Presence of Left-to-Right Atrial Frequency Gradient in Paroxysmal but Not Persistent Atrial Fibrillation in Humans

Sorin Lazar, MD; Sanjay Dixit, MD; Francis E. Marchlinski, MD; David J. Callans, MD; Edward P. Gerstenfeld, MD

Background—Recent studies have demonstrated spatiotemporal organization in atrial fibrillation (AF), with a left-to-right atrial frequency gradient during AF in isolated sheep hearts. We hypothesized that human AF would also manifest a left-to-right atrial frequency gradient.

Methods and Results—Thirty-one patients aged 56.7 ± 10.5 years with a history of paroxysmal or persistent (>1 month) AF were included. Recordings were made at each pulmonary vein (PV) ostium and simultaneously from the coronary sinus (CS) and posterior right atrium (RA) during AF. Sequential fast Fourier transforms (FFTs) were performed. FFT profiles were analyzed to determine the dominant frequency (DF). There were 18 patients with paroxysmal AF and 13 with persistent AF. In the paroxysmal group, there was a significant left-to-right atrial DF gradient, with DF highest at the PV/atrial (LA) junction, intermediate at the CS, and lowest in the RA (6.2 ± 0.8, 5.5 ± 0.7, and 5.1 ± 0.6 Hz, respectively; P < 0.001). There were no patients in whom DF was greater at the RA than the PV/LA junction. In the persistent group, there was no significant difference between DF recorded from the LA/PV junction, CS, and RA (6.1 ± 0.7, 5.8 ± 0.6, and 5.8 ± 0.6 Hz, respectively; P = NS).

Conclusions—In humans with paroxysmal AF, DFs are highest at the PV/LA junction, intermediate in the CS, and slowest in the posterior RA. These findings agree with animal models that suggest that the posterior LA may play an important role in maintaining paroxysmal AF. The role of the posterior LA in persistent AF requires further study. (Circulation. 2004;110:3181-3186.)

Key Words: atrium ■ fibrillation ■ Fourier analysis

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in humans. Although previously thought to be a “random” arrhythmia, animal and human studies have shown various degrees of spatiotemporal organization during sustained AF.1–6 In humans, Haissaguerre and colleagues7 showed that the onset of AF is frequently triggered by atrial premature beats that originate from sleeves of atrial muscle that extend into the pulmonary veins (PVs). Others have reported focal firing within the PVs during sustained AF.8 However, the role of the left atrium (LA) and PVs in the maintenance of sustained AF in humans is still emerging.

Recently, Mansour and colleagues,9 using optical and electrical mapping techniques, have shown a gradient of frequencies between the left and right atria in the acetylcholine-mediated, pacing-induced model of sustained AF in isolated sheep hearts. In their experiments, the LA demonstrated organized electrical activity with the presence of a dominant frequency (DF), which was consistently higher than those in the recordings from the right atrium (RA). The authors interpreted these findings as suggesting that the LA may be the “driver” of sustained AF.

However, AF induced by burst pacing in isolated Langendorff perfused sheep hearts under high doses of acetylcholine and calcium channel blockers may not be mechanistically similar to clinical AF in humans. The purpose of the present study was to evaluate the DFs of electrical signals from the LA and RA in patients undergoing PV isolation and to determine the presence of a hierarchy of frequencies, if any, between the two. We hypothesized that, similar to the observations in sheep hearts, human AF will demonstrate higher frequencies in the posterior LA/PV junction than in the anterior LA (coronary sinus [CS]) and RA. We also examined whether any difference between RA and LA frequencies was present in patients with persistent AF compared with those with paroxysmal AF.

Methods

Patients with paroxysmal or persistent AF referred for PV isolation at the University of Pennsylvania Health System were included in the study. All patients signed an informed consent. AF was defined as having typical disorganized atrial activity on the 12-lead ECG. Paroxysmal AF was defined as AF episodes that terminated spontaneously and typically lasted <48 hours. For this study, we defined persistent AF as sustained AF that persisted continuously for at least the past month.
before the ablation procedure. These patients had reverted to AF after prior cardioversions, and no further cardioversion attempts were made before they underwent the ablation procedure.

Cardiac rhythm was documented by 12-lead ECG during the initial clinic visit, and all patients were given transtelephonic loop recorders for daily, along with any symptoms, to document the cardiac rhythm. Antiarrhythmic drugs (including β-blockers) were held for 4 days before the procedure and instructed to transmit strips twice weekly before the ablation procedure. In addition, patients requiring isoproterenol for AF induction, the drug was discontinued 2 weeks before the procedure.

Electrophysiology Study

Decapolar catheters (6-mm center-to-center bipole spacing, Irvine Biomedical Inc) were placed in the posterior RA and CS (Figure 1). The RA catheter was positioned with the distal electrode at the RA/superior vena cava junction and was used for RA recordings. The CS catheter was positioned via the right internal jugular vein with the proximal bipole at CS ostium. A decapolar circular mapping catheter (10-pole 20-mm Lasso, 6-mm bipole spacing, Biosense Webster) was introduced into the LA via a transseptal approach for sampling at each PV/LA junction. The CS catheter was positioned with the distal electrode at the RA/superior vena cava/RA junction. CS catheter is positioned with proximal electrode at CS ostium. The other catheter is an ablation catheter located in the LA.

Figure 1. Position of electrodes inside heart. In this left anterior oblique view, circular decapolar mapping catheter has been placed at os of right superior PV. Decapolar catheter in RA is positioned in posterior RA, with distal electrode at superior vena cava/RA junction. CS catheter is positioned with proximal electrode at CS ostium. The other catheter is an ablation catheter located in the LA.

Intracardiac bipolar signals were recorded with the Cardiolab electrophysiologic system (GE Medical Systems) at 1000 Hz/channel with a frequency range from 30 to 500 Hz and analyzed offline. In a subset of patients, longer recordings for up to 2 minutes were made. Intraatrial bipolar signals were recorded with the Cardiolab electrophysiologic system (GE Medical Systems) at 1000 Hz/channel with a frequency range from 30 to 500 Hz and analyzed offline.

Figure 2. A, Examples of signal recorded from circular mapping catheter before (Lasso) and after (filtered) processing. B, FFT profile obtained from filtered recordings. Freq indicates frequency.

Patients presenting to the electrophysiology laboratory in sustained AF had all recordings made immediately after transseptal puncture. Patients with paroxysmal AF who presented to the electrophysiology laboratory in sinus rhythm had AF provoked by either isoproterenol infusion inducing ectopy that triggered sustained AF or atrial pacing. In patients requiring isoproterenol for AF induction, the drug was discontinued and a 5-minute waiting period observed before any intracardiac recordings were made.

Signal Processing

Bipolar signals recorded from the PV ostium include both local LA signals and sharp PV electrograms. These PV electrograms contain high-frequency "spike" components with multiple harmonics that preclude interpretation of frequency spectra. To determine the frequency of local LA activation at the PV ostium and filter out these high-frequency spikes, we used methodology analogous to that described by Botteron and Smith.2 The signals were filtered with high-pass (cutoff 1 Hz) filter, rectified, and then low-pass (cutoff 20 Hz) filtered to remove baseline wander and the high-frequency PV potentials. This leaves a smoothed signal with peaks at the time of local electrical activation (Figure 2). The filter cutoff values chosen were physiologically reasonable, because it is untenable to expect local atrial activation to occur at a rate faster than 20 Hz (50-ms cycle length) in human subjects.

A 2048-point fast Fourier transform (FFT) was performed for each successive 2-second segment recorded from each RA and PV bipolar. Two-second segments were chosen on the basis of preliminary analysis and prior work demonstrating that window lengths <6 seconds were needed to have the resolution necessary to observe varying states of organization of the AF signal.10 Each spectra was examined for the presence of the DF (highest/narrowest peak). The DF from the bipoles was greater than corresponding CS and RA DF. Patients presenting to the electrophysiology laboratory in sustained AF had all recordings made immediately after transseptal puncture. Patients with paroxysmal AF who presented to the electrophysiology laboratory in sinus rhythm had AF provoked by either isoproterenol infusion inducing ectopy that triggered sustained AF or atrial pacing. In patients requiring isoproterenol for AF induction, the drug was discontinued and a 5-minute waiting period observed before any intracardiac recordings were made.

Figure 2. A, Examples of signal recorded from circular mapping catheter before (Lasso) and after (filtered) processing. B, FFT profile obtained from filtered recordings. Freq indicates frequency.

Figure 3. FFT profiles from RA, CS, and each PV from patient with paroxysmal AF. In this case, DF for each PV was greater than corresponding CS and RA DF. LIPV indicates left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior PV; and Freq, frequency.
Statistical Analysis

Comparisons of baseline characteristics between patients with paroxysmal and persistent AF were made with Student’s *t* test or the χ² test as appropriate. Mean DFs for the RA, CS, and LA/PV junction were compared among patients by ANOVA. Pairwise DF comparisons between RA and CS or CS and LA/PV were made after Bonferroni correction for multiple comparisons. Comparison of variance among the 3 groups was performed with the Levene statistic. All statistical analysis was performed with SPSS for Windows, version 11.5. *P*<0.05 was considered significant.

Results

Thirty-one patients with paroxysmal (n=18) or persistent (n=13) AF were included in the study. There was no difference between age (paroxysmal versus persistent 54±10 versus 57±10 years), gender (83% versus 85% male), LA size (4.4±0.5 versus 4.8±0.6 cm), number of prior antiarrhythmic drugs used (2.7±1.2 versus 3.1±1.1 drugs), patients treated with amiodarone (5/18 [23%] versus 4/13 [31%]), or prior history of AF (7.9±7.2 versus 7.0±7.8 years) between groups. One patient in the paroxysmal group had mild to moderate mitral regurgitation; no others had greater than mild mitral regurgitation. No patients had clinical congestive heart failure. Patients with paroxysmal AF tended to have higher left ventricular ejection fraction than those with persistent AF (60±7% versus 50±13%; *P*=0.01). In the paroxysmal AF group, 3 patients developed spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF, whereas 15 patients presented in spontaneous AF before the procedure and presented to the laboratory in sustained AF

Paroxysmal AF Group

In the paroxysmal AF group, adequate signals were available from a total of 69 PVs in 18 patients, and simultaneous recordings were available from the RA in all 18 patients and from the CS in 16 patients. In 2 patients, CS recordings were not used because of a large ventricular and small atrial signal. Overall, there was a significant difference among mean DFs recorded simultaneously from the LA/PV junction, CS, and posterior RA (6.2±0.8, 5.5±0.7, and 5.1±0.6 Hz, respectively; ANOVA *P*<0.001; Figure 4). The mean DF was highest at each PV/LA junction, intermediate in the CS, and lowest in the posterior RA. In a pairwise analysis, DFs recorded from the posterior RA were significantly higher than those recorded from the CS (mean difference 0.5±0.4 Hz, *P*<0.01), those from the CS were significantly greater than those from the posterior RA (mean difference 0.5±0.7 Hz, *P*<0.01), and those from the LA/PV junction were significantly higher than those from the RA (mean difference 1.1±0.7 Hz, range 0.4 to 2.6 Hz; *P*<0.05). There were no significant differences overall among DFs recorded from the 4 PV/LA junction regions (right superior PV 6.2±0.9, right inferior PV 6.0±0.7, left superior PV 6.3±0.9, and left inferior PV 6.2±0.9 Hz; *P*=NS). There were no individual patients in whom the DFs recorded from the RA were greater than those recorded from the PV/LA junction. For the 3 patients who developed spontaneous AF <48 hours before the procedure, the DF (LA/PV versus CS versus RA: 5.9 versus 5.4 versus 5.1 Hz) was not significantly different from others in the paroxysmal group with “provoked” AF (LA/PV versus CS versus RA: 6.2 versus 5.6 versus 5.1 Hz; *P*=NS).

We also compared spatiotemporal DF variability by examining DF variance among all bipoles and 2-second segments among the PV/LA, CS, and RA regions. Although there was no significant difference in variance among the individual PVs in the paroxysmal group, there was a significant difference in variance between the LA/PV, CS, and RA sites (0.35 versus 0.18 versus 0.21 Hz, respectively; *P*<0.01), with the greatest spatiotemporal variability manifested in the LA/PV recordings.

A typical example of recordings from 1 patient with paroxysmal AF is shown in Figure 5. Note that although the mean DF of each PV/LA junction is greater than for the corresponding CS and RA, the magnitude of this difference varies throughout the 20-second recording.

Persistent AF Group

In the persistent AF group, recordings were made from 48 PVs in 13 patients with persistent AF (persistent AF duration range 1 to 24 months). Overall, there was no significant difference between DFs recorded from the LA/PV junction, CS, and RA (6.1±0.7, 5.8±0.6, and 5.8±0.6 Hz, respectively; *P*=NS). The mean paired LA/PV to RA DF difference was 0.2±0.3 Hz (range 0 to 0.7 Hz; *P*=NS). There were no significant differences overall among DFs recorded from the 4 PV/LA junction regions (right superior PV 5.9±0.6, right inferior PV 6.0±0.6, left superior PV 6.2±0.6, and left inferior PV 6.2±0.8 Hz; *P*=NS) in the persistent group. There was also no significant difference in DF variance among the individual PVs or among the LA/PV, CS, and RA sites (0.26 versus 0.30 versus 0.28 Hz, respectively; *P*=NS) in the persistent AF group. A typical example of recordings from 1 patient with persistent AF is shown in Figure 6.
When we compared the paroxysmal and persistent AF groups, the main difference in DF gradient was due to a higher DF recorded at the RA region in the persistent AF group. The RA DF was significantly greater in the persistent AF group compared with the paroxysmal AF group (persistent versus paroxysmal: 5.8 versus 5.1 Hz; \(P<0.001\)), whereas the DFs of the CS (5.8 versus 5.6 Hz, \(P=\text{NS}\)) and PV/LA region (6.1 versus 6.2 Hz, \(P=\text{NS}\)) were not significantly different.

To further validate the averaging of the bipoles in each region together, we performed a sensitivity analysis. We took the lowest

**Figure 5.** Temporal variation of DFs around PVs compared with CS and RA for patient with paroxysmal AF. Top, Mean DF (averaged over all 5 catheter bipoles) of each PV compared with corresponding CS and RA for each recorded 2-second segment. Mean±1 SD bars for 20-second recordings are shown to right for each region. Mean DF of each PV was greater than for corresponding CS and RA; however, magnitude of these differences varied throughout time. Note that for right superior PV (RSPV), 6- to 8-second interval shows increase in DF compared with CS and RA; however, during 10- to 12-second interval, RSPV, CS, and RA DFs are similar. Middle, Corresponding FFTs for these segments. This change in RA vs CS vs PV DF is reflected in raw data (bottom), where one can appreciate increased local activation frequency in PV compared with CS and RA. RIPV indicates right inferior PV; LSPV, left superior PV; LIPV, left inferior PV; and Freq, frequency.

**Figure 6.** Graphs of temporal variation for each PV vs CS vs RA DFs for successive 2-second segments (averaged over 5 bipoles) in patient with persistent AF. There is no significant difference between mean PV and RA DFs for each PV. RSPV indicates right superior PV; RIPV, right inferior PV; LSPV, left superior PV; LIPV, left inferior PV; and Freq, frequency.
Comparison of DFs Recorded Over 2 Minutes

<table>
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<tr>
<th>Patient/Site</th>
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<th>Persistent Group,* Hz</th>
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<tr>
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<td>Last 20 Seconds</td>
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<tr>
<td>RA</td>
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<tr>
<td>RA</td>
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<td>LIPV</td>
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LIPV indicates left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; and RSPV, right superior PV.

*Mean±SD DF averaged over 5 bipoles and 20 seconds in each region.

Longer-Term Recordings

For 6 patients, 3 from the paroxysmal AF group and 3 from the persistent AF group, we recorded longer AF intervals of 2 minutes each to examine how consistent the DF was over time. We compared the mean RA and PV DF during the first 20 seconds with that of the last 20 seconds of 2-minute recordings. There was excellent agreement among recorded RA frequencies (r=0.99) and PV frequencies (r=0.93) during the 2 time periods (Table).

Discussion

Our study has 2 important findings. First, the present study confirms that there is an LA-to-RA frequency gradient during paroxysmal AF in humans. Second, we have found that this LA-to-RA frequency gradient appears to be attenuated in patients with long-lasting (>1 month) persistent AF. These findings agree with animal models that suggest that in induced paroxysmal AF, the posterior LA may serve an important role in maintaining induced AF; however, the lack of an LA-to-RA frequency gradient in persistent AF suggests that this effect may wane with time and that the maintenance of persistent or chronic AF may have less dependence on posterior LA anatomy.

Moe originally hypothesized that the maintenance of AF was due to multiple circulating reentrant wave fronts, and experiments with acenontine demonstrated that AF could persist independently of focal discharge. The landmark finding by Haissaguerre et al that the atrial muscle fascicles in the PVs trigger AF in most patients has concentrated attention on the PVs and posterior LA. Although the crucial role of the posterior LA in initiating AF is now widely accepted, its role in the maintenance of sustained AF is less clear. Studies by Skanes et al and Mansour et al in the acetylcholine-mediated sheep model of AF found that the fastest periodic frequencies occur in the posterior LA. They hypothesized that functional or anatomically based reentrant wave fronts, or rotors, located in the LA were the source of this periodic activity and were the drivers of AF. Morillo et al described faster frequencies in the LA compared with the RA in a canine model of rapid atrial pacing–induced AF. Sih and colleagues also using the canine rapid atrial pacing model, examined differences between acute and persistent AF. They noted an LA-to-RA frequency gradient in both acute and persistent AF, with faster frequencies noted in both the RA and LA during persistent compared with acute AF. However, acute AF in that study was induced by burst atrial pacing in dogs with no history of AF or electrical remodeling.

There have been few studies of RA and LA activation frequencies during sustained AF in humans. Harada et al performed intraoperative mapping in 10 patients with chronic AF. They found evidence of repetitive activation during AF in the LA and concluded that the LA was the driver of AF in the majority of patients. In a recent surgical study, Todd and colleagues performed total surgical isolation of the PVs and posterior LA/PV region in 14 patients with chronic AF. They showed that posterior LA isolation led to isolated AF in the isolated PV region in 4 patients and cured AF in all 14 patients after a mean of 25 months of follow-up, which highlights the importance of the posterior LA/PV region in maintaining AF. Karch and colleagues performed RA basket mapping of induced nonsustained, induced sustained, and persistent AF in humans. They found that the intracardiac RF intervals were slightly shorter in the RA during persistent compared with acute AF; however, persistent AF was defined as lasting only 48 hours.

The source of the hypothesized LA drivers of AF have also been investigated. Arora and colleagues, using optical mapping of the PVs in a canine model, found that sustained reentry within the PVs was feasible in the presence of isoproterenol infusion. A recent study by Kalifa and colleagues also described evidence of sustained reentry at the LA-PV junction in the sheep model during periods of increased intra-atrial pressure. Although Tada and colleagues found evidence of repetitive firing from the PVs during ongoing AF, Ndreppea and colleagues, using basket mapping of the LA, found that the posterior LA, not the PVs, was the driver of AF in these patients.

Although findings from the present study corroborate the observations during AF in animal hearts, the hierarchy of DF during human AF neither proves nor disproves a reentrant mechanism as the driver of AF. Possible causes of this LA-to-RA gradient include (1) intermittent firing (due to abnormal
automaticity or triggered activity) from the PVs during ongoing AF; (2) intermittent functional or anatomic reentry, “anchored” to the PVs, LA appendage, posterior LA, or other LA structure, with fibrillatory conduction to the remainder of the atrium; or 3) shorter refactoriness in the posterior LA than in the anterior LA and RA. We found that the LA-to-RA frequency gradient was not continuously present but varied over time. Skanes and colleagues found in the sheep model that periodic activation at a single site was often transient, lasting from 4 to 14 activations or 3 to 4 seconds. This makes intermittent VF firing, LA reentry, or reentrant wave fronts migrating into and out of the field of view of the bipolar recordings a more likely explanation for the LA-to-RA frequency gradient than simply differences in RA and LA refractoriness.

Interestingly, in patients with long-lasting (>1 month) persistent AF, which has been largely untested in animal models, there appeared to be little overall difference between RA, CS, and PV/LA DFs. This was predominantly due to an increase in the DF of the RA to that of the LA, which led to a loss of the LA-to-RA frequency gradient. The mechanism of this change cannot be determined from the present study; however, it is possible that once AF persists and the atria are remodeled, AF maintenance may be less dependent on posterior LA anatomy and may consist more of the multiwavelet theory of the atria are remodeled, AF maintenance may be less dependent on posterior LA anatomy and may consist more of the multiwavelet theory.

Study Limitations

The present study has several limitations. Because these recordings were performed in humans as part of a prolonged clinical ablation procedure, we could not sample from multiple simultaneous sites and limited the recordings to the areas of greatest interest, namely, the areas around the PVs, CS, and RA free wall. Recordings from other LA and RA sites may have further validated the findings.

In a select group of patients, we found the reproducibility of the FFT measurements to be excellent over a prolonged (2-minute) recording period. This supports the presence of organization and spatiotemporal stability during AF found by others using surface ECG monitoring for up to 24 hours. However, we cannot comment on the reproducibility of FFT profiles over longer recording periods or repeated AF episodes.

The electrode size of the RA and CS catheter was larger than the LA circular mapping catheter to allow for internal cardioversion. Although this may theoretically affect the recorded atrial rate, spectral measures such as DFs have been shown to be robust in the face of varying electrode configuration. Furthermore, the absence of an LA-to-RA frequency gradient in patients with persistent AF suggests that electrode size did not bias the recorded DF.

It is theoretically possible that the DF of a particular catheter bipolar might reflect overlapping activation from 2 adjacent wave fronts rather than activation of a single wave front. Although this might cause a transient increase or doubling of the recorded DF, the presence of a consistent LA-to-RA frequency gradient persisting across multiple time segments and patients makes this an unlikely explanation of our findings.

Conclusions

In humans with clinical paroxysmal AF, DFs are highest at the PV/LA junction, intermediate in the CS, and slowest in the posterior RA. This LA-to-RA frequency difference appears to be attenuated in patients with long-lasting (>1 month) persistent AF. These findings are consistent with observations made in animal models that suggest that in paroxysmal AF, the posterior LA may serve an important role in maintaining AF. The role of the posterior LA in maintaining persistent AF requires further study.

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References

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