Human Atrial Fibrillation Initiates via Organized Rather Than Disorganized Mechanisms

Amir A. Schricker, MD, MS; Gautam G. Lalani, MD; David E. Krummen, MD; Wouter-Jan Rappel, PhD; Sanjiv M. Narayan, MD, PhD

Background—It is unknown how atrial fibrillation (AF) is actually initiated by triggers. Based on consistencies in atrial structure and function in individual patients between episodes of AF, we hypothesized that human AF initiates when triggers interact with deterministic properties of the atria and may engage organized mechanisms.

Methods and Results—In 31 patients with AF, we mapped AF initiation after spontaneous triggers or programmed stimulation. We used 64-pole basket catheters to measure regional dynamic conduction slowing and to create biaxial activation maps during transitions to AF. Notably, AF did not initiate by disorganized mechanisms, but by a dominant reentrant spiral wave (76%) or a repetitive focal driver. Both mechanisms were located 21±17 mm from their triggers. AF-initiating spirals formed at the site showing the greatest rate-dependent slowing in each patient. Accordingly, in 10 of 12 patients with multiple observed AF episodes, AF initiated using spatially conserved mechanisms despite diverse triggers.

Conclusions—Human AF initiates from triggers by organized rather than disorganized mechanisms, either via spiral wave re-entry at sites of dynamic conduction slowing or via repetitive focal drivers. The finding that diverse triggers initiate AF at predictable, spatially conserved functional sites in each individual provides a novel deterministic paradigm for AF with therapeutic implications. (Circ Arrhythm Electrophysiol. 2014;7:816-824.)

Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ cardiac electrophysiology ■ spiral waves

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Although AF has highly variable activation, multiple lines of evidence indicate that AF exhibits underlying spatial-temporal organization. This includes stable inter/intra-atrial frequency gradients, consistent activation vectors, and evidence for stable rotors and focal drivers of ongoing AF. We thus hypothesized that, despite its potential complexity, AF initiates from potentially diverse triggers by organized mechanisms that may involve dynamic conduction slowing. We tested this in patients with AF by detailed mapping of the majority of both atria assessed systematically after triggers that initiated AF and ectopic beats that did not, relative to the regional rate-response of conduction.

Methods

Study Design and Enrollment
We enrolled consecutive subjects with symptomatic AF undergoing ablation at the Veterans Affairs and UC San Diego Medical Centers. The study was approved by our joint VA/University of California San Diego Institutional Review Board, and all patients provided informed consent. Subjects were ≥21 years old with paroxysmal or persistent AF despite class I or III antiarrhythmics. The only exclusion was inability or refusal to provide consent. To study AF initiation, we included patients in sinus rhythm spontaneously or after cardioversion (31/57 screened patients).

Electrophysiology Study
Antiarrhythmic medications (Table 1) were discontinued for 5 half-lives (>60 days for amiodarone; median 202 days). Catheters were advanced to the right atrium (RA), coronary sinus, and transeptally to left atrium (LA). A 64-pole basket catheter (Constellation, Boston Scientific, Natick, MA) was advanced to map the LA. RA recordings were made using a second basket (simultaneously) in 17 patients.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=31)</th>
<th>Paroxysmal Patients With AF (n=21)</th>
<th>Persistent Patients With AF (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±9</td>
<td>61±10</td>
<td>63±9</td>
<td>0.16</td>
</tr>
<tr>
<td>Men</td>
<td>30 (97%)</td>
<td>20 (95%)</td>
<td>10 (100%)</td>
<td>...</td>
</tr>
<tr>
<td>History of AF, mo</td>
<td>33 (20–87)</td>
<td>29 (19–53)</td>
<td>65 (40–113)</td>
<td>0.44</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>42±7</td>
<td>40±5</td>
<td>48±6</td>
<td>0.01</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>57±9</td>
<td>61±8</td>
<td>50±7</td>
<td>0.01</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>15 (48%)</td>
<td>10 (48%)</td>
<td>5 (50%)</td>
<td>0.90</td>
</tr>
<tr>
<td>≥2</td>
<td>16 (52%)</td>
<td>11 (52%)</td>
<td>5 (50%)</td>
<td>0.90</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>30 (97%)</td>
<td>21 (100%)</td>
<td>9 (90%)</td>
<td>0.14</td>
</tr>
<tr>
<td>III–IV</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (10%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (n)</td>
<td>25 (81%)</td>
<td>17 (81%)</td>
<td>8 (80%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>10 (32%)</td>
<td>9 (43%)</td>
<td>1 (10%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Prior stroke/ TIA (n)</td>
<td>6 (19%)</td>
<td>3 (14%)</td>
<td>3 (30%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Coronary artery disease (n)</td>
<td>11 (35%)</td>
<td>7 (33%)</td>
<td>4 (40%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Prior ablation</td>
<td>5 (16%)</td>
<td>1 (5%)</td>
<td>4 (40%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previously failed &gt;1 antitachy (n)</td>
<td>9 (29%)</td>
<td>5 (24%)</td>
<td>4 (40%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Class I agent</td>
<td>8 (26%)</td>
<td>6 (29%)</td>
<td>2 (20%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Sotalol</td>
<td>13 (42%)</td>
<td>8 (38%)</td>
<td>5 (50%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>5 (16%)</td>
<td>3 (14%)</td>
<td>2 (20%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>10 (32%)</td>
<td>6 (29%)</td>
<td>4 (40%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Concomitant drug therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>17 (55%)</td>
<td>11 (52%)</td>
<td>6 (60%)</td>
<td>0.69</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>17 (55%)</td>
<td>10 (48%)</td>
<td>7 (70%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>11 (35%)</td>
<td>6 (29%)</td>
<td>5 (50%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Statin</td>
<td>19 (61%)</td>
<td>15 (71%)</td>
<td>4 (40%)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values are n (%), mean±SD or median (interquartile range). ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; NYHA, New York Heart Association; and TIA, transient ischemic attack.

Data Acquisition During AF

Electrograms were filtered at 0.05 to 500 Hz and recorded at 1 kHz (Bard, Lowell, MA). To study AF initiation from diverse triggers, we analyzed spontaneous and pacing-induced initiations. In sinus rhythm, we waited ≤10 minutes to map spontaneous ectopy that did not (Figure 1A) or a quadrupolar RA catheter at the septum (to indicate RA initiation of AF if activation earlier than any LA electrode). Inter electrode separation was 4 to 6 mm along each spline, with interspline separation of 4 to 6 mm proximally and distally, with worst case average of ≤10 mm for equatorial electrodes. This resolution was considered sufficient to identify changes in activation from a paced or sinus rhythm pattern to a reentrant wave or ectopic driver at AF onset. Heparin was infused to maintain activated clotting time >350 seconds.

Affiliation

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Spatial Mapping of Baseline Rhythm, Trigger, and AF Initiation

Bipolar activation times were analyzed at each electrode for baseline rhythm, the trigger beat, and then AF initiation. The trigger beat was defined as the first cycle departing from baseline rhythm (Figure 1B), whereas AF onset was identified by variations in CL and electrogram morphology (or for induced AF) dissociation from pacing. Because intra-atrial propagation in AF quickly becomes non-1:1 with ambiguous propagation, we focused on the first 3 cycles of sustained AF. These electrograms are typically discrete, without fractionation, allowing construction of unambiguous isochronal maps. Activation time at each electrode was defined as the point of steepest slope of the first negative deflection in software using filtering, and then manually over-read blinded to the spatial map (Figure 1C).

Propagation maps for each cycle were constructed from activation times using custom software written in Matlab (Mathworks, Natick, MA). Isochrones were constructed by drawing contour lines at early (red) to late (blue) activated regions. Figure 2 shows biatrial isochronal maps for a sinus beat and a LA premature atrial complex (PAC) oriented as in Figure 1A. A spiral wave was defined as re-entrant around a specific region, showing early-occlusion–late activation. Focal activation was defined as centrifugal emanation from an origin. The trigger of spontaneous AF was the PAC site. For induced AF, the trigger was the site of pacing. In patients with multiple AF initiations, we studied whether AF initiation occurred at conserved sites, defined if their type (ie, spiral wave versus focal driver) and location (≤1 electrode distance) were consistent between initiations.

Quantification of Spatial Separation Between Triggers and AF-Initiating Mechanisms

Atrial geometric contours (NavX, St. Jude Medical, Minneapolis, MN) for each patient were used to compute distances between the trigger and site of each AF initiation. Separation of the (x, y, z) coordinates of each electrode (NavX; Figure 1D) was measured as the average of the Euclidean (ruler) and shortest distance over a best-fit computed ellipsoid registered to each patient’s atrium.

Conduction Restitution

We studied rate-dependent conduction slowing (restitution) in both atria en route to AF in a subset of 22 patients during burst pacing. Conduction slowing was defined by activation time prolongation by ≥10 ms (absolute) and ≥20% (relative) between fastest and slowest rates.

Statistical Analysis

Continuous data are represented as mean±SD or, if non-normally distributed, as median (interquartile range). Comparisons were made with Student t tests if normally distributed or with Mann–Whitney U test otherwise. Paired continuous variables were compared using Wilcoxon signed-rank test. Categorical data are summarized with frequency counts and percentages. The Fisher exact test was applied to contingency tables. To account for multiple observations per subject, mixed model analysis is used and continuous variables summarized using estimated means and SEs. A probability of ≤0.05 was considered statistically significant.
Results

Patient Characteristics
Table 1 summarizes our study patients. We mapped 62 AF initiations (median, 1 [interquartile range, 1–2] per patient), comprising 28 spontaneous and 34 induced (27 burst pacing, 3 single extrastimulus, and 4 isoproterenol). Control data consisted of 50 spontaneous PACs in 12 patients, which failed to initiate AF (median, 5 [interquartile range, 2–6] per patient).

Differences Between AF-Initiating and Noninitiating Ectopy
Both AF-initiating ectopy (n=28) and non–AF-initiating ectopy (n=50) arose biatrially (Table 2), with a nonsignificant trend toward LA predominance (P=0.23; Table 2). Ectopic beats that initiated AF were more premature than non-AF-initiating ectopy (coupled 370±25 versus 502±19 ms; P<0.001; Table 2).

Identification and Classification of AF-Initiating Mechanisms
We found that AF initiation was not disorganized but exhibited 2 spatially organized mechanisms. The first comprised a reentrant spiral wave, demonstrating sequential activation (clockwise or counterclockwise; Figure 3) seen in 76% (n=45) initiations. The second mechanism comprised a repetitive focal driver (Figure 4) in 27% (n=16) initiations. In 2 AF initiations, both mechanisms were observed. Three AF initiations were excluded because of poor electrogram quality that reduced confidence in measurements.

Figure 1. Catheter placement and recordings of atrial fibrillation (AF) initiation. A, Fluoroscopy showing 64-pole basket catheter in each atrium, implanted ECG monitor (Reveal, Medtronic, MN), catheters in the coronary sinus and left atrium (LA), and esophageal temperature probe. B, ECG and intracardiac signals of spontaneous paroxysmal AF after a premature atrial complex (PAC) trigger, with (C) example activation time marking of electrogram. D, NavX shells of both atria indicating the trigger and region of interest of AF initiation, with separation computed from respective (x, y, z) coordinates. CAU indicates caudal from the fluoroscopy system; CS, coronary sinus; FOV, field of view; IVC, inferior vena cava; LAO, left anterior oblique; MV, mitral valve; RA, right atrium; SVC, superior vena cava; and TV, tricuspid valve.

Figure 2. Biatrial spatial activation maps for a sinus beat and premature atrial complex (PAC) in a 74-year-old man with paroxysmal atrial fibrillation (AF). A, Sinus activity propagates centrifugally in the right atrium (RA) and conducts via Bachmann’s bundle to the left atrium (LA). B, Non-AF-initiating PAC from the lateral LA shows noncentrifugal activation in the RA, with preferential septal-to-lateral slowing (zig-zag line). C, Corresponding intracardiac recordings. CS indicates coronary sinus; IVC, inferior vena cava; SVC, superior vena cava.
AF-Initiating Mechanism 1: Dominant Reentrant Spiral Wave

Figure 3A and 3B illustrates isochronal maps of AF initiation by a spontaneous PAC in the lateral RA with conduction slowing in the inferior RA, leading to a spiral wave and AF. Figure 3C and 3D shows a distinct AF initiation in this patient, 10 minutes later and from LA burst pacing. Notably, these diverse triggers initiated 2 AF episodes by engaging a similar, spatially conserved spiral wave.

Overall, AF-initiating spiral waves formed in biatrial locations (Table 3) and occurred after spontaneous triggers that were coupled 380±12 ms from baseline. Figure I in the Data Supplement depicts additional examples of spiral wave AF initiations.

AF-Initiating Mechanism 2: Repetitive Focal Driver

The remaining 27% of AF episodes were initiated by a repetitive focal driver. Figure 4 shows a spontaneous PAC from the inferior LA that triggered a focal driver (CL 150 ms) at the anterior LA that drove the atria into AF. Overall, repetitive focal drivers were biatrial (Table 3) and occurred after triggers coupled 345±21 ms from baseline beats (P=0.17 versus spiral waves). Figure I in the Data Supplement illustrates an additional AF focal driver. There was no statistically significant association between type of initiation mechanism and type of AF (P=0.21) or history of prior ablation (P=0.20).

### Table 2. Characteristics of Ectopy

<table>
<thead>
<tr>
<th>Ectopy</th>
<th>Non–AF-Initiating PACs (n=50)</th>
<th>AF-Initiating PACs (n=28)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coupling interval, ms</td>
<td>502±19</td>
<td>370±25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrium</td>
<td>24 (48%)</td>
<td>19 (68%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Right atrium</td>
<td>23 (46%)</td>
<td>7 (25%)</td>
<td>(LA vs RA)</td>
</tr>
<tr>
<td>Septum</td>
<td>3 (6%)</td>
<td>2 (7%)</td>
<td>...</td>
</tr>
</tbody>
</table>

Values are n (%) or estimated mean±SE of the estimate. AF indicates atrial fibrillation; LA, left atrium; PAC, premature atrial complex; and RA, right atrium.
Spatial Separation of Triggers From AF-Initiating Mechanisms

AF initiation sites were separated by 21±17 mm from their preceding trigger (spiral waves, 23±3 mm; focal drivers, 15±5 mm; \( P=0.17 \)) that did not differ for paroxysmal or persistent AF (21±3 versus 20±4 mm; \( P=0.79 \)). Indeed, in 12 AF initiations the mechanisms (spiral waves) were contralateral to its trigger. There was no significant difference in spatial separation between an observed AF-initiating mechanism in each patient and PACs that did and did not initiate AF (18.0±13.4 versus 22.9±13.0 mm; \( P=0.43 \)), suggesting insufficient prematurity as the reason why AF did not initiate in these cases.

Role of Functional Conduction Slowing In AF Initiation

Figure 5 shows AF initiation that followed progressive RA conduction slowing with increasing rate, creating block then a spiral wave. Dynamic conduction slowing occurred at the site of AF initiation (by 113±74%, 52±34 ms from baseline) in 86% of patients (19/22). In all but 1 patient, a spiral wave formed at this site. The 3 AF initiations without defined conduction slowing (25±21% or 9±3 ms; \( P=0.04 \)) were initiated by a focal driver.

We developed a predictive index for the site of spiral wave formation. Prefibrillatory slowing was defined as the slope of the restitution curve at shortest pacing CL (Figure 5B), calculated for each electrode. The atrial site with the greatest rate-related slowing in conduction was identified. Four patients showed <20 ms conduction prolongation between fastest and slowest rates, that is, below our definition for slowing. The site of maximum prefibrillatory slowing predicted the site of AF initiation in 16 of the remaining 18 patients (89%).

Conservation of AF-Initiating Mechanisms Despite Varying Triggers

Twelve patients showed multiple AF initiations (43 initiations, median 3 [interquartile range, 2–4] per patient). Spiral waves initiated 24 of 26 AF episodes (n=8 patients) and focal drivers initiated 9 of 10 episodes in 2 patients. Thus, AF-initiating mechanisms were conserved in 10 patients (83%; 95% confidence interval, 52%–98%). In each patient, both the type and the location of mechanisms were conserved despite diverse triggers.

![Figure 3](http://circ.ahajournals.org/)

**Table 3. Characteristics of Initiating Mechanisms**

<table>
<thead>
<tr>
<th>AF-Initiating Mechanism</th>
<th>Spiral Wave (n=45)</th>
<th>Focal Driver (n=16)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle length, ms</td>
<td>103±6</td>
<td>201±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrial</td>
<td>28 (62%)</td>
<td>14 (88%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Right atrial</td>
<td>17 (38%)</td>
<td>2 (13%)</td>
<td>(LA vs RA)</td>
</tr>
</tbody>
</table>

Values are n (%) or estimated mean±SE of the estimate. AF indicates atrial fibrillation; LA, left atrium; and RA, right atrium.
CLs that initiated AF. Figure 4 shows 5 conserved focal AF drivers (CL 153±4 ms) at the LA roof despite preceding LA PAC triggers at diverse locations. Figure 6 summarizes trigger and AF-mechanism locations for all AF initiations in patients with multiple AF initiations.

Discussion
This study shows that AF is not initiated by complex mechanisms, but by an orderly process of conduction slowing causing block and formation of an organized spiral wave or focal driver with subsequent fibrillatory conduction. Organized AF-initiating mechanisms were separated spatially from their trigger and, unexpectedly, were conserved in each patient for multiple AF initiations from diverse trigger sites and types. Notably, sites of AF initiations in each patient could be predicted in sinus rhythm from the sites of maximum trigger-induced conduction slowing (prefibrillatory slowing). These data influence our conceptualization of AF initiation and may have therapeutic implications for improving ablation to prevent AF onset.

AF-Initiating Mechanisms Differ From Triggers
Prior reports have mapped spontaneous ectopic triggers for AF and demonstrated their spatial diversity in both atria and prematurity in rate using both contact and noncontact mapping. However, few studies have defined whether PACs, rapid tachycardias, or other triggers initiate AF via a second step of solitary or multiple reentrant or focal circuits or in relation to conduction slowing that may represent the increasingly studied atrial properties of fibrosis/scar.

AF initiation by spiral re-entry arose at sites of maximum prefibrillatory slowing detected in pacing that were not evident in sinus rhythm (i.e., not anatomic). Spatially, the separation of AF-initiating sites from triggers may be explained by the distance needed for conduction block and the formation of a reentrant circuit. We focused on regions of maximum change in conduction time between fastest and slowest rates (i.e., restitution), rather than absolute conduction time. Although regions upstream from the AF initiation site also showed conduction delay, the greatest rate-dependent change (prefibrillatory slowing) reflected conduction block/re-entry at the site of AF onset.
The fact that AF initiation by focal drivers also followed premature beats suggests that they may represent micro-reentry or triggered activity. Studies are needed to define if regional restitution represents zones bordering fibrosis.\textsuperscript{15}

Temporally, non–AF-initiating PACs were less premature than AF-initiating PACs and caused less conduction restitution. Future work should define the spatial–temporal zone of vulnerability wherein ectopic beats falling within a range of prematurity and spatial proximity may be more or less successful triggers for AF initiation.

**Consistency of Initiating Mechanisms for Diverse Triggers**

We demonstrate, for the first time, that multiple AF episodes from different triggers may initiate AF in individual patients by a conserved and deterministic mechanism. This again reinforces the concept that key mechanisms for AF are not chaotic. Future studies should examine a greater number of spontaneous and induced initiations, and study if regions exhibiting the steepest rate-related conduction represent specific fiber angles,\textsuperscript{16} fibrosis, or scar\textsuperscript{13} or are predicated on spatial distributions of dynamic gradients of conduction or repolarization.\textsuperscript{17}

**Clinical Implications**

Our results suggest a novel mechanism for the greater success of wide area circumferential ablation (≈2 cm from PV triggers) over PV ostial ablation,\textsuperscript{18} by ablating regions where AF actually initiates from PV or atrial triggers. These results suggest that ablation at sites of conduction restitution may complement trigger isolation. Importantly, preventive strategies could be based on these results. For instance, spiral wave AF initiation could be prevented by pre-emptive pacing to prevent re-entry or drug approaches to ameliorate conduction restitution. Patients with focal AF initiators may be treated by strategies to prevent triggered activity. These results complement our recent data that human AF may be perpetuated by localized sources, supported by the acute and chronic elimination of AF by targeted ablation.

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**Figure 6.** Conserved initiation of atrial fibrillation (AF) in 10 patients with multiple initiations. Right and left atria displayed for each patient with the location of the conserved initiating mechanism and triggers for each individual initiation. Section headings display the number of conserved initiations engaging the common initiating mechanism. Numbers in parentheses indicate multiple triggers from that location. Triggers depicted outside both atria represent an interatrial septum origin.
Study Limitations
Our 128 mapping electrodes covered the vast majority of the endocardial surfaces of both atria and likely provided sufficient resolution to identify changes in propagation at AF onset using each patient as their own control. Nevertheless, higher resolution would be preferred. Distance estimates from (x, y, z) coordinates likely included errors from cardiorespiratory motion; however, this is likely considerably less than the separation of trigger to AF-initiating site (21±17 mm). We did not dissect precise location data that may be difficult to define, for instance, given difficulties in assigning PV ostial locations in funnel-shaped antrums, but instead defined the functional relationship between any trigger and AF initiation. However, studies should reference trigger and AF initiation sites to anatomic sites of pathophysiology, such as scar, fibrosis,21 or fiber angles.16 Pacing from multiple locations in the same patient would shed light on the interaction of triggers with regional anisotropy, but was not performed because the protocol was already lengthy. Conduction time was used as a surrogate for conduction velocity that is accurate unless marked changes in propagation direction occur, which was not observed. We did not ablate initiating mechanisms because analysis was performed offline, but ongoing studies of prospective ablation are planned. Finally, we deliberately included both induced and spontaneous AF to study whether initiations were conserved between them. Several recent reports show that both forms of AF showed conserved frequency and rate gradients22 or spatial propagation23 in the same patient.

Conclusions
AF initiation is not a disorganized process, but operates by the dynamic formation of a spiral wave at sites of conduction slowing, or a focal driver. These mechanisms are often spatially conserved for a given patient despite triggers with diverse spatial locations and prematurities and are spatially separated from their trigger. These data open the possibility of new strategies to prevent AF onset by modulating these patient-specific AF-initiating mechanisms.

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Disclosures
Drs Narayan and Rappel are authors of intellectual property owned by the University of California Regents and licensed to Topera Inc. Topera does not sponsor any research, including that presented here. Drs Narayan and Rappel hold equity in Topera. Dr Narayan reports having received honoraria from Medtronic, St. Jude Medical, and Biotronik. The other authors report no conflicts.

References


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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL FIGURES

Supplemental Figure 1
SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1:

**Additional AF initiations.** (a) Spontaneous AF initiation by a clockwise spiral wave in the high septal right atrium in a 67-year-old man with persistent AF. (b) Spontaneous initiation of paroxysmal AF via a repetitive focal driver in a 57-year-old man, in which the focal driver in the low posterior RA for the first 2 AF cycles continued into sustained AF. (c) Two pacing-induced initiations in a 61-year-old man with paroxysmal AF. Each initiation demonstrates the same clockwise spiral wave in the mid posterior left atrium that initiates AF. In this patient rapid burst pacing was performed in the right superior pulmonary vein at cycle length 280 ms (214 bpm; initiation #1) and cycle length 500 ms (120 bpm; initiation #2).