Electrophysiologic Characteristics of Paroxysmal and Chronic Atrial Fibrillation in Human Right Atrium

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OBJECTIVES
The aim of the study was to analyze the electrophysiologic characteristics of paroxysmal (PAF) and chronic (CAF) atrial fibrillation (AF) in the human right atrium (RA).

BACKGROUND
Differences that exist between PAF and CAF and the mechanisms of self-sustenance of these arrhythmias are incompletely understood.

METHODS
A total of 53 patients with PAF (25 patients, mean age 59 ± 6.1 years, 3 women) and CAF (28 patients, mean age 59 ± 13 years, 7 women) underwent multisite mapping of the RA during ongoing AF using a 64-electrode basket catheter. Quantitative evaluation and three-dimensional activation patterns were performed using a computerized system.

RESULTS
Patients with PAF, as compared with patients with CAF, had significantly longer AF cycle length, shorter time intervals with type III AF throughout the RA and a smaller number of endocardial breakthroughs (mean 51 ± 19 vs. 104 ± 40, p < 0.001). The majority of endocardial breakthrough points (88% in PAF patients and 98% in CAF patients) were located in the septal region and coincided anatomically with major interatrial connection routes. Coexistence of re-entrant and apparently focal activation determined maintenance of AF in the RA in PAF, whereas random re-entry was documented more frequently in patients with CAF. In patients with CAF, the duration of arrhythmia (in years) correlated strongly with the percentage of time during which type III AF was observed in the lateral wall of the RA (r = 0.71).

CONCLUSIONS
Clinical PAF and CAF, as recorded in the RA, have, at least quantitatively, distinct electrophysiologic features and different mechanisms of maintenance. (J Am Coll Cardiol 2001;38:1143–9) © 2001 by the American College of Cardiology

Atrial fibrillation (AF) is still a therapeutic challenge, in part due to incomplete understanding of the underlying pathologic and electrophysiologic mechanisms (1). Most of the information available has been derived from experimental studies in animals in which various techniques have been used to induce and perpetuate AF (2–7). Mapping studies of human AF are still very rare (7–9). In these studies, either extended but low resolution mapping of both atria (7) or high resolution mapping of limited areas of the atria have been reported (8,9). Although the concepts yielded by these studies are appealing, there are still gaps in the understanding of the pathophysiology of AF. Several other aspects of AF such as relative contribution of focal and re-entrant activation, differences between paroxysmal and chronic forms, role of the different atrial regions in AF perpetuation and the mechanisms of maintenance have not been fully elucidated. Clarification of the characteristics of the activation during AF is of obvious relevance, especially when ablative techniques are considered (10,11).

In this study, using a computerized mapping system, we sought to analyze the three-dimensional activation patterns in the right atrium (RA) in patients with paroxysmal AF (PAF) and chronic AF (CAF). We specifically concentrated on the electrophysiologic differences between PAF and CAF, regional characteristics of activation and their contribution to AF perpetuation as well as the mechanisms of AF maintenance in paroxysmal and chronic variants.

METHODS

Patient population. The study population consisted of 53 patients with AF. The patients were divided into two groups: group I included 25 patients with PAF (more than two episodes of AF per month), and group II included 28 patients with CAF (more than three months). Both groups were referred for electrophysiologic study and, if indicated, ablation by targeting foci initiating AF episodes or isolation of the pulmonary veins. Clinical characteristics are shown in Table 1.

Basket catheter (BC) deployment and electrophysiologic study. Electrophysiologic study was performed after the procedure was explained and written consent had been obtained. All antiarrhythmic drugs were discontinued at least 5 plasma half-lives before the study. Three patients in the group with PAF were treated with amiodarone within the last six months. Patients were mildly sedated with midazolam 1 to 2 mg administered intravenously.

The BC (Constellation, EP Technologies, San Jose, California) was deployed into the RA through an 11-F
sheath using one of the femoral veins under local anesthesia (Fig. 1).

Technical data and details of BC deployment have been reported previously (12). Briefly, from 64 electrodes, 56 bipolar electrograms were derived by combining sequential pairs along each of the splines (seven bipoles per spline). Electrode pair 1/2 was located in the high RA, whereas electrode pair 7/8 was located in the low RA. The relationship between the BC splines and the RA was determined by using the fluoroscopic markers mounted on the splines in two fluoroscopic angles (left anterior oblique coronary artery 45° and right anterior oblique coronary artery 30°). A 16-pole electrode catheter with an interelectrode distance of 2 mm was positioned in the coronary sinus to record from the left atrium. A third catheter was used for mapping and radiofrequency ablation in the right and the left atria. The left atrium was accessed through a trans-septal approach.

Simultaneous surface 12-lead electrocardiogram and bipolar intracardiac electrograms were continuously acquired with a filter bandwidth of 30 to 500 Hz, digitized (1,000 samples/s) and displayed on a high-resolution monitor at a speed of 200 mm/s for inspection and review. Anticoagulation was performed by bolus administration of 5,000 IU of heparin followed by continuous intravenous heparin infusion adjusted to maintain activated clotting time at about 300 s.

Quantitative evaluation of AF. Atrial fibrillation episodes were quantitatively evaluated using a custom-designed software (13). Ten-second intervals of AF including 56 bipolar electrograms and up to 10 reference signals were analyzed (Fig. 2). The software provides three ways of evaluating the timing and the spread of activation: electrogram option, tables and propagation map. In electrogram option, all 56 bipolar electrograms are displayed with activation time marked with a red bar. In the table option, a table containing time of all activations, AF cycle length, number of activations and mean cycle length for 10-s time intervals for all 56 recording sites was generated by the software. Propagation maps were displayed as color-coded isochrones with red indicating the head of activation front, pink indicating the earliest activated regions and yellow, green and blue indicating intermediate activated regions. The software allows a free selection of the time window for animation and millisecond per millisecond freezing of the animated view.

Definitions. An interpotential interval of 50 ms was selected as a minimal AF cycle length as used in other studies (14). For classification of the AF, we used criteria of Konings et al. (8). Activation through the entire RA was defined as homogeneously regular (type I AF dominated the entire RA activation), nonhomogeneous (coexistence of type I AF in one region and type II or III AF in another region) and homogeneously irregular (type III AF was observed throughout the RA) (Fig. 2).

Endocardial breakthroughs (new wavelet formation) were considered as a sudden and unexpected appearance of electrical activity in electrode pairs not related to activation or slow conduction in any of the surrounding electrodes that had a radial distribution (Fig. 3, time 0). The excitation was considered as re-entrant if a region was re-excited by an impulse that propagated continuously from an adjacent region.

Statistical analysis. Data are presented as mean ± SD, percentage or range. Two-tailed Student t test or Wilcoxon rank test for continuous unpaired data were used to test statistical differences. Discrete variables were analyzed with Fisher exact test. Correlation between parameters was performed by calculating Pearson’s correlation coefficient. Differences were considered significant at a p value <0.05.
Figure 2. Three types of activation observed in the right atrium (RA). Three surface electrocardiographic leads, 56 bipolar basket catheter electrograms and CS electrograms are shown. (Left) Homogeneously regular activation. During a homogeneously regular pattern, the entire RA was activated from a single wave front emerging from the high anteroseptal area (electrode B 1/2). (Middle) Nonhomogeneous activation. Type II and III atrial fibrillation (AF) are observed along the posterior and septal regions of the RA (splines A to D), whereas the lateral wall (splines G and H) is activated by type I AF. (Right) Homogeneously irregular activation. Complex activity (AF type II and III) is observed throughout the RA. Splines E and F were located across the tricuspid annulus.

Figure 3. Three-dimensional activation patterns in a patient with paroxysmal atrial fibrillation. Isochrones are drawn every 5 ms. Splines A and B are located in the posterior wall, splines B, C and D in the septal wall, spline E across the tricuspid annulus and splines G and H are located in the lateral wall of the right atrium (RA). Electrode pairs 1/2 are located in the upper RA, whereas electrode pairs 7/8 are located in the lower RA. Grey ellipse shows position of the tricuspid valve. Red represents the head of activation front. At time 0, an early breakthrough is observed in the high septal region. After 74 ms, almost the entire RA was activated from that spot. At the level of electrode pair B 6/7 (low posterior region), the main wave front is divided into two wave fronts heading toward the low posterior (electrode B 7/8) and posteroseptal (electrode C 5/6) regions. After 107 ms, the lateral wave front crossed the isthmus region and emerged at the low septal region, whereas the posteroseptal wave front activated most of the posteroseptal area. At 174 ms, two wave fronts are just re-entering the posterior and the lateral regions again.
RESULTS
At the time of the electrophysiologic study, 16 patients in the PAF group were on AF. In the remaining nine patients with PAF, AF was induced during pacing maneuvers. Episodes lasting >10 min were mapped and analyzed.

**Distribution of the AF cycle lengths.** Atrial fibrillation cycle lengths were simultaneously measured in 56 locations throughout the RA. Values obtained in the high, mid-, and low sections of the lateral, posterior, and septal walls of the RA are shown in Table 2. Since the anterior wall of the RA was frequently contaminated by a large far-field ventricular signal, the cycle lengths in this region were disregarded. As seen in the Table, patients with PAF had significantly longer cycle lengths and a greater degree of regional disparity as compared with the patients with CAF.

**Regional differences in AF types.** In both groups of the patients, all three types of AF were found. Table 3 summarizes the right atrial regional distribution of the AF types expressed as percentage of time (10 s interval) during which these types of AF were recorded. Type I AF was recorded for longer periods in the lateral and posterior walls of the RA in patients with PAF. Type II AF was recorded for a significantly longer time in the septal wall in patients with PAF as compared with the same region in the patients with CAF. Type III AF was recorded for a significantly longer time in all RA regions in patients with CAF as compared with patients with PAF.

**Right atrial activation patterns.** Considering the entire RA, three different activation patterns were also observed: homogeneously regular, nonhomogeneous and homogeneously irregular (Fig. 2 and Table 4). During the homogeneously regular pattern, the RA activation manifested features of a focal activation. Most frequently, the impulse originated from the high anteroseptal region in which case the lateral and septal walls were activated in a craniocaudal direction. Occasionally, the focus of origin jumped to the low posteroseptal region. The constant fusion in the isthmus region ruled out macro–re-entry as an underlying mechanism. At the moment of transition, two wave fronts coming from the high anterolateral and the low posteroseptal regions collided in the middle of the interatrial septum. The nonhomogeneous pattern was the most common activation pattern in RA in both groups of patients. During this activation pattern, a mixture of different types of AF in the RA (with type I AF in the lateral wall and types II and III in the posterior and septal walls) was observed. In patients with PAF, type I AF in the lateral wall lasted longer than it did in patients with CAF (6,144 ± 3,688 ms vs. 3,744 ± 3,935 ms, p = 0.032). However, six patients with PAF and nonhomogeneous activation pattern (28%) manifested periods of regularization along the entire RA lasting for a mean of 667 ± 348 ms. In none of the patients with CAF were such periods observed (0%, p = 0.033). Constantly, upon the termination of the regularization period, the earliest activity in the RA emerged from the septal area. The homogeneously irregular pattern (mostly type III AF) was observed in eight patients with CAF (28%) and in none of the patients with PAF (0%, p = 0.007). No type I AF could be observed in this subgroup of patients.

**Endocardial breakthroughs.** Using the freezing function of the software, the propagation maps were analyzed millisecond per millisecond throughout the 10 s interval, and the total number of the breakthroughs was calculated. In the group of patients with PAF, a total of 1,258 endocardial breakthroughs (mean 51 ± 19 per patient) were observed. In the septal region, 1,108 endocardial breakthroughs (88%)

**Table 2.** Distribution of the AF Cycle Lengths in Different Regions of the RA in Patients With PAF and CAF

<table>
<thead>
<tr>
<th>RA Region</th>
<th>Lateral</th>
<th>Posterior</th>
<th>Septal</th>
</tr>
</thead>
<tbody>
<tr>
<td>High RA (ms)</td>
<td>181 ± 21*</td>
<td>159 ± 34</td>
<td>161 ± 36</td>
</tr>
<tr>
<td>Mid-RA (ms)</td>
<td>177 ± 33</td>
<td>155 ± 31</td>
<td>157 ± 33</td>
</tr>
<tr>
<td>Low RA (ms)</td>
<td>175 ± 34†</td>
<td>157 ± 36</td>
<td>155 ± 33</td>
</tr>
</tbody>
</table>

*p < 0.01 for all comparisons between patients with PAF and CAF; †p = 0.07 compared with low posterior region. All other differences between lateral and posterior or septal regions in patients with PAF were significant; †p < 0.05 compared with respective values in the posterior wall. All other differences between lateral and posterior or septal regions in patients with CAF were insignificant.

AF = atrial fibrillation; CAF = chronic atrial fibrillation; PAF = paroxysmal atrial fibrillation; RA = right atrium.

**Table 3.** Percentage of Time During Which Different Types of AF Are Encountered During 10 s of the Processed Data

<table>
<thead>
<tr>
<th>RA Region</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral wall</td>
<td>76 ± 27*</td>
<td>16 ± 17</td>
<td>8 ± 19*</td>
<td>56 ± 41</td>
<td>14 ± 20</td>
<td>30 ± 39</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>42 ± 34*</td>
<td>39 ± 32</td>
<td>19 ± 30*</td>
<td>14 ± 28</td>
<td>27 ± 32</td>
<td>59 ± 41</td>
</tr>
<tr>
<td>Septal wall</td>
<td>27 ± 30</td>
<td>53 ± 36</td>
<td>20 ± 32*</td>
<td>28 ± 38</td>
<td>19 ± 22</td>
<td>53 ± 39</td>
</tr>
</tbody>
</table>

*p < 0.05 compared with respective values in the CAF group.

AF = atrial fibrillation; CAF = chronic atrial fibrillation; PAF = paroxysmal atrial fibrillation; RA = right atrium.
were observed. Of these breakthroughs, 383 (35%) emerged from the high anteroseptal region, 292 (26%) originated from the midseptal region and 433 (39%) emerged from the low posteroseptal region. The remaining breakthroughs originated from the lateral (79 breakthroughs, 6.3%) or the posterior wall (71 breakthroughs, 5.6%) of the RA.

In 20 patients with CAF, 2,078 endocardial breakthroughs were observed (mean 104 \pm 40 breakthrough points per patient, p < 0.001, compared with patients with PAF). In eight patients with homogeneously irregular AF due to the presence of continuous electrical activity throughout the RA, the endocardial breakthrough points could not be observed. Of these, 2,041 breakthroughs (98%) emerged from the septal region (901 [44%] from the high anteroseptal area, 465 [23%] from the midseptal area and 675 [33%] from the low posteroseptal area). In the lateral and posterior walls, 19 and 18 breakthroughs emerged, respectively (1% each).

Mechanism of AF maintenance in the RA. In patients with homogeneously regular activation of the RA, AF was maintained by constant driving of the RA from wave fronts originated from the septum area. Considering the number of breakthroughs observed during 10 s of animated data, it was calculated that, in patients with PAF, the RA was driven by one impulse every 196 ms (range: 143 to 312 ms). In patients with CAF the mean frequency of driving was one impulse every 96 ms (range 69 to 156 ms). No synchronization between septally-located breakthrough points was observed. In patients with a nonhomogeneous activation (Table 4), two types of activation were observed: focal activation from the septal area and re-entrant activation (Fig. 3). Both types of activation were observed throughout the interval of analysis. In patients with PAF, re-entrant activation frequently died out (periods of regularization) but was repeatedly generated by impulses emerging from the septal area. In patients with homogeneously irregular AF (eight patients in the CAF group), only random re-entrant activation was observed (Fig. 4). The septal and other areas of the RA displayed the same activation pattern. Two to five coexisting wave fronts in the RA were observed throughout the recording time.

**Correlation between duration and type of AF.** A strong correlation was found between the duration of AF (in years) and the percentage of time that type III AF occupied the lateral wall of the RA (r = 0.71, p < 0.001). As expected, a negative correlation was found between the duration of AF and the percentage of time during which type I AF was observed in the lateral wall of the RA (r = −0.67, p < 0.001). No other correlation between the duration of AF and other types of AF or AF parameters was found.

**Table 4. Right Atrial Activation Patterns**

<table>
<thead>
<tr>
<th>RA Activation Pattern</th>
<th>PAF</th>
<th>CAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homogeneously regular</td>
<td>4 (16)*</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Nonhomogeneous</td>
<td>21 (84)</td>
<td>18 (65)</td>
</tr>
<tr>
<td>Homogeneously irregular</td>
<td>0 (0)</td>
<td>8 (28)†</td>
</tr>
</tbody>
</table>

*Numbers in brackets percentage; †p = 0.007 compared with the same pattern in the PAF group.

CAF = chronic atrial fibrillation; PAF = paroxysmal atrial fibrillation; RA = right atrium.

![Figure 4](image-url). Random re-entry in a patient with chronic atrial fibrillation. A time window of 100 ms is shown. Spline locations were: splines A and B in the posterior wall, splines C and D in the septal wall, spline E across the tricuspid annulus and splines F, G and H in the lateral wall. At time 0, two wave fronts in the right atrium were observed. After 20 ms, the posterior wave front goes up the posterior wall, whereas the lateral wave front is divided into two wave fronts going up and down the lateral wall. After 40 ms the posterior activation front reaches the high right atrium. The lateral wave fronts move toward the higher and lower areas. A new wave front moves toward the tricuspid annulus (electrode pair G 5/6). At 60 ms, posterior and lateral wave fronts enter the high septal region. At 80 ms, a collision of wave fronts is observed in the high septal region, and a new division is observed in the low lateral region. At 100 ms, one of the lateral wave fronts crossed the isthmus region and entered the septal region, whereas the other wave front re-enters the midlateral wall. Meanwhile, the septal wave front is divided into two wave fronts, heading for collision with the wave front coming through the isthmus and the other one (electrode pair A 3/4) moving toward the midposterior section.
DISCUSSION

Recent advances in the ablative therapy of AF have augmented interest in mapping studies. It is expected that accurate mapping could provide clues that could help identify the suitable targets for ablation therapy. Identification of these areas might help in achieving a high success rate in ablating AF with less extensive and invasive ablation approaches (10,11).

Data from our study demonstrate that AF represents a continuum of diverse electrophysiologic characteristics and mechanisms of maintenance. Coexistence of mechanisms of focal and re-entrant activation, mutually influencing each other, and significant regional differences in three-dimensional activation patterns are key features of this disease.

Differences between PAF and CAF. Our data showed that a considerable difference exists between PAF and CAF in terms of cycle lengths and the activation patterns. The fact that CAF manifested shorter cycle lengths throughout the RA could be explained by atrial remodeling (15), which brings a reduction in refractory periods and, thus, an increase in the number of reactivations per time unit (16). Furthermore, type III AF was observed for a significantly longer time in CAF as compared with PAF in most of the RA regions. The strong correlation found between the duration of AF and the time that type III AF persisted in the lateral wall of the RA, to our knowledge, has not been reported before. This finding might have clinical implications. As demonstrated recently, the presence of complex activity in the lateral wall could be indicative of advanced disease that heralds a limited therapeutic success (10). The lack of correlation between AF duration and AF type in other RA regions could be explained by the fact that, in these regions, activation is complex even in the early stages of the disease.

Endocardial breakthrough points. The septal location of the vast majority of the endocardial breakthrough points and the tendency to cluster at spots coinciding with the major interatrial connections strongly suggest that these breakthroughs represent left atrial impulses entering the RA. Thus, it appears that the left atrium plays a critical role in patients with PAF and at the early stages of the CAF. Several recent studies have stressed the importance of the left atrium as a driving chamber in AF (17–21). Additionally, many recent human studies have reported that the vast majority of the premature beats triggering AF come from the pulmonary veins (22,23). Our study demonstrated that, in patients with CAF, the number of left-to-right impulses is doubled as compared with PAF. Our findings are supported by a recent study in dogs that reported a 25% increase in disorganization of the AF in the left atrium in chronic, as compared with acute, AF (24). In fully developed CAF (eight patients with homogeneously irregular activation pattern), the importance of these “septal focal activations” appeared to be reduced since re-entrant activation seems also to self-perpetuate in the RA.

Mechanism of AF maintenance. Based on the data of our study, we hypothesized that AF in the RA is maintained by two mechanisms. First, there is a mixture of focal and re-entrant activation. This pattern was observed in patients with PAF and in the majority of patients with CAF. Impulses originated locally from the septal area fractionated during propagation and produced re-entrant wavelets in different RA areas. Re-entrant activation was frequently self-extinguished (regularization periods) and reinitiated by impulses of septal origin. Second, atrial fibrillation in the RA also maintained by random re-entry independent of focal activation. At this stage, the whole RA was activated by multiple random re-entrant wavelets (eight patients with homogeneously irregular AF). Due to faster rates of activation, focal activation could not be observed.

Implications of the study. Our data have implications for ablation strategy of the AF. Since, in the early stages of the disease, the focal activation (firing foci in the left atrium or septal breakthroughs in the RA) plays a critical role, ablation of responsible foci could postpone the development of AF. The finding of a strong correlation between the duration of AF and the persistence of complex activity in the lateral wall of the RA warrants an early application of the ablation to avoid this stage. Moreover, finding of persistent type III AF in the lateral wall of the RA could imply a limited therapeutic success (10) or an extensive ablation procedure.

Study limitations. Our study has two limitations. First, our data pertain to the RA only. Thus, an impulse considered as focal in the right side of interatrial septum could be a part of a re-entrant wave front in the left atrium. Some recent studies have demonstrated, however, that similar mechanisms operate also in the left atrium as well (25). Second, although the characteristics of AF are studied with a multiple simultaneous recording system covering the entire RA endocardial surface, the resolution provided by BC is low. This precluded us from reporting detailed activation patterns during AF or analyzing local factors that govern the fibrillation process.

Conclusions. Paroxysmal AF and CAF differ in electrophysiologic characteristics and the mechanisms of maintenance. Paroxysmal AF is perpetuated by septal impulses probably of left atrial origin entering the RA through the interatrial connections. Chronic AF is maintained by a combination of the focal activation and re-entry at earlier stages and by random re-entry at the later stages of the disease.

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REFERENCES