Noninvasive Characterization of Epicardial Activation in Humans With Diverse Atrial Fibrillation Patterns

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Background—Various mechanisms of atrial fibrillation (AF) have been demonstrated experimentally. Invasive methods to study these mechanisms in humans have limitations, precluding continuous mapping of both atria with sufficient resolution. In this article, we present continuous biatrial epicardial activation sequences of AF in humans using noninvasive electrocardiographic imaging (ECGI).

Methods and Results—In the testing phase, ECGI accuracy was evaluated by comparing ECGI with coregistered CARTO images during atrial pacing in 6 patients. Additionally, correlative observations from catheter mapping and ablation were compared with ECGI in 3 patients. In the study phase, ECGI maps during AF in 26 patients were analyzed for mechanisms and complexity. ECGI noninvasively imaged the low-amplitude signals of AF in a wide range of patients (97% procedural success). Spatial accuracy for determining initiation sites from pacing was 6 mm. Locations critical to maintenance of AF identified during catheter ablation were identified by ECGI; ablation near these sites restored sinus rhythm. In the study phase, the most common patterns of AF were multiple wavelets (92%), with pulmonary vein (69%) and non–pulmonary vein (62%) focal sites. Rotor activity was seen rarely (15%). AF complexity increased with longer clinical history of AF, although the degree of complexity of nonparoxysmal AF varied widely.

Conclusions—ECGI offers a noninvasive way to map epicardial activation patterns of AF in a patient-specific manner. The results highlight the coexistence of a variety of mechanisms and variable complexity among patients. Overall, complexity generally increased with duration of AF. (Circulation. 2010;122:1364-1372.)

Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ electrophysiology ■ medical imaging

Atrial fibrillation (AF) is the most common cardiac arrhythmia, accountable for frequent hospitalizations and increased risks of stroke, heart failure, and mortality.1,2 Published guidelines classify patients into groups on the basis of the clinical duration and behavior of AF (paroxysmal, persistent, long-standing persistent, permanent).3 Although this approach has served clinicians well, it does not take into account mechanisms of the arrhythmia.

Clinical Perspective on p 1372

Mechanisms of initiation and perpetuation of AF continue to be the subject of ongoing intense investigation.4–8 Proposed mechanisms include “multiple wavelet,”9 “mother rotor/fibrillatory conduction,”10 and “pulmonary vein/focal source.”11 Contributions from the autonomic nervous system play a role in AF as well.12 To improve the treatment of AF, it is incumbent to understand the underlying mechanism in each individual patient. The Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society 2007 Expert Consensus Statement on the Surgical and Catheter Treatment of Atrial Fibrillation summarizes the state of knowledge as follows: “Although much has been learned about the mechanisms of AF, they remain incompletely understood. Because of this, it is not possible to precisely tailor an ablation strategy to a particular AF mechanism.”13 Currently, there is a paucity of simultaneous biatrial mapping data during AF in humans. In this article, we present simultaneous biatrial epicardial activation sequences during AF for a wide range of AF phenotypes. Maps were obtained with the use of noninvasive electrocardiographic imaging (ECGI)14,15 and analyzed in terms of the mechanisms and complexity of activation patterns.

Methods

Thirty-six subjects included in this study had a history of AF and were referred from Washington University electrophysiology and cardiothoracic surgery services. All protocols were approved by the...
institutional review board at Washington University, and informed consent was obtained from all patients.

ECGI System

ECGI methodology was described in detail previously.\textsuperscript{14,15} Two hundred fifty-six carbon electrodes were applied to the patient’s torso surface and connected to a portable mapping system. Computed tomographic (CT) markers were attached to each electrode. After electrode application, patients underwent thoracic noncontrast gated CT imaging with axial resolution of 3 mm. Scans were gated at 20\% of the R-R interval (atrial diastole) if in sinus rhythm. If patients undergo repeat ECGI over time, the electrode strips are placed in the same location, and an additional CT scan is not needed. Atrial epicardial surface geometry and body surface electrode positions were labeled and digitized from CT images.

The 256 channels of body surface potentials were sampled at 1-ms intervals. During the catheter electrophysiological study, body surface potentials were acquired during atrial pacing from various locations and during AF. Several minutes of data were recorded from each patient. T-Q segments were used for analysis of AF.

The body surface potentials and geometric information (torso-heart geometric relationship) were combined by ECGI algorithms to noninvasively construct epicardial potential maps, electrograms, activation sequences (isochrones), and repolarization patterns. Activation movies for several consecutive beats were constructed by animating the activation wavefront on the patient-specific CT-derived epicardial surface.

ECGI has been validated extensively (see the online-only Data Supplement for relevant references). In the atria, ECGI has been used to map sinus rhythm activation\textsuperscript{14,15} and repolarization\textsuperscript{16} with findings similar to those from the invasive mapping of Durrer et al.\textsuperscript{17} Atrial reentry and focal mechanisms have been demonstrated with ECGI of ishmustus-dependent right atrial (RA) flutter,\textsuperscript{14} focal left atrial (LA) tachycardia,\textsuperscript{18} and incomplete pulmonary vein (PV) isolation,\textsuperscript{19} all of which were validated during endocardial mapping and ablation. In addition, ECGI mapping of scar-related atypical PV flutter was validated during surgical mapping.\textsuperscript{20} ECGI maps the entire epicardium during a single beat. Unlike catheter mapping, it does not require accumulating data from many beats to complete a map, nor does it require signal averaging from multiple beats. It can record continuously and capture the dynamics of electric excitation.

Testing Phase

Simulation of Focal Atrial Activation With Pacing During Bialtrial ECGI Mapping

Previous studies have reported the accuracy of ECGI for predicting ventricular pacing sites to be 2 to 10 mm.\textsuperscript{21} Because of complex atrial anatomy and various known locations of AF triggers, ECGI was performed on 6 patients undergoing a PV isolation procedure during pacing from various known sites of AF initiation (testing phase). Locations of pacing sites were recorded onto electroanatomic maps (CARTO, Biosense-Webster), and the paced anatomic structure (eg, specific PV) was identified. ECGI maps were analyzed to determine the pacing site location on the basis of earliest activation, location of a potential minimum during early depolarization, and corresponding potential maximum during repolarization (Figure 1). When possible, the distance between the ECGI site and the site on the catheter electroanatomic map was measured (with the use of Amira 4.1, Visage Imaging).

Correlation of Simultaneous Invasive Catheter Mapping With Noninvasive ECGI During AF

Of the 6 patients who underwent ECGI during the testing phase, 3 developed AF during the electrophysiological procedure. Catheter mapping findings during AF were recorded, including locations of high-frequency activation and location of ablation that terminated AF, and compared with simultaneous ECGI activation movies.

Study Phase

Analysis of AF

Activation movies were constructed during long R-R intervals (300 to 1000 ms) for the 26 patients who underwent ECGI during AF. Visual analysis of at least 5 movies for each patient was performed. A wavelet was defined as a contiguous area of epicardial activation that was observed over a minimum of 5 ms. Wavelet propagation was observed each millisecond, and the number of simultaneous wavelets was recorded every 5 ms throughout the movie. The mean number of simultaneous wavelets participating in AF (“number of wavelets”) was recorded. The locations and number of epicardial activation sites that initiated new wavefronts (“number of focal sites”) were recorded. These focal sites may be spontaneous depo-
Table. Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>Mean (Range)</th>
</tr>
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<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Male</td>
<td>24 (67)</td>
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<tr>
<td>Female</td>
<td>12 (33)</td>
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<tr>
<td>Race</td>
<td></td>
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<tr>
<td>White</td>
<td>33 (91)</td>
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<tr>
<td>Black</td>
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<tr>
<td>Other</td>
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<tr>
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<td>8.3 (0.2 to 30)</td>
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<td>Clinical classification of AF</td>
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<tr>
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<td>Persistent</td>
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<td>Long-standing persistent</td>
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<td>Hypertension</td>
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<td>2 (6)</td>
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<tr>
<td>Cerebrovascular accident</td>
<td>4 (11)</td>
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<td>LA dimension, cm</td>
<td>4.4 (3.5 to 5.7)</td>
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<tr>
<td>Mitral regurgitation</td>
<td>0.86 (0 [none] to 3 [severe])</td>
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<td>Antiarrhythmic medication</td>
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<td>Prior PV isolation</td>
<td>7 (19)</td>
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<tr>
<td>Prior maze</td>
<td>2 (6)</td>
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<tr>
<td>Prior Fontan</td>
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</tbody>
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Results

Testing Phase

Simulation of Focal Atrial Activation With Pacing

During the testing phase, ECGI was performed on 6 patients during PV isolation procedures with pacing from various atrial locations. A total of 37 paced events were recorded in all 4 PVs, posterior LA, mitral isthmus and annulus, coronary sinus, atrial septum, sinus node, and atrial appendages. The cardiac structure being paced was correctly identified by ECGI in all 37 pacing events (100% accuracy). Relative to electroanatomic maps, ECGI-determined pacing locations were accurate within 6.3±3.9 mm (Figure 1).

Correlation of Simultaneous Invasive Catheter Mapping With Noninvasive ECGI During AF

Three patients had AF during PV isolation procedures, allowing for simultaneous catheter mapping and ECGI. One patient demonstrated an intermittent driver in the right inferior PV during catheter mapping. AF terminated with ablation in the inferior-posterior LA. ECGI immediately before this ablation lesion (Figure 2) repeatedly demonstrated the following: (1) right inferior PV focal site; (2) LA posterior wall focal site; and (3) a critical isthmus in the inferior-posterior LA with a unidirectional activation pattern at the location where ablation restored sinus rhythm. These patterns were seen consistently in several ECGI movies analyzed for this patient (Movie II in the online-only Data Supplement).

In a second patient, AF organized into atypical flutter after ablation, with variable cycle length (270 to 310 ms) and variable activation sequence as reflected in coronary sinus electrograms. Detailed entrainment mapping suggested the septum to be a critical part of the circuit, and ablation along the posterior septum resulted in sinus rhythm. ECGI during atypical flutter demonstrated a repetitive pattern with a cycle length between 260 and 410 ms involving the septum (Figure 3). Other wavelets were present with this pattern. Movie III in the online-only Data Supplement shows activation during several cycles of this pattern.

A third patient demonstrated an intermittent driver in the right PV during mapping and termination of AF with isolation. ECGI at that time showed frequent right PV focal site activation. This pattern was seen consistently in several ECGI movies. Additional focal sites were seen in other locations during AF but disappeared after sinus rhythm was restored.

Study Phase

Analysis of AF

In the study phase of 26 patients, AF imaged with ECGI showed diverse activation patterns, as follows.

- Number of wavelets: For most patients (24/26; 92%), at least 2 simultaneous wavelets (range, 1 to 5) were visible. Individually, each patient had a consistent number of wavelets (±1 wavelet). For example, AF judged to have 2 wavelets produced at least 2 simultaneous wavelets. Wavelets were visible in all 8 patients classified as having paroxysmal AF, 9 of 13 patients with persistent AF, and 12 of 17 patients with long-standing persistent AF. The sum of wavelets was highest in patients with long-standing persistent AF (mean ± SD, 2.7 ± 1.3 wavelets).

- Wavelets were longer in duration in patients with persistent AF (mean ± SD, 210 ms ± 73 ms) compared with patients with paroxysmal AF (mean ± SD, 154 ms ± 37 ms) or long-standing persistent AF (mean ± SD, 153 ms ± 35 ms). Wavelet duration was longest in patients with long-standing persistent AF, possibly reflecting a more complex arrhythmia.

- Wavelet length was shorter in patients with persistent AF (mean ± SD, 2.2 ± 0.4 mm) compared with patients with paroxysmal AF (mean ± SD, 2.8 ± 0.7 mm) or long-standing persistent AF (mean ± SD, 2.8 ± 1.2 mm). Wavelet length was longest in patients with paroxysmal AF, possibly reflecting a more complex arrhythmia.

- Wavelet propagation velocity was similar in patients with paroxysmal AF (mean ± SD, 0.6 ± 0.2 m/s), persistent AF (mean ± SD, 0.6 ± 0.2 m/s), and long-standing persistent AF (mean ± SD, 0.6 ± 0.2 m/s). Wavelet propagation velocity was longest in patients with paroxysmal AF, possibly reflecting a more complex arrhythmia.

- Wavelet shape was similar in patients with paroxysmal AF (mean ± SD, 0.6 ± 0.2 m/s), persistent AF (mean ± SD, 0.6 ± 0.2 m/s), and long-standing persistent AF (mean ± SD, 0.6 ± 0.2 m/s). Wavelet shape was longest in patients with paroxysmal AF, possibly reflecting a more complex arrhythmia.
wavelets never had $\geq 4$ wavelets over the course of imaging. Rarely (2/26; 8%), the predominant mechanism was a single-wave macroreentry, involving both atria.

- Rotors: Rotor pattern was less common (4/26; 15%) and was observed in the posterior LA, often near PV ostia and occasionally in the anterolateral RA. Rotors rarely sustained $>1$ full rotation before breaking into less organized wavelets. Although the rotors seemed short-lived, in the 4 patients with rotor patterns, the location of the rotor was reproducible in several ECGI movies. Interestingly, rotors were only seen in patients with nonparoxysmal AF.

- Focal sites: Radial epicardial activation from a focus frequently occurred near the PVs (18/26; 69%) during AF. Non-PV focal sites were also common (16/26; 62%) and were predominately seen in LA posterior wall, coronary sinus, lateral RA, or vena cavae. By convention, these locations are called focal sites, although their underlying cellular mechanisms and role in initiating AF are not known. These focal sites were seen in addition to simultaneous activation wavelets during AF.

- Examples of several AF activation patterns are shown in Figures 4 through 7. The dynamic activation patterns, often involving several wavelets with wave break and shifting pivot points, are best presented in the activation movies in the online-only Data Supplement.

- Figure 4 shows 2 examples of left PV focal sites during AF in a patient with an 8-year history of paroxysmal AF. Radial spread of the activation wavefront is seen, with delay across the posterior LA. Movie IV in the online-only Data Supplement demonstrates these findings over a longer time period (800 ms or $\approx 4$ cycles). In addition to the left PV focal sites, a recurring left-to-right activation pattern is seen. One to 2 simultaneous wavelets are present during AF. These findings were reproducible in 4 of the 5 ECGI movies used for analysis.

- Figure 5 shows 2 examples of a focal site with a rotor pattern around a right PV during AF in a patient with a 2-year history of persistent AF, refractory to several antiarrhythmic medications. Movie V in the online-only Data Supplement shows these findings over a longer time.
interval (1400 ms). Two to 3 simultaneous wavelets are seen, frequently with the use of right inferior PV as a pivot. At times, the right inferior PV has repetitive focal activation, whereas at other times, there is no clear focal activity. These findings were reproducible in 4 of the 5 ECGI movies used for analysis.

Figure 6 demonstrates the less common phenomenon of single-wave macroreentry in a young patient with a structurally normal heart and paroxysmal nonsustained AF induced during an electrophysiological study. A broad, slow-moving wavefront is seen in both LA and RA. Movie VI in the online-only Data Supplement is shown with a transparent atrial shell to visualize the entirety of the activation wavefront. No focal sites are detected. This pattern was seen in 5 of 5 ECGI movies used for analysis.

Figure 7 is an example of a more complex AF pattern in a patient with long-standing persistent AF. Time-lapse images demonstrate rotor patterns near PV ostia and posterior LA. Movie VII in the online-only Data Supplement shows continuous AF imaging (900 ms), demonstrating at least 4 simultaneous wavelets, a high degree of wavefront curvature, and frequent wave breaks. These features were seen in 5 of 5 ECGI movies used for analysis.

Analysis of AF Complexity

Among 26 patients imaged during AF, there were significant differences in complexity (number of wavelets and focal sites) between the clinical groups (paroxysmal, persistent, long-standing persistent). Patients with paroxysmal AF had fewer wavelets (1.1 ± 0.2 wavelets) than patients with persistent AF (2.2 ± 0.9 wavelets; *P* = 0.017) or long-standing persistent AF (2.6 ± 0.5 wavelets; *P* < 0.005). In aggregate, the 3 groups were significantly different with regard to number of wavelets (ANOVA, *P* = 0.011; Figure 8A).

Similarly, patients with paroxysmal AF had fewer focal sites (1.0 ± 0.7 focal sites) than patients with persistent (2.3 ± 1.1 focal sites; *P* = 0.034) or long-standing persistent AF (3.2 ± 1.8 focal sites; *P* = 0.034). In a comparison among the 3 groups, disparities were significantly different (ANOVA, *P* = 0.031; Figure 8A).

Within the paroxysmal AF group, there was relative homogeneity and simplicity in the number of wavelets and focal sites. With the sum of the mean number of wavelets and focal sites used as a complexity index, patients with paroxysmal AF had significantly fewer wavelets and focal sites than patients with persistent or long-standing persistent AF (ANOVA, *P* < 0.005).
ysmal AF had values that ranged from 1 to 3.5, with a mean of 2.1 (Figure 8B). In general, paroxysmal AF patients had 1 to 2 wavelets with 0 to 2 focal sites. In contrast, patients with persistent AF demonstrated considerable heterogeneity. Patients in this group had 1 to 4 simultaneous wavelets and 1 to 4 focal sites visible during AF. The complexity index ranged from 2 to 7, with a mean of 4.5. At the extremes, the “simplest” AF pattern among the patients with persistent AF had a single wavelet and a single focal site in the RA (complexity index of 2). The most complex AF pattern in this group had an average of 5 wavelets and at least 2 identifiable focal sites contributing to AF.

The patients with long-standing persistent AF had the most complex AF patterns. One patient in this group, who had undergone 3 prior catheter ablations, exhibited the most complex AF pattern of the entire cohort, with a mean of 3 wavelets arising from a total of 6 identifiable focal sites (2 PVs, coronary sinus, RA, and 2 sites in the posterior LA). Graphically (Figure 8B), the persistent and long-standing persistent groups demonstrated overlap with regard to the complexity index, whereas the paroxysmal group did not.

Although patients who have had prior surgical or catheter ablation represent a clinically important type of AF, the effect of previous intervention may introduce artificial complexity to the AF patterns. When these patients were removed from analysis, measurable differences remained between paroxysmal and nonparoxysmal AF in regard to the mean number of wavelets (1.1 ± 0.2 versus 1.7 ± 0.6; *P* = 0.010), number of focal sites (1.0 ± 0.7 versus 2.6 ± 1.1; *P* = 0.015), and complexity index (2.1 ± 0.7 versus 4.4 ± 1.5; *P* = 0.007). Patients

**Figure 6.** Example of single-wave biatrial reentry in a patient with paroxysmal AF (Movie VI in the online-only Data Supplement). ECGI isochrone map of both atria in the right posterior and anterior views during 100 ms of AF demonstrates a single spiral wave. The broad, sweeping activation wavefront involves both atria and propagates predominantly in a counterclockwise fashion (white arrows, anterior view). Although the surface ECG did not demonstrate clear regularity, this pattern on ECGI was highly repetitive. Black line marks the atrial septum. The movie in the online-only Data Supplement demonstrates this repetitive pattern. LSPV indicates left superior PV; LIPV, left inferior PV; RSPV, right superior PV; RII PV, right inferior PV; LAA, LA appendage; RAA, RA appendage; MV, mitral valve; and TV, tricuspid valve.

**Figure 7.** Examples of complex rotor physiology in posterior LA in a patient with long-standing persistent AF (Movie VII in the online-only Data Supplement). A, Activation pattern during AF (46 to 73 ms) of both atria (posterior view). Activation wavelets are shown in red. White arrows indicate propagation direction of the wavelet. The white stars denote pivot points of wavelet rotation. At 46 ms, a focal site emerges from left superior PV (LSPV) and triggers a wave of radial activation (51 ms). The emerging wavelet pivots around an area in the LA posterior wall (59 to 63 ms) (star) and then propagates toward the right PVs (63 to 73 ms). The movie in the online-only Data Supplement demonstrates this repetitive pattern. B, Activation pattern during AF at a different time point. At 503 ms, a wavelet at 503 ms breaks into 2 on the posterior LA wall (508 to 525 ms) and propagates around 2 pivot points (stars). At 533 ms, the wavelets coalesce and terminate. LIPV indicates left inferior PV; RSPV, right superior PV; RII PV, right inferior PV; and PA, posteroanterior.
Discussion

AF is characterized by a dynamically changing activation sequence. This hallmark of AF poses severe limitations on point-by-point catheter mapping of AF, which requires a stable, monomorphic arrhythmia. Simultaneous recording from many electrodes over a long duration is required to accurately map AF. Invaluable invasive multichannel mapping studies have been conducted on epicardial and endocardial atrial surfaces in animals. However, animal models differ from humans in many ways, including ion-channel profiles of atrial myocytes, anatomic substrates, and remodeling processes. Observations from direct epicardial recordings in humans have been instrumental toward characterization of AF but are limited by access to only certain portions of the atria, with relatively short time periods for recording data in an open chest, under the influence of general anesthesia on autonomic tone. In other studies, invasive endocardial mapping of AF was performed with the use of multichannel catheter (basket or balloon) arrays in LA and RA and PVs. Although this approach is less invasive than surgical mapping, it still involves the effects of sedation, and the intra-atrial presence of the array limits mapping time. The mapping resolution is compromised by the limited number of recording electrodes.

The present study applies ECGI as a noninvasive mapping tool for studying mechanisms of human AF. ECGI can map the epicardial activation pattern of AF on both atria continuously and with high spatial resolution. There is no surgery, sedation, or invasive intervention involved, and therefore the AF pattern can be observed in “real-world” conditions, over long periods of time (minutes to hours). The pacing data presented here determine the atrial accuracy of ECGI at 6 mm, which is comparable to previously published data from ventricular ECGI reconstructions. The overlap of clinical findings from electrophysiological catheter mapping and ablation with simultaneous ECGI corroborates the noninvasive findings.

This study is the first to report detailed, 3-dimensional mapping of biatrial epicardial activation during AF in humans. Major findings include the following: (1) ECGI is feasible in most patients, even with low-amplitude fibrillatory atrial signals; (2) epicardial activation patterns are variable within the population, but specific and reproducible activation patterns are present in individual patients; (3) the most common activation pattern consisted of multiple concurrent wavelets with simultaneous focal sites from areas near the PVs; (4) complexity of AF increased with duration-based clinical classification of AF; (5) however, among persistent and longstanding persistent AF, there was overlap in complexity.

The human data presented here are consistent with data from models of AF mechanisms and highlight the coexistence of a variety of mechanisms, as reported in animals and humans. Specifically, the number of simultaneous wavelets (1–5) and the observation that the wavelets change position from beat to beat are consistent with the direct epicardial mapping of Allessie et al. The frequency of PV focal sites is consistent with the findings of Haissaguerre et al. The observation of rotor patterns in certain areas (posterior LA, PVs, lateral RA) is consistent with the observations of Jalife et al. Although rare, single-wavelet reentry was described by Cox et al. The relative contribution of each mechanism to initiation and maintenance of AF remains to be determined.

Data reported here have implications for treatment of AF. Our observation that patients with paroxysmal AF have simpler activation patterns, often involving the PVs, could explain the greater success rates of catheter ablation in these patients. On the other hand, the wide range of AF complexity and mechanisms in nonparoxysmal AF, including rotor activity in areas not usually targeted for ablation, may help to explain the variability of reported ablation success in these patients. Additionally, persistent AF may be simple and relatively organized in one patient (Figure 5) but quite complex in another (Figure 7). Clinical categories do not reliably reflect AF complexity. As such, ECGI may have a role in identifying persistent AF patients who would be more likely to benefit from an ablation procedure or an antiarrhyth-
mic drug. Conversely, ECGI may identify patients who are unlikely to benefit from catheter or surgical ablation because of complex atrial activation patterns that may be difficult to treat with current strategies. Finally, ECGI offers an opportunity to noninvasively follow therapy (pharmacological or procedural) outcome over time and to better understand why AF recurs in some patients.

The AF activation patterns were often repeated in a given patient. However, the repetition of patterns decreased in more complex AF. The data were collected over a period of minutes to hours, and therefore the long-term reproducibility of AF patterns remains unanswered. Establishing reproducibility will be a key factor in determining a patient-specific ablation strategy, which would be tailored to the AF pattern of an individual patient by indicating the areas to target as repetitive focal sources.

Several key limitations are worth noting. First, ECGI reconstructs potentials on the atrial epicardial surface. Although atria are generally thin, evolving evidence suggests at least a modest difference between endocardial and epicardial activation. The image described as a “focal site” may well be epicardial breakthrough of intramural activation. Second, ECGI cannot differentiate microreentry from focal activity. Third, this first ECGI AF study sought to obtain data from a wide range of phenotypes. The effect of previous catheter ablation and surgery may confound the association between long-standing AF duration and complexity. Future studies should focus on each subgroup with greater detail. Additionally, validation of AF activation patterns with correlating invasive data was only available for 3 of the 26 patients. Ongoing prospective studies are investigating the dynamic changes of AF mechanisms during catheter ablation, which may provide additional correlating invasive data. Finally, a limitation for ECGI is the inherent AF signal quality, which is often of low amplitude on the body surface. By considering at least 5 AF activation movies (ranging from 500 to 1000 ms) for each patient and limiting the definition of focal site to cycle lengths of at least 100 ms, nonphysiological artifacts were minimized.

In conclusion, ECGI can noninvasively image electric activation during AF in a wide range of patients. In this initial feasibility study, a variety of AF mechanisms coexisted, and complexity increased with longer duration of AF. If the ability of ECGI to distinguish AF activation patterns among the clinically defined subgroups is validated further in larger prospective studies utilizing invasive recordings, this noninvasive technology has the potential to advance our understanding of AF mechanisms. Ultimately, ECGI could be utilized clinically to form individualized, mechanism-based treatment plans. This later hypothesis requires testing in randomized trials.

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Disclosures

Drs Lindsay and Rudy are members of the scientific advisory board of CardioInsight Technologies Inc. Dr Rudy holds equity in CardioInsight Technologies. CardioInsight Technologies does not support any research conducted by Dr Rudy, including that presented here. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Atrial fibrillation (AF) is the most common cardiac arrhythmia, accountable for frequent hospitalizations and increased risks of stroke, heart failure, and mortality. Various mechanisms of AF have been demonstrated in experimental models. Invasive methods to study these mechanisms in humans have limitations, precluding continuous mapping of both atria with sufficient resolution in a closed chest. This article presents simultaneous biatrial epicardial activation sequences during AF for a range of AF phenotypes in 26 patients, obtained noninvasively with the use of ECG imaging. From a diagnostic standpoint, ECG imaging offers a way to describe a particular patient’s AF with the use of continuous noninvasive mapping of atrial electric activity. By imaging atrial electrophysiology, it offers an advantage over the current classification of AF, which relies on historical descriptors of duration and method of AF termination (paroxysmal, persistent, or permanent). Better identification of specific phenotypes ultimately may translate into tailored, patient-specific treatment plans that maximize benefit while minimizing risk. Examples include predicting and monitoring response to antiarrhythmic drug therapy or developing a customized catheter ablation lesion set. In this article, locations critical to maintenance of AF were identified in 3 patients during catheter ablation procedures and correlated with the ECG imaging findings. Ablation near these sites restored sinus rhythm. Prospective studies in homogeneous phenotypic subgroups would be needed to better define the role of ECG imaging in the treatment of patients with AF.
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With simpler forms of AF, an isochrone map can represent the overall pattern of AF. However, for most patients, the patterns of atrial activation involve several wavelets with frequent wavebreaks and shifting pivots, making static isochrones less robust. The following online movies highlight various epicardial activation patterns observed during AF.

Online Movie II (for Figure 2 in text).

Simultaneous endocardial mapping and ECGI imaging was performed. This patient had an intermittent high-frequency driver in the RIPV detected during invasive mapping. AF terminated with ablation in the inferior-posterior LA. This movie shows ECGI imaging of 1200 ms of AF (from three joined shorter movies) immediately prior to the ablation lesion that restored sinus rhythm. The movie demonstrates: 1) RIPV focal site; 2) left atrial posterior wall focal site; 3) a critical isthmus in the inferior-posterior LA with a wavelet wavebreak pattern. The red star identifies the ablation location that restored sinus rhythm, which is in the same location as the inferior-posterior isthmus.
Online Movie III (for Figure 3 in text).

Simultaneous endocardial catheter mapping and ECGI imaging was performed. This patient had an atypical atrial flutter that developed during AF ablation. The atrial activation pattern and cycle length were variable (270-310 ms), but entrainment data suggested septal reentry. AF terminated with ablation in the posterior left atrial septum. This movie shows ECGI imaging of 2000 ms of the atypical atrial flutter prior to conversion to sinus rhythm. A repeating pattern can be seen every 260-410 ms with septal reentrant activation. Additional wavelets are present, which likely contributed to the variation in invasively measured cycle length and activation sequence determined from coronary sinus recordings. This pattern was consistently seen in several ECGI movies.

Online Movie IV (for Figure 4 in text).

800 ms of continuous AF are shown in the posterior view (approximately 4 cycles). This patient had eight years of paroxysmal AF. Pertinent findings include left PV focal sites, a left-to-right activation pattern with delay in the posterior left atrium, and one or two simultaneous wavelets. These findings were reproducible in 4 of the 5 ECGI movies used for analysis.
Online Movie V (for Figure 5 in text).

1400 ms of AF (from three joined movies) are shown in the posterior view. This patient had two years of persistent AF, refractory to several antiarrhythmic medications. Pertinent findings include two examples of a focal site with a rotor pattern around the right inferior PV. Two to three simultaneous wavelets are present, frequently using the RIPV as a pivot. At times, the RIPV has repetitive activation, while at other times, there is no clear focal activity. These findings were reproducible in 4 of the 5 ECGI movies used for analysis.

Online Movie VI (for Figure 6 in text).

250 ms of continuous AF are shown in the posterior view, with a transparent atrial shell to visualize the entirety of the activation wavefront. The wavefront on the posterior wall has a brighter color, while the wavefront on the distant anterior structures has a faded color. This young patient had a structurally normal heart with nonsustained AF induced during an EP study. The movie demonstrates the less common phenomenon of single wave macroreentry, which has been observed by Konings et al.35 A broad, slow-moving wavefront is seen using both left and right atria in a pattern that is
similar (but not exactly the same) during each cycle. This pattern was seen in 5 of 5 ECGI movies used for analysis.

**Online Movie VII (for Figure 7 in text).**

900 ms of continuous AF are shown in the right posterior view, to demonstrate the influence of right atrial activation. This patient had long-standing persistent AF, refractory to antiarrhythmic medication. The movie demonstrates at least 3 simultaneous wavelets, high degree of wavefront curvature, and frequent wavebreaks. Rotor patterns are seen on the posterior left atrium and right atrium. These features were seen in 5 of 5 ECGI movies used for analysis.
## Supplemental Table 1: Detailed Patient AF Characteristics

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<th>Patient #</th>
<th>Clinical Group</th>
<th>Mapped Rhythm</th>
<th># Wavelets</th>
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Supplemental References

ECGI has been extensively validated in animal models and human studies. A list of relevant references is provided below:

Animal Models:


Human Studies:


