisted, but with a lower amplitude and a delay of 10 to 50 msec.

After ablation the angiograms of the pulmonary veins of 23 patients were unremarkable except for a luminal irregularity (possibly a small thrombus) in 1 patient. Twenty of the sites of successful ablation were located at or near a branching point.

**TABLE 2. OUTCOME OF IN-HOSPITAL ABLATION ACCORDING TO LOCATION OF FOCUS.*

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*For each procedure, the numbers of targeted foci, eliminated foci (successes), nonablated foci (failures), and recurrent foci are indicated. Failures were mainly due to infrequent ectopic beats that did not permit mapping.

†LSPV denotes left superior pulmonary vein, RSPV right superior pulmonary vein, LIPV left inferior pulmonary vein, and RIPV right inferior pulmonary vein.

‡The total number of procedures is the number of successes plus the number of failures.

DISCUSSION

This study indicates that the vast majority of atrial premature beats that initiate frequent paroxysms of atrial fibrillation originate in the pulmonary veins. These foci trigger atrial fibrillation with a burst of rapid discharges and respond to local radio-frequency ablation with a catheter.

The pulmonary veins were identified as major sources of atrial triggers (ectopic beats) by means of intracardiac mapping, fluoroscopy, and angiographic imaging. Such venous foci were previously observed in a few patients who underwent atrial ablation for paroxysmal atrial fibrillation.20 In our study of patients who had not previously undergone ablation for atrial fibrillation, 94 percent of the atrial triggers originated in the pulmonary veins. This prevalence was similar to that in the subgroup of patients with structural heart disease, but a larger series is needed to confirm this result.

All the patients were enrolled because they had frequent and drug-resistant paroxysmal atrial fibrillation, and the high prevalence of foci in the pulmonary veins may therefore reflect an anatomical site or mechanism that is particularly arrhythmogenic and resistant to conventional drug therapy rather than the true prevalence in the general population with atrial fibrillation. In some patients, however, isolated ectopic beats could not be recorded during mapping, because of long-lasting atrial fibrillation requiring cardioversion, because no such beats were present, or both. This suggests that our methods and results could be applied to a broader range of clinical situations with the use of more reliable provocative procedures and simultaneous multielectrode mapping.

The pulmonary-vein foci exhibited unique charac-
in the superior veins matches the dominant anatom-
ways. The predominant distribution of foci atrium to the venous wall with complex path-
vation of muscular bands extending from the left other pulmonary veins reflects the physiologic acti-

venous pacing, but the effects of stimulation through conduction time was also reproduced by local spikes indicate a rapidly conducting structure. A long meters long, since the morphologic features of the discontinuous conduction or a tissue several centi-
meters long, as the morphologic features of the spike indicate a rapidly conducting structure. A long conduction time was also reproduced by local venous pacing, but the effects of stimulation through pacing therapy have not been explored.

The recording of spikes during sinus rhythm in other pulmonary veins reflects the physiologic activation of muscular bands extending from the left atrium to the venous wall with complex pathways. The predominant distribution of foci in the superior veins matches the dominant anatomical pattern of these atrial extensions. The reasons why pulmonary veins become arrhythmogenic are unknown. However, their architectural topography can accommodate various electrophysiologic mech-

Figure 4. Effects of Successful Radio-Frequency Ablation within the Superior Pulmonary Veins in Two Patients.
The tracings in the upper panel were recorded in a patient with dilated cardiomyopathy. Before ablation (left-hand side), a multicomponent electrogram was recorded in the right superior pulmonary vein (RSPV) with a terminal spike (asterisk). After ablation at this site (right-hand side), the spike disappeared. The tracing in the lower panel shows an example of ablation within the pulmonary vein resulting in slow and dissociated automatic spike activity in the left superior pulmonary vein (LSPV), marked by asterisks.

The successful ablation of foci was safely achieved, and the procedure eliminated previously frequent atrial fibrillation without a need for antiarrhythmic drugs in 84 percent of the patients during hospital monitoring and in 62 percent after discharge. Of note, most of the recurrent atrial fibrillation was associated with recurrent ectopic beats, indicating that a better technique of mapping or of ablation may further improve these results. Important limitations inherent in the management of atrial fibrillation are the difficulty of obtaining reliable data on arrhyth-

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mia and its initiation on an outpatient basis and the uncertain duration of asymptomatic episodes. Additional studies are necessary to evaluate the role of ablation of triggering ectopic foci in preventing atrial fibrillation, as well as the safety of ablation in the pulmonary veins, before widespread application of ablation for the treatment of this common cardiac-rhythm disturbance can be recommended.

REFERENCES