

Characterization of Foci and Breakthrough Sites During Persistent and Long-Standing Persistent Atrial Fibrillation in Patients: Studies Using High-Density (510–512 Electrodes) Batrial Epicardial Mapping

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Background—We previously demonstrated that persistent and long-standing persistent atrial fibrillation is maintained by activation emanating from foci and breakthrough sites of different cycle lengths (CLs). The purpose of this study was to characterize the behavior of focal and nonrandom breakthrough activation identified during high-density mapping of atrial fibrillation in these patients.

Methods and Results—During open heart surgery, we recorded activation from both atria simultaneously using 510 to 512 epicardial electrodes along with ECG lead II in 12 patients with persistent and long-standing persistent atrial fibrillation. For each patient, analysis of 32 consecutive seconds of activation from identified focal (sustained and/or intermittent) and nonrandom breakthrough sites was performed. Multiple foci (sustained and/or intermittent) of different CLs were present in both atria in 11 of 12 patients; 8 foci were sustained, and 22 were intermittent. Temporal CL behavior of sustained foci varied over time (≤ 20 ms of the mean CL). For intermittent foci, no activation periods were due to a spontaneous pause (18 of 22) or activation of the focus by another wave front (11 of 22). All patients had breakthrough activation. Seven patients had 12 nonrandom breakthrough sites. Periods of no breakthrough activation were caused by a spontaneous pause (6 of 12 patients) or activation from another wave front (4 of 12) or were uncertain (5 of 12). Focal and nonrandom breakthrough activation sometimes produced repetitive “wannabe” (incomplete) reentry in 6 of 12 patients.

Conclusions—During persistent and long-standing persistent atrial fibrillation, sustained foci manifested variable CLs. Spontaneous pauses or activation from other wave fronts explained the intermittency of foci and nonrandom breakthrough. Focal and nonrandom breakthrough activation occasionally produced wannabe reentry. (*J Am Heart Assoc.* 2017;6:e005274. DOI: 10.1161/JAHA.116.005274.)

Key Words: arrhythmia (mechanisms) • atrial fibrillation • breakthrough sites • cardiac mapping • foci

Over the years, many atrial activation mapping studies in patients with atrial fibrillation (AF) have described the presence of foci suggestive of or thought to act as drivers maintaining AF.^{1–11} However, these studies did not further characterize the putative focal driver or drivers. Recently, in patients with persistent and long-standing persistent (LSP) AF,

we demonstrated that atrial activation results from wave fronts emanating from multiple focal (sustained and/or intermittent) and breakthrough sites of different cycle lengths (CLs).¹¹ Atrial activation from these sites during the AF resulted largely in collision and fusion of wave fronts at continuously varying sites, the latter because of the different CLs of the activation wave fronts. Thus, the study supported the likelihood that focal and nonrandom breakthrough sites act as drivers. No reentry was seen. The purpose of this study was to characterize further the sustained and intermittent focal and nonrandom breakthrough activation identified during high-density mapping of AF in patients with persistent and LSP AF.

Methods

The research protocol was approved by the institutional review board at University Hospitals Cleveland Medical Center. Twelve patients with persistent and LSP AF (1 month to 9 years in duration) were studied during open heart surgery

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Table 1. Patient Characteristics

Patient No.	Age	Sex	AF Duration	Valvular Disease	CAD
1	80	F	3 months	MR, TR	–
2	60	M	>1 year	MR	–
3	57	M	>1 year	MS	–
4	68	F	1 month	MR	–
5	67	M	1 month	MR	–
6	62	M	1 month	MR	–
7	79	F	>1 year	TR	–
8	78	M	9 years	AS	+
9	70	M	9 years	AS, TR	–
10	70	F	8.5 years	AS	–
11	80	F	2.5 years	TR	–
12	63	M	>1 year	MR, TR	+

– indicates absent; +, present; AS, aortic stenosis; CAD, coronary artery disease; F, female; M, male; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation.

(Table 1). All patients gave written informed consent before their surgery.

Data Acquisition

Using standard techniques described previously,¹¹ atrial epicardial mapping studies were performed during open heart surgery in patients with persistent and LSP AF after the heart was exposed using standard surgical procedures. Studies were performed on a beating heart at normothermia either prior to or during cardiopulmonary bypass. All patients underwent a transesophageal echocardiography study prior to mapping the AF to screen for the presence of a left atrial thrombus. If the latter was found, the patient did not undergo mapping. Three electrode arrays with a total of 510 electrodes (first 4 patients) or 512 electrodes (subsequent 8 patients) covering a total area of 92.85 cm² were placed on the atrial epicardial surface of both atria for simultaneous recording, as described previously.¹¹ The interelectrode distance between each bipolar electrode pair was 1.2 or 1.5 mm, respectively. Atrial electrograms (AEGs) from 510 to 512 electrodes (255–256 bipolar pairs) along with ECG lead II were simultaneously recorded for 1 to 5 minutes during persistent and LSP AF. Data were digitally recorded and processed with an Active Two system (BioSemi). All AEGs were sampled at 1024 Hz and digitized at 24 bits. Data were transferred in real time and stored on a laptop computer for further analysis (CEPAS; Cuoretech Pty Ltd).

Activation Sequence Analysis

Sequential activation maps of persistent and LSP AF were constructed for a period of 32 consecutive seconds per

patient using a custom-designed algorithm that has been previously described in detail.^{11,12} All isochronal lines were determined by activation times from recorded bipolar AEGs. Once the activation sequence maps were constructed, the earliest sites of activation compared with their neighbors were identified, and the morphology of the unipolar AEGs were characterized at these sites. All bipolar AEGs were subjected to CL variation and dominant frequency (DF) analyses to detect mean CL, standard deviation, and DF.¹³ Data are presented as the mean CL±SD because 1000/DF is equivalent to the mean CL.

Definitions

As described previously,¹¹ a *focus* was defined as a site (1) that had the earliest activation compared with its neighboring sites, (2) that manifested a QS morphology in the unipolar AEG, and (3) from which wave fronts emanated. A *sustained focus* was defined as a focus from which wave fronts emanated continuously during the 32 seconds of analysis. An *intermittent focus* was defined as a focus that was not continuous during 32 seconds of analysis. A *breakthrough activation site* was defined as a site (1) that had the earliest activation compared with its neighbors, (2) that manifested a unipolar AEG morphology with an initial r or R wave, and (3) from which wave fronts emanated. *Nonrandom breakthrough activation* was defined as a breakthrough activation site (1) that recurred at the same site, (2) that had at least 1 episode in which there were ≥3 consecutive breakthrough activations, and (3) from which wave fronts emanated. All other breakthrough activation sites were considered random. *Reentry* was defined as circus movement with head–tail interaction. “Wannabe” reentry was defined as a wave front that circulated around a functional line of block that wanted to become (ie, “wannabe”) a reentrant circuit but could not complete the revolution because it either collided with a wave front from a focal or breakthrough site or encountered a line of block.¹²

Characteristics of Focal and Breakthrough Epicardial Atrial Activation

For sustained focal sites, the mean CL and DF of bipolar AEG recordings during consecutive 4-second segments were measured using CL variability detection and DF analyses. To characterize the periods of time when intermittent focal and nonrandom breakthrough sites ceased to initiate a wave front, as demonstrated in the activation sequence maps, both the previous CL and that noninitiating CL at the sites of focal and/or nonrandom breakthrough were measured and compared. When the noninitiating CL interval was <10% of the site’s previous CL, it was characterized as an invading

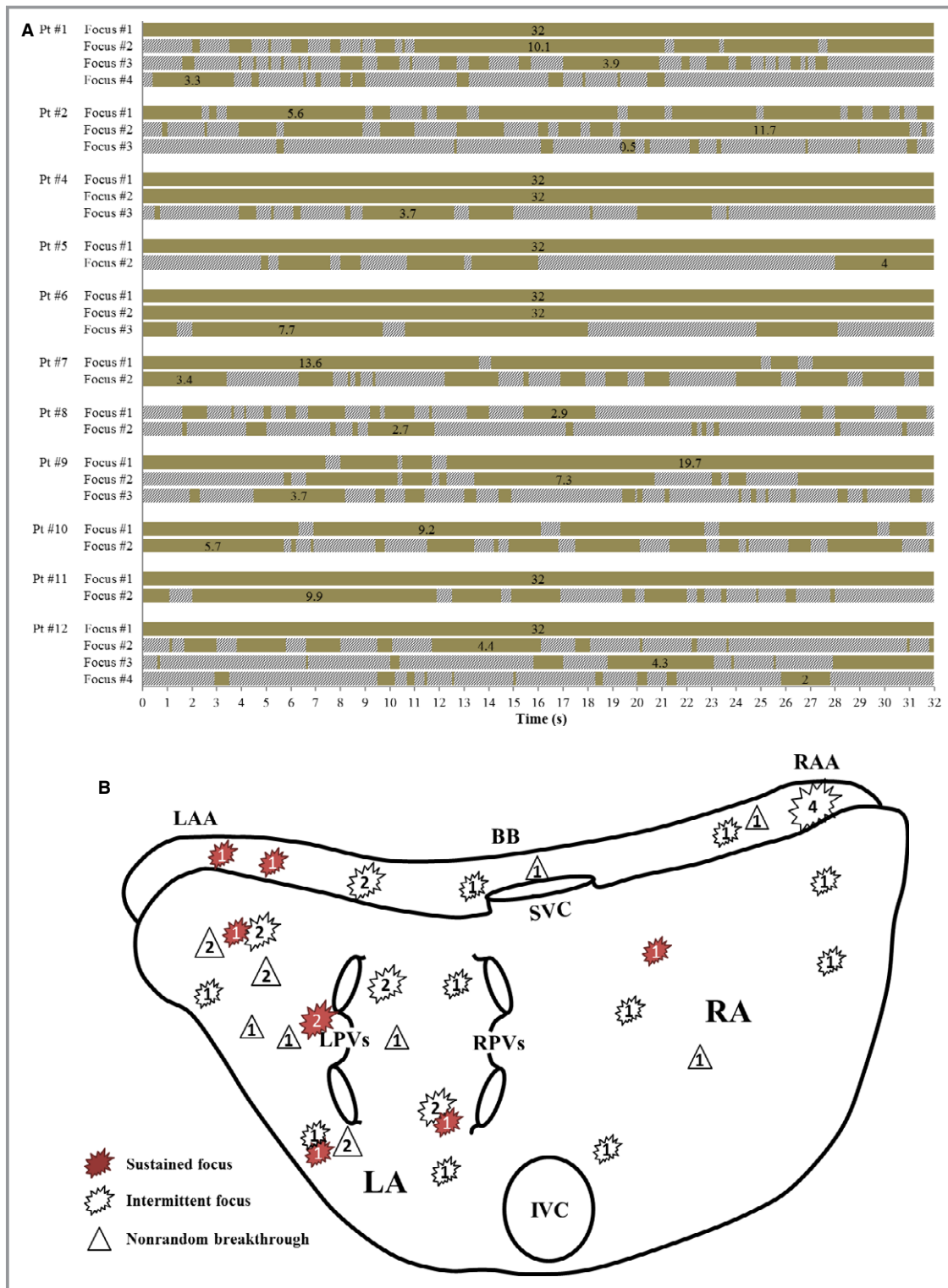


Figure 1. A, Temporal behavior of focal QS activation during the 32 seconds of analysis from 11 patients. The time bar illustrates the time course of active (solid) and inactive (hatched) focal QS activation. The maximum duration of focal QS activation per site is indicated by number. B, Diagrammatic representation of the atria. Each burst simply denotes the location of a focus on the atria (closed burst, sustained focus; open burst, intermittent focus). Delta simply denotes the location of a nonrandom breakthrough site on the atria. Numbers indicate the number of patients in which focal QS activation and nonrandom breakthrough activation were identified at that site. BB indicates Bachmann’s bundle; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LPVs, left pulmonary veins; Pt, patient; RA, right atrium; RAA, right atrial appendage; RPVs, right pulmonary veins; SVC, superior vena cava.

Table 2. Summary of Intermittent Foci and Nonrandom Breakthrough Activation During Persistent and long-standing persistent atrial fibrillation

Patient	Intermittent Foci				Nonrandom Breakthrough			
	No.	Location	Disappearance	Mean CL±SD (ms) at Longest Duration	No.	Location	Disappearance	Mean CL±SD (ms) at Longest Duration
1	3	RAA btwn PV Left BB	SP or IW SP uncertain	178±11 170±12 179±12
2	3	Left BB RAA LA	SP SP or IW SP	184±16 196±17 172±4	2	LA btwn PV	Uncertain Uncertain	184±18 172±4
3	3	LA LA LA	SP SP or IW SP	175±9 177±14 161±11
4	1	RAA	SP	171±12	1	RA	SP	151±26
5	1	RA	SP	164±17	2	Right BB Right BB	Uncertain Uncertain	173±15 139±21
6	1	Right BB	SP or IW	177±14
7	2	LA btwn PV	SP SP or IW	188±9 203±13
8	2	Btwn PV LA	SP or IW SP or IW	211±33 169±9	1	LA	SP or IW	187±21
9	3	Left BB btwn PV LA	IW SP SP or IW	174±8 182±4 145±12	1	LA	SP or IW	153±24
10	2	LA RAA	SP IW	179±9 201±12
11	1	Btwn PV	IW	185±14
12	3	RA RA RA	SP or IW SP SP	143±9 159±12 149±8	2	LA btwn PV	IW Uncertain	177±13 136±1
Mean	2±0.9	176±18	1.7±0.8	165±17

... indicates none; BB, Bachmann's bundle; btwn, between; CL, cycle length; IW, invading wave front; LA, left atrium; PV, pulmonary vein; RA, right atrium; RAA, right atrial appendage; SD, standard deviation; SP, spontaneous pause.

activation wave front. When the CL interval was >10% of the previous CL, it was characterized as a spontaneous pause with activation from another wave front.

Statistical Analysis

Data were presented as the mean±SD using Minitab (Minitab Inc).

Results

Overall Findings

During persistent and LSP AF, multiple foci (sustained, range 1–2; intermittent, range 1–3) of different CLs were present in both atria in 11 of 12 patients. Figure 1A shows summary data for the temporal behavior of all sustained

and intermittent foci during the 32 seconds of analysis from 11 patients. A total of 8 sustained foci (mean CL 170±19 ms; range 142–200 ms; duration 32 seconds) and 22 intermittent foci (mean CL 176±18 ms; range 143–211 ms) were identified in 11 patients. Temporal CL behavior of all 8 sustained foci varied over time. In consecutive 4-second segments in 6 of 8 foci, there was a maximum consecutive mean CL change of >10 ms. Regarding the temporal behavior of intermittent foci, the duration of individual episodes of intermittent focal activation was variable. Periods of no focal QS activation were caused by either a spontaneous pause (18 of 22 foci) or early activation of the focal site by wave fronts originating from another focus or a breakthrough site (11 of 22 foci) (Table 2). Eight intermittent foci exhibited both a spontaneous pause and activation from an invading wave front during the 32 seconds of analysis.

Breakthrough activation sites were found in all patients, with only 1 patient demonstrating breakthrough sites. A total of 12 nonrandom breakthrough sites (mean CL 165 ± 17 ms; range 136–187 ms) were identified in 7 patients. The disappearance of nonrandom breakthrough sites was due to a spontaneous pause (6 of 12 patients) or activation of the nonrandom breakthrough site by another wave front (4 of 12 patients) (Table 2). The locations of all foci and nonrandom breakthrough sites are summarized in Figure 1B and Table 2. Focal and nonrandom breakthrough sites were found in both atria but were located predominantly in the left atrium.

No epicardial macro reentry was demonstrated in any patient studied; however, wannabe reentry was present in all patients. In 6 of 12 patients, some episodes were generated by focal or nonrandom breakthrough activation. The longest duration per patient of wannabe reentry generated by focal or nonrandom breakthrough activation ranged from 0.4 to 9.2 seconds.

Temporal Characterization of Focal and Nonrandom Breakthrough Activation

Temporal behavior of sustained foci

Figure 2 shows the temporal behavior of consecutive mean CLs in 4-second segments during the 32 seconds of recording for the 8 sustained foci. The mean CL of each consecutive 4-second segment varied over time. The maximum change in consecutive mean CLs for any site was 20 ms. The average mean CL for a site was calculated from the 8 means making up the 32 seconds of recording. The average change in the mean of the mean CL for all sites was 15.5 ms (range

8–20 ms). Six sustained foci had at least 1 consecutive mean CL change of >10 ms, whereas the other 2 had consecutive mean CL changes of <10 ms. Thus, the sustained foci were not characterized by a constant mean CL but rather by a mean CL that fluctuated, on average, 15.5 ms but never >20 ms.

Figure 3 is a representative example of the temporal behavior of the mean CL of a sustained focus (patient 4, sustained focus 2 in Figure 2). Figure 3A shows 32 seconds of a bipolar recording from this sustained focal site. In the right panel, DFs of the bipolar AEGs are shown for the duration of the displayed AEG recording to the left. The shaded areas in the top bipolar AEG panel show the location and duration of each of the 4-second recordings seen in the 3 panels below. Figure 3B through 3D show lead II and a bipolar AEG from the sustained focus, along with its corresponding unipolar components (U1 and U2), demonstrating a QS morphology in each unipolar AEG. Figure 3B shows the recording from 4 to 8 seconds (DF 6 Hz, mean CL 167 ms). Figure 3C shows the recording from 12 to 16 seconds (DF 5.5 Hz, mean CL 175 ms). Figure 3D shows the recording from 24 to 28 seconds (DF 5.3 Hz, mean CL 187 ms). Overall, the mean CL of this sustained focus varied over time from 167 to 187 ms.

Temporal behavior of intermittent foci and nonrandom breakthrough sites

The intermittent disappearance of focal and nonrandom breakthrough activation was caused by either an invading wave front from another site (focal or breakthrough) or a spontaneous pause. Figure 4 is a representative example from patient 6 of the disappearance of an intermittent focus,

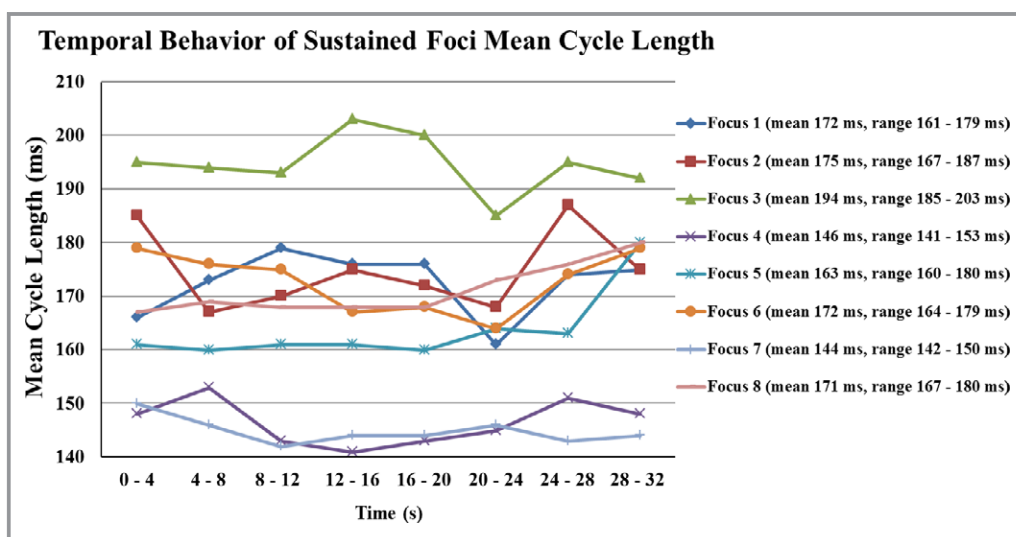


Figure 2. The temporal behavior of 8 sustained foci. Each point denotes the mean cycle length of 4-second segments (x-axis) during the 32 seconds of recording.

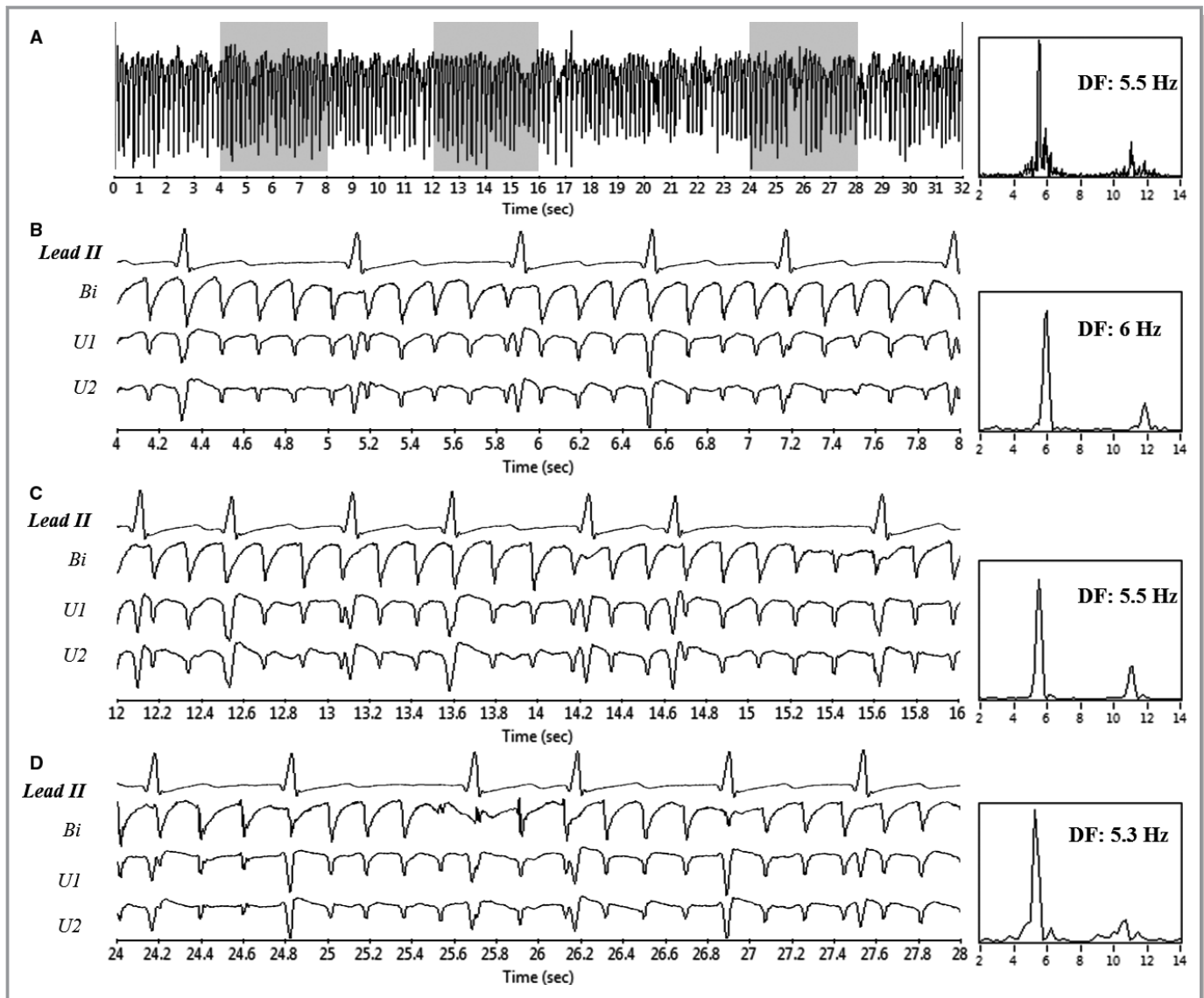


Figure 3. A representative example (patient 4) of the temporal behavior of a sustained focus. The power spectrum is shown to the right of the traces with the dominant frequency (DF) for the DF analysis during the recording shown. A, A bipolar recording of 32 seconds from a sustained focal site. B through D, Recording of lead II and a bipolar atrial electrogram with unipolar components (U1 and U2): 4 to 8 seconds (B), 12 to 16 seconds (C), and 24 to 28 seconds (D).

caused in this case by an invading wave front originating from a sustained focus. The top panel of Figure 4 shows the activation sequence maps of 10 consecutive beats during AF recorded from the Bachmann’s bundle electrode array, which covers the left atrial appendage, Bachmann’s bundle, and the right atrial appendage (RAA). A 10-ms isochronal color bar from 0 to 220 ms is shown at right. The bottom panel of Figure 4 shows selected bipolar AEGs (sites a through g) recorded simultaneously during AF from 2 foci (sites b and f) and 5 nearby sites (a, c, d, e, and g). As seen in the top panel, because the CL of sustained focal site b is shorter than that of intermittent focal site f, the wave front from sustained focal site b progressively invades the area previously activated by

the site f wave front. The site b wave front eventually prevented initiation of activation from intermittent focal site f for several consecutive activation windows. This is clearly demonstrated in the 10 consecutive activation sequence panels. In activation sequence 1 (Figure 4, top left panel), 1 wave front from sustained focal site b propagates toward the left atrial appendage, where it collides with another wave front. It also propagates toward the RAA, where it collides with a wave front from intermittent focal site f near site d. In activation sequence 2, the wave front from sustained focal site b propagates farther toward the RAA and collides with the wave front from intermittent focal site f near site e. In activation sequence 3, the wave front from sustained focal

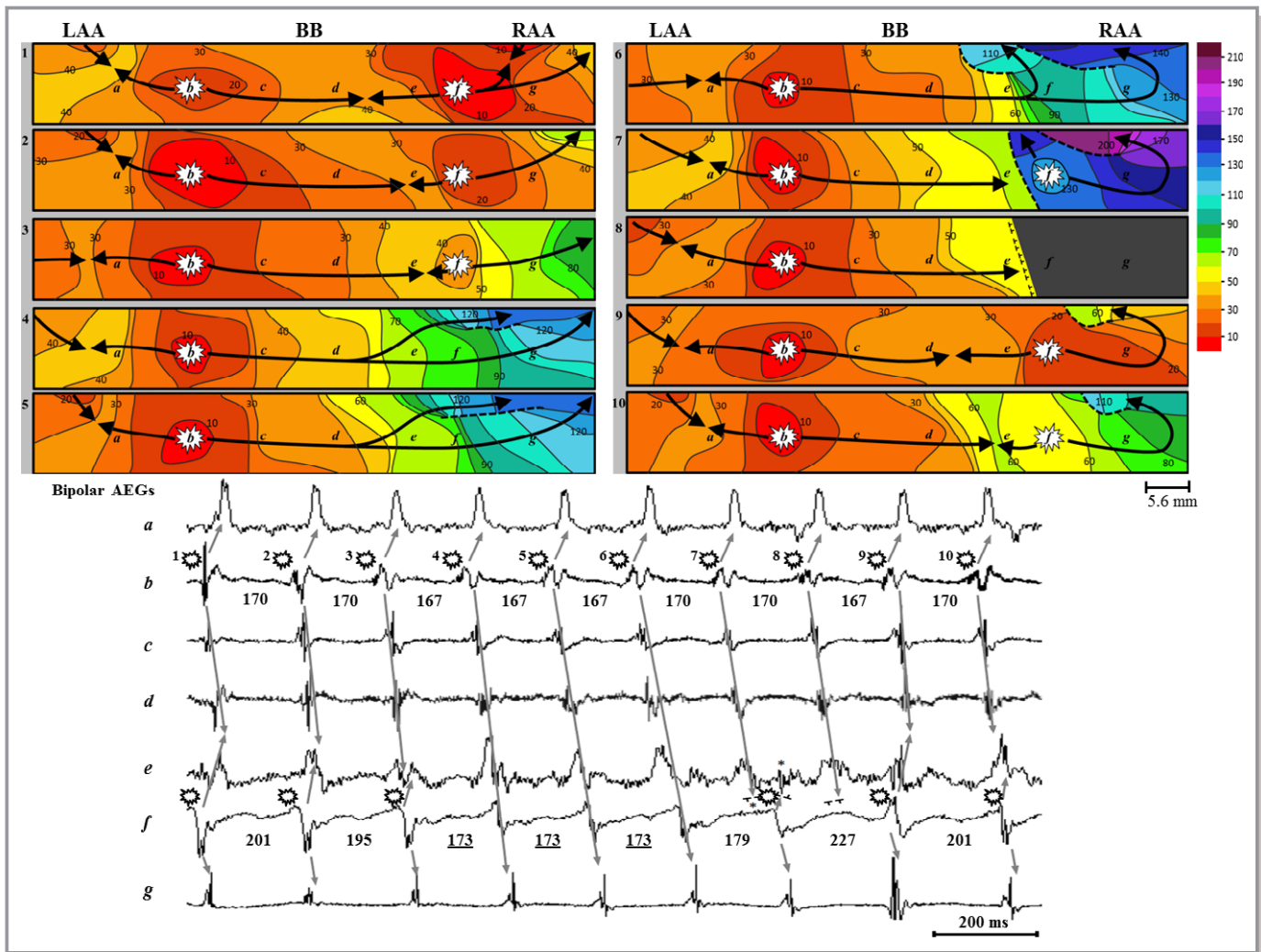


Figure 4. A representative example (patient 6) of the temporal behavior of an intermittent focus: disappearance caused by an invading wave front. Top panel, Activation sequence maps of 10 consecutive beats during AF recorded from the LAA, BB, and RAA, with the locations of recording sites a through g. A 10-ms isochronal color bar is shown at right. Foci are denoted by burst symbols. The black arrows indicate activation wave fronts. Black areas indicate nonactivation. Dashed lines indicate a functional line of block. T-bars indicate block due to effective refractory period (ERP). Bottom panel, Bipolar AEGs from selected sites a through g. Numbers 1 to 10 above site b correspond to the activation sequence maps. Focal activations are denoted by burst symbols. AEG indicates atrial electrogram; BB, Bachmann’s bundle; LAA, left atrial appendage; RAA, right atrial appendage.

site b propagates even farther toward the RAA and collides with the wave front from intermittent focal site f between sites e and f. Finally, in activation sequence 4, the wave front emanating from sustained focal site b completely invades the area of intermittent focal site f, thereby preventing initiation of activation from that site. Sustained focal activation from site b then dominates activation throughout activation sequence panels 4 to 6 (Figure 4). During activation sequences 4, 5 and 6, a functional line of block (Figure 4, dashed line) and areas of slow conduction (crowding of isochrones) develop. Then, in activation sequence 7, the wave front from sustained focal site b blocks in an area of previous slow conduction, allowing intermittent focal site f to reappear. In activation sequence 8, the wave front from sustained focal site b blocks, presumably,

in fact, almost surely, due to refractoriness from the prior activation from site f. In activation sequence 9, the wave front from sustained focal site b once again collides with the wave front from intermittent focal site f, again near site d. In activation sequence 10, the prior activation pattern begins to repeat itself. In addition, wannabe reentry is generated from focal QS activation during activation sequences 6 to 10 in the RAA (note the pivoting wave front around a function line of block in these activation sequences) (Figure 4).

Selected AEGs are shown in the bottom panel of Figure 4, along with burst symbols and propagation arrows illustrating the above description. There were sustained 170-ms CLs at focal site b and intermittent 200 ms CLs at focal site f; however, when sustained focal site b invaded intermittent

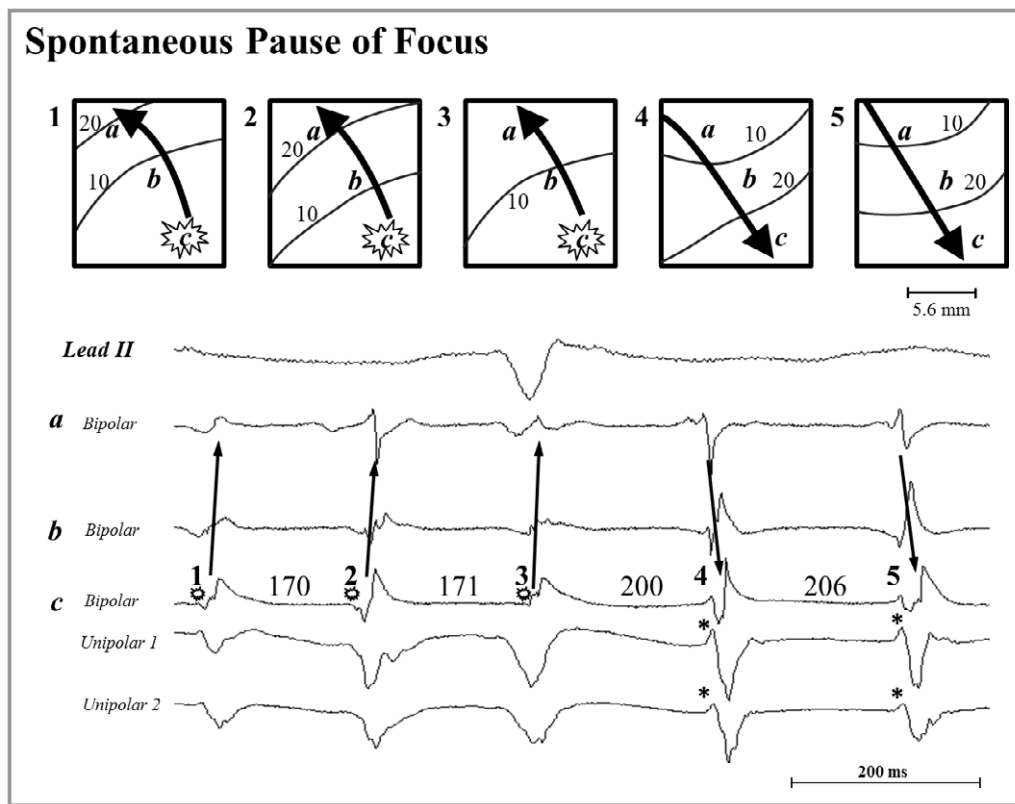


Figure 5. A representative example (patient 4) of the temporal behavior of an intermittent focus: disappearance due to a spontaneous pause. Top panel, A magnified area of the activation sequence maps of 5 consecutive beats during AF. Bottom panel, Selected bipolar atrial electrograms (a through c), unipolar components of focal site c and lead II recorded simultaneously during AF. Numbers 1 to 5 above site c correspond to the activation sequence maps. Focal activations are denoted by burst symbols. *rS morphology.

focal site f, the 3 CLs recorded at site f (underlined CLs at the bottom of Figure 4) followed the CLs of sustained focal site b (<10% of previous CL). When focal activation of site f reappeared, it returned to its intrinsic, longer CL.

Figure 5 is a representative example in patient 4 of the disappearance of a focus due to a spontaneous pause. The top panel shows a magnified section of the activation sequence maps for 5 consecutive beats during AF. The bottom panel shows bipolar AEGs at selected sites a, b, and c located in the right atrium showing a spontaneous pause of focal activation at site c, thereby allowing activation of site c by another wave front. The bipolar and both unipolar (U1 and U2) AEGs from focal site c are shown. Activations 1, 2, and 3 show that a wave front from focal site c propagated to site a at a CL of 171 ms. The unipolar AEGs from focal site c demonstrate a QS morphology, indicating that the wave front was emanating from this site. After a spontaneous pause at site c, denoted by a longer CL (>10% of previous CL), activations 3 and 4 show an invading wave front propagating in the opposite direction from site a to site c. The unipolar AEGs from site c now demonstrate an rS morphology (denoted by an asterisk in Figure 5), indicating

that the site was passively activated by another wave front from a different direction, as demonstrated in the activation sequence maps (activations 4 and 5).

Spatial Characterization of Focal and Nonrandom Breakthrough Activation

The wave fronts generated from focal and breakthrough sites largely produced collision and merging with other wave fronts at continuously varying sites.¹¹ This nonuniform conduction sometimes produced areas of slow conduction and functional lines of block. Occasionally, as a result, activation from a focal or nonrandom breakthrough site generated a pivoting wave front around a functional line of block, producing wannabe reentry. In Figure 4, when a functional line of block (dashed line) was present in the RAA (activation sequences 6, 7, 9, and 10), wannabe reentry was seen to develop from activation from a focal QS site. Figure 6 shows how a repetitive wannabe reentry pattern developed over a period of ≈10 seconds during activation from a focus in the left atrium (patient 11). The top panel of Figure 6 shows a detailed area of activation sequence maps during 7 AF activations. The first

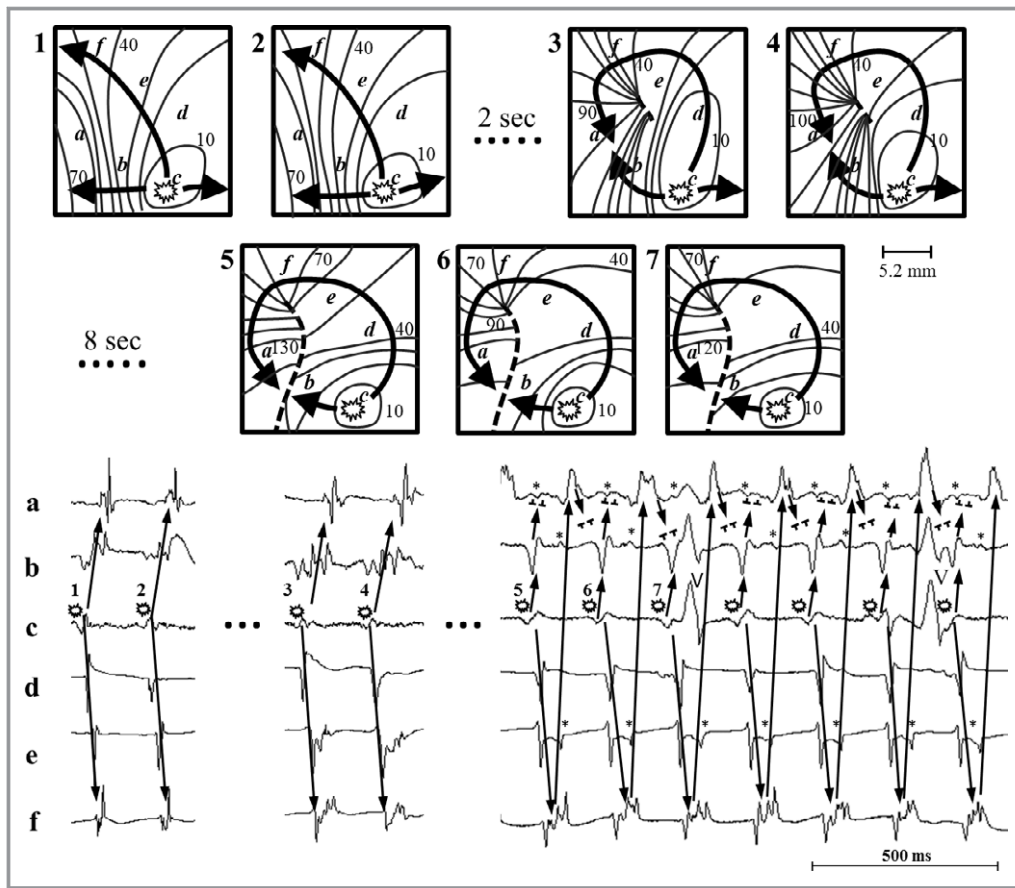


Figure 6. A representative example (patient 11) of the spatial characterization of focal activation: formation of wannabe reentry. Top panel, A magnified area of the activation sequence maps during atrial fibrillation recorded from the left atrium with the locations of recording sites a through f. Focal activation is denoted by burst symbols. Black arrows indicate activation wave fronts. Dashed line indicates a functional line of block. Bottom panel, Bipolar atrial electrograms from sites a through f. Numbers 1 to 7 above site c correspond to the activation sequence maps. Focal activations are denoted by burst symbols. *Double potential. T-bars denote conduction block. Time lapse is denoted by dots.

2 consecutive beats demonstrate the presence of slow conduction, denoted by crowding of isochrones. Then, as the slow conduction increases over the next 2 seconds (not shown), the following 2 consecutive activation maps show further slowing of conduction (denoted by further crowding of isochrones). The latter is associated with the formation of a short functional line of block and with curvature of 2 different wave fronts originating from the same focus, which shortly results in their collision. Then, after 8 seconds, the next consecutive activation maps show 3 consecutive beats of wannabe reentry cycles that occur around a functional line of block that formed in the area of slow conduction.

The bottom panel of Figure 6 shows selected bipolar AEGs recorded simultaneously from a focal site (c) and 5 nearby sites (a, b, d–f) that are in or near an area of slow conduction (activation sequences 1 and 2) and a functional line of block (dashed lines, activation sequence 3–7) during AF. The wave front generated from repetitive activation emanating from focal

site c propagated in a radial-type activation pattern but with different conduction velocities, denoted by different intervals between isochrones. After a functional line of block developed, repetitive wannabe reentrant activation formed. This occurred when propagation from the focus traveling along one side of the functional line of block pivoted around one end but failed to complete the rotation when it collided with the functional line of block. In addition, wannabe reentry sometimes developed from activation from a nonrandom breakthrough site (Figure 7). Focal and nonrandom breakthrough activations generating repetitive wannabe reentry were present in 6 of 12 patients.

Discussion

Major Findings

Using high-density simultaneous biatrial epicardial mapping in patients with persistent and LSP AF, we characterized focal

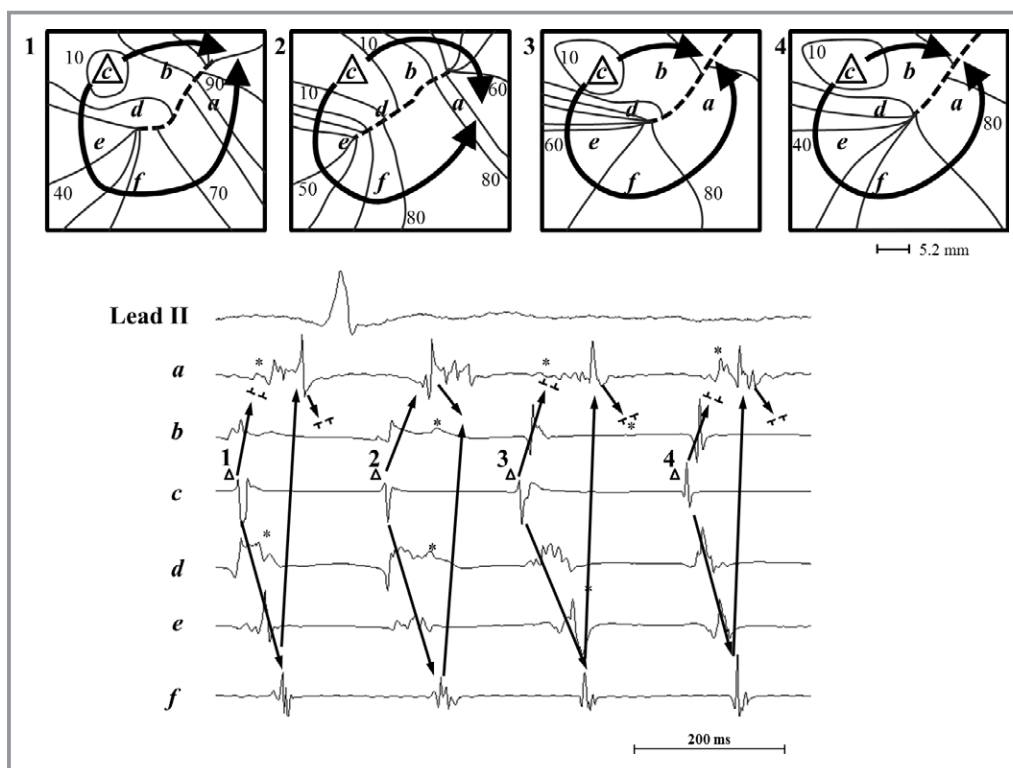


Figure 7. A representative example (patient 3) of a repetitive nonrandom breakthrough activation generating repetitive wannabe reentry. Top panel, A magnified area of the activation maps of 4 consecutive beats during atrial fibrillation (AF) recorded from the left atrium with the locations of recording sites (a through f). Nonrandom breakthrough activation is denoted by the delta symbol (Δ). Bottom panel, Selected bipolar atrial electrograms recorded simultaneously during AF from a nonrandom breakthrough (site c) and 5 nearby sites (a, b, d, through f) around a functional line of block (dashed line). *Double potential. T-bars denote conduction block.

(sustained and/or intermittent) and nonrandom breakthrough activation during 32 seconds of classical activation sequence maps in 12 patients. Our results demonstrated in these patients (1) that atrial activation was caused by wave fronts emanating from foci and/or breakthrough sites of different but short CLs, (2) that the mean CL of sustained foci varied over time, (3) that the disappearance of both intermittent focal and nonrandom breakthrough activation was caused by either a spontaneous pause or early activation of the site by another wave front, and (4) that focal and breakthrough activation occasionally generated wannabe reentry.

Previous Mapping Studies During Persistent and LSP AF in Patients

Using endocardial catheter mapping in paroxysmal and/or persistent AF, sustained focal sources have been identified by QS morphology activation⁹ or periodically organized activation.^{7,10} In addition, sustained and intermittent focal sources were found in patients with paroxysmal and persistent AF.⁵ In several epicardial mapping studies in patients with persistent

and LSP AF, focal activation was identified in the left and/or right atrium,¹⁻⁴ and repetitive activation patterns were found in the left atrium,¹⁴⁻¹⁷ suggestive of a driver mechanism. In addition, high-density sequential area epicardial mapping^{18,19} in patients with LSP AF found random and intermittent focal wave fronts, but no sustained focal activation was found. A recent endoepicardial right atrial mapping study in patients with AF found that intermittent focal wave fronts (35% focal and 65% breakthrough) frequently appeared in the endocardium and epicardium.²⁰ A noninvasive mapping study⁶ showed that in paroxysmal and persistent AF patients, simultaneous intermittent focal activation from areas near the pulmonary veins (69% of patients) and from nonpulmonary vein areas (62% of patients) was present. Recently, in a noninvasive mapping study in patients with persistent and LSP AF,⁸ intermittent QS focal activation was identified in both atria.

Our finding of the presence of sustained and intermittent foci and breakthrough activation during AF concurs, in whole or in part, with the findings of others; however, most previous studies recorded only bipolar AEGs, recorded for short

periods, and were not well characterized. Moreover, the recording resolution of most studies was modest at best. Without the determination of unipolar QS morphology, we can suggest only that repetitive focal wave fronts identified in other studies could correspond to our finding of atrial activation from focal and/or nonrandom breakthrough sites. Furthermore, wannabe reentry may explain why some low-resolution endocardial mapping data have been interpreted as showing reentry and why ablation of the putative “rotor” core may be efficacious, as perhaps focal and/or breakthrough sites were actually ablated. Finally, the focal and breakthrough-initiated wannabe reentry that we described has some similarity to a noninvasive mapping study⁸ in which focal activation initiated reentry.

Implications

The efficacy of both catheter and surgical ablation of persistent and LSP AF has been suboptimal, mainly because of the complexity of atrial activation during AF and the absence of clear targets. Understanding the mechanism presents opportunities for new approaches to the treatment of persistent and LSP AF, especially for ablation. Study of the mechanisms maintaining AF has been limited by the difficulty in mapping this complex arrhythmia and by questions about recording techniques and analysis algorithms used.^{21–26} Our data describe a new paradigm for the mechanism that maintains persistent and LSP AF, to which we have added the temporal and spatial behavior of the focal and nonrandom breakthrough sites from which the wave fronts emanate to produce AF. Finally, the data from our study offer the potential for improving current ablation approaches to treating persistent and LSP AF by targeted ablation of focal and nonrandom breakthrough sites.

Study Limitation

AEGs from the endocardium and the atrial septum were not obtained, precluding identification and characterization of the source of the epicardial breakthroughs and perhaps even the focal QS activations. We did not record from the pulmonary veins, but our left atrium and Bachmann’s bundle recording arrays basically surround the pulmonary veins. A unipolar QS electrogram might not identify the exact location of a focus because the impulse may originate from an area close by from which conduction does not generate enough of a signal from the atrial myocardium to be appreciated in the unipolar AEG. The same may also apply to activation from a subepicardial reentrant circuit. Although we characterized some foci as continuous over the 32 seconds of analysis, we do not know if, ultimately, they became intermittent. We cannot rule out the possibility that breakthrough activation was the result of

reentry, including subepicardial reentry and/or foci originating at a distance from the breakthrough site.

Conclusions

In our high-density, simultaneous, biatrial, epicardial mapping study in patients with persistent and LSP AF, each sustained focus manifested minimal fluctuations in CLs over time. Intermittent foci and nonrandom breakthrough sites manifested variability in periods of activity. Spontaneous pauses or activation from other wave fronts explained the intermittency of the intermittent foci and nonrandom breakthrough. Focal and breakthrough activation sometimes generated wannabe reentry.

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Disclosures

None.

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