Identification of the Substrate of Atrial Vulnerability in Patients With Idiopathic Atrial Fibrillation

Hemanth Ramanna, MD; Richard N.W. Hauer, MD; Fred H.M. Wittkampf, PhD; Jacques M.T. de Bakker, PhD; Eric F.D. Wever, MD; Arif Elvan, MD; Etienne O. Robles de Medina, MD

Background—Experimental studies have shown that atrial fibrillation (AF) causes remodeling, which facilitates AF perpetuation. AF may also occur in patients without remodeling and underlying structural cardiac disease. The substrate for enhanced vulnerability in these patients is unknown.

Methods and Results—We studied 43 patients without structural heart disease: 18 patients with documented sporadic paroxysmal AF and 25 control patients without AF. In each patient, a decapolar catheter was positioned against the right atrial free wall, and a quadripolar catheter was positioned in the right atrial appendage. Unipolar electrograms were recorded. Atrial vulnerability was assessed according to an increasingly aggressive stimulation protocol. Mean local fibrillatory interval (FI) was used as an index of local refractoriness. Spatial dispersion of refractoriness was assessed through the calculation of the coefficient of dispersion (CD), which was defined as the SD of mean local FI expressed as a percentage of the mean FI. In the AF group, AF was induced with a single extrastimulus in 16 of 18 patients; the CD was 5.4±2.6, and the mean FI was 164±29 ms. In the control group, AF could be induced only with more aggressive pacing in 23 of the 25 patients; the CD was 1.4±0.7 (P<0.0001), and the mean FI was 175±26 ms (NS).

Conclusions—Patients with idiopathic AF showed increased dispersion of refractoriness, which may be the substrate for the observed enhanced inducibility and spontaneous occurrence of AF. (Circulation. 2000;101:995-1001.)

Key Words: atrium ■ fibrillation ■ electrophysiology

Atrial fibrillation (AF) may occur in patients without structural cardiac disease. In animal models, sustained AF causes remodeling of the atria, which facilitates AF perpetuation.1,2 In patients, however, AF may also occur without previous remodeling. The initiation of AF requires a trigger, which often is atrial tachycardia or atrial premature depolarizations.3,4 Not all patients with atrial arrhythmias, however, will develop AF; therefore, the presence of a trigger alone may not lead to AF. A substrate for atrial propensity to fibrillation (ie, atrial vulnerability) may also be required for AF initiation.

Atrial vulnerability may be increased in the presence of the dispersion of electrophysiological properties, as suggested on the basis of experimental data.5,6 With the use of epicardial multielectrode recordings during cardiac surgery, Ramdat Misier et al7 found increased dispersion of refractoriness and shortened refractory periods in patients with idiopathic AF compared with control patients. However, these patients had frequent AF episodes, so it is unclear whether the observed electrophysiological changes in dispersion were the cause or the result of AF.

The aim of the present study was to assess whether patients with idiopathic paroxysmal AF without electrophysiological remodeling have specific atrial electrophysiological properties that might increase the propensity to AF in comparison with control subjects.

Methods

Patients
A total of 245 patients (age <60 years) undergoing an electrophysiological study at the Heart-Lung Institute for supraventricular tachycardia were screened for inclusion on the basis of the criteria listed in Table 1. Informed consent was obtained from the patients, and the study was approved by the hospital review board. All patients had a physical examination and underwent ECG, echocardiography, and biochemical and hematological testing to exclude structural heart disease and conditions with potential effects on cardiac hemodynamic or electrophysiological functions. Telemetry was performed for 24 hours before the electrophysiological study.

Of these 245 patients, 23 had prior documented AF; 4 were excluded due to an abnormal echocardiogram, and 1 was excluded due to alcoholism. Thus, 18 patients with AF remained, and they were assigned to the AF group. Of the patients without AF, 25 were randomly selected and assigned to the control group. The study was...
carried out during the routine electrophysiological investigation before catheter ablation of the tachycardia.

**AF Group**

The 18 patients in the AF group (15 men and 3 women, mean age 33.1 ± 9.2 years, maximum age 46 years) had prior paroxysmal AF episodes. ECG documentation of ≥ 1 episode was required for inclusion in the study, and each patient was specifically questioned about the duration and onset of previous episodes. All patients were able to distinguish AF episodes from their regular supraventricular tachycardia. A rapid irregular heartbeat was interpreted as an AF episode. These patients had experienced a median of 1 (mean 1.8, SD 2.5, range 1 to 12) episode of AF with a median duration of 1 hour (range 0.25 to 4 hours). The last spontaneous symptomatic episode of AF preceded the electrophysiological study by a median of 162 days (range 6 to 529 days). None of the patients had AF episodes during the telemetric observation period. In this group, all patients had an accessory atrioventricular pathway, of which 2 were concealed (accessory pathway location: 14 left free wall, 1 left posteroseptal, 2 right free wall, and 1 parahisian), and 7 patients with atrioventricular nodal reentrant tachycardia (AVNRT). Telemetry did not reveal any AF episodes.

**Control Group**

The 25 control patients (17 men and 8 women, mean age 33.5 ± 11.0 years, maximum age 52 years) did not have a history of AF or episodes of irregular heartbeat. There were 18 patients with accessory pathways, of which 2 were concealed (accessory pathway location: 14 left free wall, 1 left posteroseptal, 2 right free wall, and 1 parahisian), and 7 patients with atrioventricular nodal reentrant tachycardia (AVNRT). Telemetry did not reveal any AF episodes.

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**Figure 1.** Fluoroscopic image in anteroposterior projection showing decapolar catheter at right atrial lateral free wall and quadripolar catheter in right atrial appendage. Decapolar catheter position was consistent in all patients and was designed to maximize number of electrodes with firm wall contact and to maintain catheter stability for duration of study protocol. In addition, ventricular far field interference in unipolar electrograms was minimized with the use of this position.

**Figure 2.** Histogram of mean fibrillatory intervals at a single atrial recording site. Intervals have been grouped into 10-ms bins. There is a large peak at 150 ms and a small peak at 300 ms. Intervals related to secondary peak, caused by undetected intrinsic deflections, were discarded. Mean fibrillatory interval at this recording site was defined as average of intervals in first peak: in this case, 154 ms. This mean fibrillatory interval was used as an index for local refractoriness.

**Figure 3.** Mean fibrillatory intervals (in ms) for each measurable atrial recording site in a typical patient (patient 17) with prior paroxysmal AF (A) and in a control patient (patient 11) (B). Patient with prior AF has more inhomogeneity of mean fibrillatory intervals than does control patient. AF could be induced with a single extrastimulus in patient with AF; in control patient, it was induced with burst pacing only. *Electrodes marked had inadequate signal quality and thus were excluded from analysis.*

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**TABLE 1. Inclusion and Exclusion Criteria**

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<td>Inclusion in other study</td>
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<td>Control group: documented AF or episodes of irregular heartbeat</td>
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**Study Protocol**

All patients were studied in the fasting, nonsedated state. After right femoral venous access was obtained, 2 electrode catheters (electrode spacing 5 mm) were positioned in the right atrium, a decapolar catheter (Bard USCI) was positioned at the lateral free wall, and a quadripolar catheter (Bard USCI) was positioned in the appendage as shown (Figure 1). The position of the decapolar catheter was selected to maximize the number of electrodes with good tissue contact and to minimize the effects of far-field interference from ventricular activity on the unipolar electrogram. The catheters were repositioned until a stable position with ≥ 8 unipolar electrograms of > 0.5 mV was obtained during sinus rhythm. Twelve unipolar electrograms were recorded (gain 2 mV/cm, filter 0.05 to 500 Hz) (10 from the decapolar and 2 from the proximal pair of the quadripolar catheter) with the use of an electrophysiological recording system (Cardiolab; Prucka Engineering).

The inducibility of AF was assessed through programmed stimulation with the use of unipolar cathodal pacing (pulse width 2 ms). Pacing consisted of a 4-stage, progressively aggressive stimulation protocol to achieve AF with a duration of ≥ 1 minute. Stage 1 consisted of pacing at twice diastolic threshold current with an 8-pulse drive train and 1 extrastimulus starting at the tip electrode of the decapolar catheter. The extrastimulus interval S2S1 of 100 ms was incremented in steps of 5 ms until atrial capture occurred. If AF with
duration of >1 minute was not obtained in this manner, stage 1 was successively repeated at all of the other electrodes. If AF was not induced, the next stage was performed. Stage 2 consisted of pacing at 4 times diastolic threshold current with an 8-pulse drive train and 1 extrastimulus from the tip electrode of the quadripolar catheter. Stage 3 was the same as stage 2 but with 2 extrastimuli. Stage 4 consisted of multiple 5-second ramp bursts at a cycle length of 100 to 50 ms at 4 times diastolic threshold current from the tip electrode of the quadripolar catheter. Other induced types of tachycardia were sequenced at 4 times diastolic threshold current.

Data Analysis
The segment between 15 and 30 seconds after AF onset was used for electrogram analysis. Fibrillatory intervals were measured through the detection of the intrinsic negative deflections with negative slopes of >0.5 mV/s. For each recording site, histograms of fibrillatory intervals were plotted. Under sensing of intrinsic deflections, resulting in multiples of fibrillatory intervals, was detected through the observation of secondary peaks in the histogram. Such intervals were discarded, as described by Opthof et al. For each recording site, the sum of all discarded intervals was calculated. If this sum exceeded 4 seconds, the electrogram recording site was excluded from further analysis.

The mean fibrillatory intervals were calculated for each site to serve as an index for the local refractory period. The average and SD values of these indices were calculated. Spatial dispersion was defined as the coefficient of dispersion (CD) and calculated as the SD of the mean fibrillatory intervals expressed as a percentage of the mean fibrillatory interval: \( \text{CD} = \frac{\text{SD of mean fibrillatory intervals}}{\text{mean fibrillatory interval}} \times 100 \). The overall mean CD value for the recording site was 85 ± 20. The overall mean CD value for the AF group was 5.4 ± 2.6, and the overall mean fibrillatory interval was 164 ± 29 ms. In 3 patients, the mean fibrillatory interval was between 200 and 225 ms. However, the irregularity and polymorphic character of the electrograms, with

Results
The measurement of fibrillatory intervals resulted in histograms such as that shown in Figure 2. The mean fibrillatory intervals detected at all recording sites were displayed as shown in Figure 3. The range of local mean fibrillatory intervals indicates the spatial dispersion measured in 1 patient. It is readily observed that in the patient with prior AF, there is more spatial dispersion of mean fibrillatory intervals than in the control patient without AF (Figure 3).

AF Group
Baseline data are given in Table 2. AF was induced with a single extrastimulus at twice diastolic threshold current in 16 of 18 patients. In the other 2 patients, only nonsustained AF episodes (2 per patient) could be induced, with a mean duration of 28 ± 4.5 seconds; more aggressive pacing was required to obtain sustained AF. Adequate recordings with a <4-second dropout were obtained from an average of 9 (range 7 to 11) electrodes per patient. Of these 15-second recordings, a mean of 1.16 (range 0.15 to 2.70) seconds were excluded due to inadequate dV/dt.

The mean number of measured fibrillatory intervals per recording site was 85 ± 20. The overall mean CD value for the AF group was 5.4 ± 2.6, and the overall mean fibrillatory interval was 164 ± 29 ms. In 3 patients, the mean fibrillatory interval was between 200 and 225 ms. However, the irregularity and polymorphic character of the electrograms, with

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AF induction indicates type of stimulation required to obtain AF; ES, extrastimulus; CB, concealed atrioventricular bypass; Flimin, mean fibrillatory interval at the recording site with the shortest fibrillar cycle length; Flimax, mean fibrillatory interval at the recording site with the longest fibrillatory cycle length; and mean Fl, average of mean fibrillatory intervals of all sites.

*Pacing at 4 times diastolic threshold current.
cycle length variations of $\geq 20\%$ of the mean cycle length, were compatible with AF.

**Control Group**
The baseline and electrophysiological parameters of the control patients are given in Table 3. Sustained AF was induced with a single extrastimulus at twice diastolic threshold current in only 2 of 25 patients. Nonsustained AF could be induced in an additional 2 patients (2 and 3 episodes, mean duration 17\pm 5.2 seconds). In these 2 and the remaining 21 patients, more aggressive pacing was required to obtain sustained AF, with 17 patients requiring burst pacing at 4 times diastolic threshold. Adequate recordings with $\geq 4$-second dropout were obtained from an average of 9 (range 8 to 12) electrodes per patient. Of these 15-second recordings, a mean of 1.62 (range 0.14 to 2.91) seconds were excluded due to inadequate dV/dt.

The mean number of measured fibrillatory intervals per recording site was 80\pm 24. The overall mean CD value for the control group was 1.4\pm 0.7, and the overall mean fibrillatory interval was 175\pm 26 ms. In 4 patients, the mean fibrillatory interval was between 200 and 225 ms. However, the irregularity and polymorphic character of the electrograms, with cycle length variations of $\geq 20\%$ of the mean cycle length, were compatible with AF.

In the control group, the patients with Wolff-Parkinson-White (WPW) syndrome had a mean CD value of 1.4\pm 0.6 and an overall mean fibrillatory interval of 173\pm 27 ms. In the patients with AVNRT, these values were 1.5\pm 1.0 and 182\pm 27 ms, respectively. These subgroups did not differ significantly.

**Comparison Between AF and Control Groups**
The electrophysiological parameters are given in Table 4. There were no significant differences in left atrial dimensions, baseline heart rate, and pacing thresholds. AF was induced more easily, with 1 extrastimulus, in the AF group than in the control group ($P<0.0001$), as shown in Figure 4. The average CD value was significantly higher in the AF group than in the control group with only minimal overlap ($P<0.0001$), as shown in Figure 5A.

Mean fibrillatory intervals did not differ significantly between the groups ($P=0.17$), as shown in Figure 5B. The shortest preexcited RR interval (ie, refractoriness of accessory pathway) and the average heart rate during AF did not differ between the groups.

**Discussion**
In the present study, patients without demonstrable structural heart disease and with short-lasting and infrequent symptom-
atic episodes of AF had increased spatial dispersion of refractoriness. This increased dispersion could not be attributed to electrical remodeling because most patients had experienced only a single, short symptomatic episode of AF that occurred a long time (median 162 days, minimum 6 days) before the electrophysiological study. Telemetric monitoring also did not reveal any asymptomatic episodes for $24$ hours before the study. In addition, in the AF group, the mean fibrillatory intervals were not significantly shorter than those in the control group. The increased dispersion of refractoriness was associated with enhanced atrial inducibility of AF, as would be expected on the basis of experimental findings.\textsuperscript{5,10} Increased dispersion of refractoriness thus may be a major predisposing factor for the initiation of AF.

Dispersion and Remodeling

Several recent experimental studies in animals have shown that AF causes shortening of refractoriness,\textsuperscript{1,2,10,11} an increase in atrial inducibility of AF,\textsuperscript{1,10} and an increase in dispersion of refractoriness.\textsuperscript{10,11} With the use of intraoperative epicardial recordings, Ramdat Misier et al\textsuperscript{7} found increased spatial dispersion of refractoriness in patients undergoing surgery for AF. These patients had frequent symptomatic AF episodes for which they were undergoing surgery, and the time from the last AF episode to the measurements was not known. It is conceivable that these patients had long-standing AF that caused atrial remodeling, as suggested by their significantly shorter average fibrillatory intervals.\textsuperscript{1,2} Thus, on the basis of their study, it was unclear whether the increased dispersion was the cause or the result of AF. These mentioned findings in experimental models\textsuperscript{1,2,10,11} and in patients\textsuperscript{7} underlie the importance of the exclusion of the effects of remodeling when studying the propensity for AF at an early stage of idiopathic AF.

Substrate for Increased Dispersion

The pathophysiology of the increased dispersion of refractoriness is not known. Atrial fibrosis, as found in structural heart disease and in the elderly,\textsuperscript{12} may give rise to electrical inhomogeneity. Our patients did not have identifiable structural heart disease, and their mean age was 33 years. Atrial dilatation may be another causative factor,\textsuperscript{13} but echocardiography did not demonstrate atrial enlargement in our patients and Doppler-derived measurements did not show increased atrial pressure. Inhomogeneity of autonomic innervation may be another mechanism for increased dispersion of refractoriness as shown by Olgin et al\textsuperscript{14} in a canine model of sympathetic denervation.

AF and WPW Syndrome

Most of the patients in the present study had WPW syndrome. Branched accessory pathways causing microreentry have been suggested as causative factors for AF. Fujimura et al\textsuperscript{15} found that in patients with WPW syndrome, AF usually was
initiated in the right atrium regardless of accessory pathway location. In addition, Wathen et al\textsuperscript{16} did not find any changes in atrial electrophysiological properties after accessory pathway ablation. In our study, the measurements and induction of AF were performed in the right atrium, whereas the accessory pathway was left-sided in most patients (AF group: 14 of 18, control group: 15 of 18). Moreover, the control group included a large number of patients who also had WPW syndrome. These patients had low dispersion and low inducibility despite their accessory pathway. The anterograde refractory period of the accessory pathway did not differ significantly between these patients and those in the AF group, and the average heart rate during AF was comparable. Therefore, a hemodynamic cause for the difference in dispersion between these patients seems unlikely. In addition, we studied control patients with AVNRT (ie, without an atrio-ventricular bypass tract). Dispersion in these patients did not differ from that in control patients with WPW syndrome. The results of our study suggest that in patients with prior paroxysmal AF, the atria had abnormal electrophysiological properties that could not be directly attributed to the accessory pathway.

**Study Limitations**

In the AF group, the incidence of AF episodes was quantified through questioning of patients about symptoms of irregular heartbeat. Asymptomatic AF episodes therefore could not be entirely excluded. In the AF group, however, 16 of 18 patients also had preexcitation and rapid ventricular rates during AF. Therefore, in this subset of patients, AF episodes would be more likely to cause symptoms than they would in the general population. In addition, AF (symptomatic or asymptomatic) during the 24-hour period before the study was excluded through the use of telemetric monitoring.

One may question the use of mean fibrillatory intervals as the most appropriate method to estimate local refractoriness. Previous experimental studies by Allessie et al\textsuperscript{17} have demonstrated an excitatory gap during AF. Nevertheless, several studies have demonstrated a strong correlation between local refractory period as measured with extrastimuli and the local mean fibrillatory interval.\textsuperscript{7,9,18,19}

Data were obtained from a small portion of the right atrium with a relatively limited number of electrodes. The septum and left atrium were not investigated. In 3 AF patients, the CD value was within the normal range (\(\leq 3.0\)). This may be due to catheter positioning; dispersion may have been increased at other positions.

**Conclusions**

Patients with idiopathic AF had increased spatial dispersion of refractoriness unrelated to electrical remodeling. This increased dispersion appeared to be the substrate for the enhanced atrial vulnerability.

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