Iterative navigation of multipole diagnostic catheters to locate repeating-pattern atrial fibrillation drivers

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Abstract

Introduction: Targeting repeating-pattern atrial fibrillation (AF) sources (reentry or focal drivers) can help in patient-specific ablation therapy for AF; however, the development of reliable and accurate tools for locating such sources remains a major challenge. We describe iterative catheter navigation (ICAN) algorithm to locate AF drivers using a conventional circular Lasso catheter.

Methods and Results: At each step, the algorithm analyzes 10 bipolar electrograms recorded at a given catheter location and the history of previous catheter movements to determine if the source is inside the catheter loop. If not, it calculates new coordinates and selects a new position for the catheter. The process continues until a source is located. The algorithm was evaluated in a computer model of atrial tissue with various degrees of fibrosis under a broad range of arrhythmia scenarios. The latter included slow and fast reentry, macroreentry, figure-of-eight reentry, and fibrillatory conduction. Depending on the initial distance of the catheter from the source and scenario, it took about 3 to 16 steps to localize an AF source. In 94% of cases, the identified location was within 4 mm from the source, independently of the initial position of the catheter. The algorithm worked equally well in the presence of patchy fibrosis, low-voltage areas, fragmented electrograms, and dominant-frequency gradients.

Conclusions: AF repeating-pattern sources can be localized using circular catheters without the need to map the entire tissue. The proposed algorithm has the potential to become a useful tool for patient-specific ablation of AF sources located outside the pulmonary veins.

KEYWORDS
atrial fibrillation (AF), atrial fibrillation ablation, multipolar diagnostic catheter, nonpulmonary-vein sources, repeating-pattern AF source detection

1 | INTRODUCTION

Haïssaguerre et al.1 suggested that ectopic beats from the pulmonary veins (PVs) may trigger atrial fibrillation (AF), which has led to an AF treatment known as PV isolation (PVI). PVI is an ablation procedure that electrically isolates the PVs from the atria by cauterizing the atrial tissue in the PV ostia using ablative energy (radiofrequency, cryoablation, laser ablation, etc.) and prevents ectopic beats from triggering AF.
However, this procedure is known to have only a 40%–60% long-term success rate.2 In many cases, PVI is ineffective because of tissue reconnection, but even in the case of complete PVI, there can be recurrence3 or continuation4 of AF. Such failures are attributed to the formation of repeating-pattern AF sources in the atria outside PVs, especially in persistent AF patients.5 Previous studies have shown that such additional sources are often functional reentry circuits that manifest themselves on the endocardium as repeating-pattern reentry, macroreentry, or focal AF drivers.6,7 Such AF drivers are usually localized with the help of the excitation phase maps of the entire atria8 constructed using 64-electrode biatrial basket catheters. However, this approach has several disadvantages compared with using conventional 20-electrode diagnostic catheters that are routinely used during PVI procedures. First, the flexible design of the splines in basket catheters has shown to result in spline deformation and interspline bunching when the catheter is placed in the left atrium.9 This phenomenon makes proper global electrode contact with the endocardium more difficult10 and reduces the left atrial coverage to less than 50%,11 thereby complicating accurate detection of AF drivers. Second, the relatively large interelectrode and nonuniform distance in the basket catheters limit the accuracy of AF source localization and can cause false detections.12

Here, we explore a fundamentally different approach for repeating-pattern AF source localization that does not involve electrophysiological mapping of the entire atria. Our method, referred to as the iterative catheter navigation (ICAN) algorithm, is based on analysis of bipolar electrograms recorded using a conventional 20-electrode catheter. Circular catheters are extensively used in clinical cardiac electrophysiology. We demonstrate that the information obtained from analysis of bipolar electrograms from these catheters is sufficient to detect an AF reentry or macroreentry source. The success of ICAN is even more evident in cases where the phase-mapping algorithm is challenged due to the low-resolution constraints of a basket catheter.

**METHODS**

**2.1 Human atrial electrophysiology model**

To test our ICAN algorithm, we generated six test cases shown in Figure 1. We simulated a 10 x 10 cm heterogeneous atrial tissue using Nygren et al13 ionic model with a spatial resolution of 0.25 mm and time steps of 0.05 ms.14 Tissue fibrosis was introduced as described in Section 1 of Supporting Information Data. We simulated reentry with a cycle length (CL) in the range of 140 to 260 ms by increasing the delayed rectifier K+ conductance value to shorten the CL or increasing the Na+ conductance value to generate longer cycle lengths.14 This covers the range of well below and above the baseline CL (178 ± 55 ms) of clinical AF.15

In some simulations (Figure 1A, 1C, 1D, and 1G), in addition to fibrosis, we introduced patchy myocardial scars by randomly removing 50% of electrical connections within a localized square...
area corresponding to "low-voltage" areas, which are common for pathological atrial myocardium and macroreentry AF drivers.16 To simulate figure-of-eight reentry, we simulated two closely spaced reentry cores (Figure 1F, Movie S1) and one anatomical figure-of-eight with a narrow conducting isthmus inside a fibrotic region (Figure 1G, Movie S2). To simulate fibrillatory activations with nonsustained singularity point reentry, in one simulation (Figure 1H, Movie S3) we introduced spatial heterogeneity in the inward rectifier channel conductance by increasing the $I_{K_{1}}$ conductance, which has been shown to be linked to AF-related remodeling,17 in the lower half of the simulated area.

2.2 | Simulation and processing of electrograms

We simulated a 20-electrode Lasso (Biosense Webster, Diamond Bar, CA), with a 7.5 mm radius and 4.5 to 1.4.5 mm interelectrode spacing (Figure 2A), to obtain 10 bipolar electrograms18 (Figure 2B). Specifically, the unipolar electrogram was calculated as in the paper by Gima and Rudy19 The bipole electrograms were then calculated as the difference of the electrograms at a unipole pair. At every catheter placement, 1-second recordings that constituted at least three rotation cycles were analyzed. Local activation times of each bipole electrogram were identified as the maximum peak positive or negative deflection within a refractory period of 50 ms.20 Bipoles with two activations separated by 10 to 50 ms were identified as long-double-potential.21 Electrograms with a peak-to-peak voltage of less than 0.1 mV were defined as low-voltage.22 CL was determined as the median of the time delays between two consecutive local activations at every bipolar electrogram. A customized program was developed to identify the activation times associated with the same wavefront as one cycle using the calculated activation times and CL. First, the algorithm identifies the bipolar with the earliest activation time in the recording. It then moves to the second activation time in the same bipolar and repeats the process for all cycles within 1 second of the recording until all the cycles within 1 second of the recording are identified.

2.3 | ICAN reentry detection algorithm

We developed an ICAN that locates a repeating-pattern AF driver using a conventional circular catheter without the need for full mapping of the entire atria in advance. In general, the algorithm detects repeating-pattern reentrant activity when either of two conditions is met. In one case, the time for all bipoles to be excited is prolonged and approaches the cycle length, suggesting that the catheter is on top of a reentry core. The other scenario finds anatomical macroreentry through detection of regions like scars that have low voltage or other electrogram abnormalities. When neither of these conditions is met, the algorithm suggests movement of the catheter in the direction toward the earliest activated bipolar, and the process is repeated.

To carry out these general principles and locate drivers of reentry, the algorithm determines, principal wave direction (PWD), conduction delay ratio (CDR), and anatomic reentry pattern (ARP) from the bipolar electrograms at every catheter placement.

The PWD (black arrow in Figure 2A) is determined as a vector starting from the catheter center and pointing to the earliest activated bipolar (bipole 6 in Figure 2). The PWD of a 1-second electrogram
recording is then determined as a vector with an angle equal to the average PWD angles of all the cycles within the recording in reference to the catheter center.

The CDR is calculated as the average ratio of the total conduction delay to CL for all the cycles. Starting from the earliest activated bipolar, the total conduction delay is determined as the sum of the time differences between the local activations of a bipolar and its following counter-clockwise bipolar, excluding the bipolar just clockwise from the earliest activated bipolar (see Figure 2C).

The ARP is calculated as $2\pi - 0.2\pi$ (the angle between a bipolar pair) times the number of low-voltage or long-double-potential bipolar electrograms from the current and prior catheter placements that are within 1.5 catheter radius of the average location of the catheter placements.

ICAN guides a catheter from initial arbitrary placement on the atrial endocardial surface towards a reentry core. The iterative process has two major steps. Step one checks the two reentry detection criteria and determines if at the current location the catheter encircles the core of a reentry source. The two reentry criteria are based on CDR and ARP.

The CDR-based criterion is satisfied when two close catheter placements (within 1 cm) have a CDR $\geq$ $Th$ and the average location of the two placements is detected as a reentry core. This criterion will be satisfied when the catheter encompasses a reentry core (Figure 3A) with a circulatory excitation through the bipoles as the reentry wavefront completes one cycle. We allow a 40% variation from a perfect circulatory excitation (CDR=1) and select a fixed value of 0.6 for $Th$ in this study.

The ARP-based criterion is satisfied when ARP $\leq 0.2\pi$ and the average location of the catheter placements that triggered this criterion is determined as a reentry core. This criterion detects cases of a reentry where a reentry core is anchored to anatomical barriers in the form of a patchy myocardial scar or fibrosis and forms a macroreentry AF source (Figure 3B).

If a reentry is not detected, the algorithm proceeds to Step two, where the algorithm shifts the catheter center by catheter radius in the direction of the PWD. At the new placement, step one is repeated until a reentry source is localized or a maximum number of placements (25 in this study) is reached.

For visualization purposes, an electrogram voltage map is constructed step by step as the catheter is navigated on the tissue. We use the natural neighbor interpolation technique to interpolate the peak-to-peak voltage of the bipolar electrograms on an interpolation grid of 0.25 mm spacing and interpolation area with a radius of 15 mm (diameter of the catheter).

2.4 | Detecting reentry sources using phase mapping and basket catheter

To compare the performance of the ICAN algorithm with the phase-mapping approach, we simulated a 64-electrode FIRMap (Abbott Electrophysiology) atrial basket catheter with a diameter of 40 mm (the highest resolution) (Figure S2). A variety of catheter placements was generated by shifting and rotating the basket catheter on the 2D atrial tissue. Seven shifts (with a spacing of 50 mm) were performed in
the highest-resolution direction and 16 shifts (with a spacing of 50 mm) were performed in the lowest-resolution direction. For every basket simulation, five different orientations (0°, 30°, 45°, 60°, and 90°) were simulated. Three orientations (ie, 0°, 45°, and 90°) of the catheter are shown in Figure S2. A total of 560 simulations were generated using this method. For each of the test arrhythmias patterns, we evaluated 560 simulations of the catheter. Phase mapping and reentry detection were carried out as described in Section 2 of the Supporting Information Data.

3 | RESULTS

3.1 | Evaluation of the ICAN algorithm

Figure 4A displays a catheter path to the reentry core starting from an arbitrary placement (L1). The algorithm guided the catheter (the black arrow) to the subsequent placement at L2 until the CDR criterion was met at L7, and a reentry core was detected between the L6 and L7 locations. Figure 5A shows a case where ICAN establishes a guidance path around the unexcitable patch and stops according to the ARP-based criterion when the catheter path of L6 to L13 with low voltages forms an (almost) closed loop. See Figure S3 for more examples of the convergence of our algorithm to the core of a reentry source.

Next, we placed the catheter in different locations across the entire simulated region for different reentry mechanisms. In each of the eight cases, we tested 114,921 uniformly spaced initial catheter locations and showed the detected reentry locations in Figure 6. A reentry detection is considered a successful detection if the detected location is within 4 mm (an ablation catheter tip diameter) from the average trajectory of the reentry core (Figure S4). Despite the stringent success criteria, the average rate of successful detection was greater than 94% in all six cases and 100% in two cases (Figure 7A). The rare false detections were the result of the detection error exceeding the 4 mm threshold. However, the average distance of the false detected reentry was only 4.52 ± 0.31 mm away from the reentry meandering path, which indicated that the false detected sources were not too far from the reentry meandering path (Figure 7B). There were no detection failures, meaning that all tests in all cases located a reentry in fewer than 25 catheter placements.
Figure 7C shows the number of placements until a reentry was detected as a function of the distance from the reentry. As shown, the number of placements before a reentry was detected linearly increased as a function of the distance of the initial catheter placement. The rate of increase was 6.25 mm per iteration, which is not too far from its optimal path (i.e., a direct path to the reentry core with 7.5 mm guidance steps). This suggests that when the initial catheter placement is far from a reentry, ICAN efficiently navigates the catheter towards the reentry core.

Another observation is that in single- and double-reentry cases (Figure 7C), an average of three iterations will be followed before a reentry is detected even when ICAN starts from an initial placement close to the reentry meandering path. This is because satisfying the CDR criterion requires at least two close placements with $\text{CDR} \geq 0.6$. Hence, even when the algorithm starts with an initial placement with $\text{CDR} \geq 0.6$, it will require another iteration. However, when the catheter is close to the reentry core, the PWD may guide the next placement away from the core, and only after the subsequent placement is made will it return the catheter back to the reentry core. That is when two close placements with $\text{CDR} \geq 0.6$ are recorded and the CDR criterion will be satisfied so that a reentry will be detected.

We also realized that the average number of iterations was higher in cases with localized patchy myocardial scars and complex fibrillatory conduction. This is due to the increase of reentry detection cases based on the ARP criterion, which required the catheter to be guided along the reentry meandering before it detected a reentry.

We investigated ICAN’s sensitivity to the error in positioning the catheter on the location that the algorithm identifies. To simulate such an error, we randomly placed the catheter over a radius $r$ area from the ICAN-recommended location at every catheter placement. The larger values of $r$ generate more inaccuracies (errors) in catheter placement. We repeated the application of ICAN on the simulation case of Figure 1A for values of $r$ from 0 mm (no error) to 20 mm with steps of 5 mm. The percentage of catheter navigations with detection failure (no source was localized or 25 catheter placements were reached) and successful source localizations were calculated for every value of $r$ (Figure 8A). Despite the large error in the catheter placement, the percentage of successful source detection remained above 92.71%. However, the algorithm started to have some difficulties locating the source in under 25 catheter placements with a catheter placement error of 20 mm. This was evident by a sudden increase in the number of detection failures when catheter placement error increased from 15 to 20 mm. Another observation was that the average number of iterations increased with catheter placement error (Figure 8B). However, it was notable that this increase was minimal for 5 and 10 mm placement errors.

We also explored the performance of our algorithm with respect to poor catheter contact with the endocardium. To simulate the...
effect of missing electrodes due to poor contact, at every catheter placement, either one or two electrodes were randomly selected and removed from the electrogram processing. The ICAN algorithm guided the catheter and detected the AF source location without the electrograms of the missing electrodes. The percentage of missing electrodes was calculated as the ratio of the missing electrodes to the total electrodes (rounded to the nearest five) for every catheter guidance path. The percentage of successful detection for 5%, 10%, 15%, and 20% missing electrodes was 97.90%, 96.2%, 93.34%, 85.8%, and 69.7%, respectively. As expected, poor contact reduced the performance; however, it is notable that ICAN was able to detect a source with an average successful rate of greater than 85% even with 15% missing electrodes.

3.2 Comparison with the phase-mapping using FIRMap basket catheter

The phase-mapping technique using a basket catheter was applied to the same set of simulated arrhythmia cases. In Figure 6, the reentry locations identified by phase mapping using two basket catheter orientations (0° and 90° rotations for orientation 1 and orientation 2, respectively) are shown. The average successful reentry localization and localization accuracy for all the 560 catheter simulations and all the simulation cases are provided in Figure 7. In four out of eight cases (Figure 7A), the rate of successful detection was 70% or less, while ICAN provided consistent performance for all cases \( p < 10^{-18} \). In addition, the discrepancy of the false detected reentry sources was greater than 20 mm for four simulation cases: fast single reentry (Figure 6B: 23.48 mm ± 13.80 mm), double reentry (Figure 6E: 18.52 ± 9.3 mm), functional figure-of-eight reentry (Figure 6F: 16.4 ± 14.35 mm), and complex fibrillatory reentry (Figure 6H: 13.63 ± 12.66 mm). However, the false detected reentry sources with ICAN formed a dense cloud of points in the vicinity of the reentry tip, with the complex fibrillatory reentry case (Figure 6H: 7.4 ± 2.5 mm) being the farthest followed by the rest of the simulation cases with a distance of about 4.4 ± 0.2 mm from the reentry meandering path.

4 DISCUSSION

Targeting the repeating-pattern AF drivers located outside PVs has been shown to improve the effectiveness of the PVI procedure in cases where the procedure fails for reasons other than PVI reconnection. This brought to the forefront the problem of identification of non-PV sources of the arrhythmia. Much outstanding research on the design of computational mapping systems for improved detection of non-PV AF drivers has been reported. For the most part, this study has focused on developing 3D electroanatomic mapping based on the electrogram characteristics from a single or multiple pole
diagnostic catheter. The methods use a single characteristic, such as cycle length, dominant frequency, or voltage, and ablate the areas with short cycle length, high dominant frequency, or low voltage, respectively. However, the methods have shown to be suboptimal with contradictory clinical outcomes at different clinical centers. One promising approach that is being actively explored is phase mapping with a multipolar basket catheter. Clinical and theoretical studies, however, show that the electrode density that can be achieved using the state-of-the-art catheters is not always sufficient to provide accurate localization and can lead to a significant number of false positives. As an alternative to basket catheters, Roney et al. explored multipolar spiral catheters, which provide higher spatial resolution but need to map the entire atrial surface. To construct the activation map of the atria, the recordings were taken from several locations and subsequently integrated into a full 3D electroanatomical map with higher spatial resolution.

Here we explore a fundamentally different approach when the source is detected without constructing and analyzing an activation map of the atria. Instead, our ICAN algorithm utilizes bipolar electrogram recordings obtained from a conventional circular catheter to iteratively guide it until the reentry core is detected.

We tested our algorithm computationally on a set of eight surrogate cases representing various reentry-driven atrial arrhythmias that cover the range of AF CLs reported in AF patients. Fibrosis-related electrogram changes such as fractionation (Figure S1) and reduced amplitude made the task of electrogram analysis and reentry detection more challenging. The simulation case in Figure 1H generated a dominant frequency gradient with the dominant frequency of the lower tissue area being almost double the dominant frequency in the upper tissue area (Figure S5). Our simulations show that ICAN is very robust to different CLs and capable of identifying not only stable and unstable reentry sources but also anchored reentry sources as well as macroreentry circuits around large patches of fibrotic tissues. The algorithm can also deal with low-amplitude, complex electrograms, and dominant-frequency gradients, which makes it suitable for using in clinical settings.

FIGURE 7  Reentry localization analysis. A, Average percentage of successful reentry localization. B, Distance of the located reentry core from the ground truth reentry meandering path. C, Average number of catheter placements until a reentry core was detected for different distances of the initial catheter placements from the ground truth. The points represent the average placements and the lines indicate the fitted lines to the corresponding data points. *p < 10^{-18}. The simulation cases A-H correspond to cases (A) to (H) in Figure 1.

FIGURE 8  Analysis of ICAN robustness to catheter misplacement with errors of 0 to 20 mm. A, The percentage of catheter navigations with detection failure (no source was localized or 25 catheter placements were reached) and successful source localizations. B, The change in the average number of iterations with respect to catheter placement error. ICAN, iterative catheter navigation.
The ICAN algorithm is less likely to produce false detections and provides significantly higher accuracy compared with the phase-mapping approach utilizing the 64-electrode FIRMMap. According to our simulations, the phase maps obtained with this particular device in fibrotic tissues could be very sensitive to catheter orientation (red/yellow asterisks in Figure 6) and significantly affect the quality of predictions. However, it worked exceptionally well when no fibrosis was introduced in the simulation (Figure S6). These observations were in agreement with the previous reports\(^3^4\) that the low-resolution basket catheters similar to FIRMMap were prone to false detections.

It should be noted, however, that robustness and high resolution come at a price of an iterative process. It is notable that even when the initial placement of the catheter is very close to the reentry core, it takes several placements of the catheter to confirm the reentry. This is the result of built-in security measures included to minimize the rate of false detections. Indeed, our algorithm does not stop when the CDR condition is first met but requires additional confirmation through more catheter placements, which explains the shift of the regression line in Figure 7C.

The convergence rate of the ICAN algorithm is proportional to the radius of the catheter (7.5 mm). By increasing the radius of the catheter, the number of catheter placements may be reduced. Yet, such acceleration would result in reduced accuracy of localization. The convergence could be accelerated if the distance from as well as the direction to the source could be estimated. Although in theory, this is possible utilizing simplified models of cardiac propagation,\(^3^7\) the feasibility of this approach in realistic highly heterogeneous cardiac tissue has yet to be determined.

Our analysis shows that the algorithm is robust: the error in positioning does not accumulate and the algorithm is self-correcting until the catheter placement error is increased to 20 mm. We extensively studied the effect of low-voltage electrograms produced by fibrosis and poor electrode contact and demonstrated the effectiveness of ICAN for dealing with low-amplitude recordings when the signal is absent due to fibrosis or poor electrode contact.

### 4.1 Clinical implications

The ICAN reentry detection algorithm, we have developed, has the potential to locate patient-specific reentry sources within the atria using a conventional diagnostic Lasso catheter with no additional cost or safety risk to the patient. The algorithm collects and integrates local real-time measurements to detect reentry as well as configures vector findings to direct the clinician operator towards the proper direction to promptly locate the reentry cores. Furthermore, our algorithm can be associated with substantial procedural time saving, as it is capable of locating the AF sustaining sources without a laborious process to construct a 3D electroanatomic map, which often requires the acquisition of thousands of local electrograms. In combination with advanced 3D anatomic mapping systems, it can result in the development of a fast and effective AF ablation targeting system. Such a system may significantly improve the success of AF ablation at first attempt and facilitate treating patients before progression of AF to the permanent stage.

### 4.2 Study limitations

Given the complexity of the propagation patterns in AF, we aimed to validate our ICAN approach for a range of clinically relevant simulations from simpler to more complex cases. Our focus was exclusively on reentry detection in AF with repeating patterns and atrial tachycardias that often develop after AF ablation and thus are of great clinical relevance. The currently established clinical procedures to treat AF patterns with very complex nonstationary activation patterns are PVI or maze procedure; those patterns are outside the scope of this study. However, repeating complex AF patterns could be detected by ICAN, as evident by our exploratory investigation performed using clinical AF data (see Figure S8). Given that the main principle of ICAN, which is finding the direction towards the wave source and making a step in this direction, can be preserved, we anticipate that the ICAN algorithm can be expanded to detect focal activity\(^3^8\) by identifying additional stopping criteria (Section 7 of the Supporting Information Data) for the focal source (see Figure S7). Focal sources can be produced by 3D scroll waves whose filaments do not intersect the surface and manifest themselves as breakthroughs as well as other types of intramural reentry.\(^7^9\)

The ICAN algorithm was tested on a flat surface rather than on a realistic 3D surface. Our algorithm hinges on deriving the local activation times, determining the local prevalent direction of wave propagation, and recognizing the presence of the source inside the catheter loop. As long as these local tasks can be solved accurately and reliably, the algorithm will guide the catheter to a source on the atrial surface no matter how complex the surface geometry and the pattern of wave propagation. In addition, the introduction of fibrotic septa in our simulations allows for meaningful modeling of fractionated electrograms without the need for 3D (Figure S1). Although we have tested our particular algorithm in a 2D atrial tissue, we do not anticipate any difficulties in 3D simulations of entire atria with realistic geometries, as such cases do not offer fundamentally different scenarios that could confound our algorithm (see Figure S8 for the convergence of our algorithm to the reentry in a realistic 3D atrial geometry as described in Section 8 of Supporting Information Data). In addition, we also used a case of clinical AF (Figure S9) to indicate the potential of our new approach for detecting AF drivers with repeating patterns. Overall, the performance of ICAN in the presence of AF patterns with very complex and nonstationary activation patterns warrants further clinical investigation.

### 5 Conclusion

We proposed the ICAN algorithm to localize repeating-pattern reentry sources by guiding a conventional 20-electrode circular catheter using the characteristic signals from the electrograms and the guidance trajectory path. This is the first work to adopt the widely available clinical electrophysiology laboratory system to iteratively navigate a conventional circular catheter towards a reentry source without the need to map the entire atria. The success
of the ICAN algorithm was verified using simulated human atrial model data with six electrical remodeling cases to represent different mechanisms of sustaining AF. The success of the ICAN algorithm was highlighted by our further analysis, which showed that the complexity of the generated simulations made it challenging for the phase-mapping algorithm to successfully locate the reentry sources using a 64-electrode FIRMMap basket catheter. This study shows that the new ICAN algorithm could play a significant role in the successful detection and ablation of reentry sources outside the PVs and in increasing the success of AF elimination procedures.

CONFLICT OF INTERESTS
The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS
Concept/design was performed by P. G., B. G., and A. M. P.; computer simulation was performed by P. G., A. S., and E. M. C. Data analysis/interpretation and statistics were conducted by P. G., A. S., and B. G. The article was drafted by B. G., A. M. P., E. M. C., and D. T. H. Funding was secured by B. G., A. M. P., and E. M. C.

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REFERENCES
1. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the 30 pulmonary veins. N Engl J Med. 1998;339(10):659-666.
2. Weerasooriya R, Khairy P, Litaijen J, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol. 2011;57(2):160-166.
3. Maesen B, Pison L, Vroomen M, et al. Three-year follow-up of hybrid ablation for atrial fibrillation. Eur J Cardiothorac Surg. 2018;53(2):126-132.
4. Scherr D, Khairy P, Miyazaki S, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. Circ Arrhythm Electrophysiol. 2014;8:18-24.
5. Theis C, Konrad T, Molnau H, et al. Arrhythmia termination versus elimination of dormant pulmonary vein conduction as a procedural end point of catheter ablation for paroxysmal atrial fibrillation a prospective randomized trial. Circ Arrhythm Electrophysiol. 2015;8:1080-1087.
6. Vaquero M, Caldo D, Jalife J. Cardiac fibrillation: from ion channels to rotors in the human heart. Heart Rhythm. 2008;5(6):872-879.
7. Hansen B, Zhao J, Fedorov V. Fibrosis and atrial fibrillation: computerized and optical mapping: a view into the human atria at submillimeter resolution. JACC: Clinical Electrophysiology. 2017;3(6):531-546.
8. Narayan SM, Krummen DE, Rappel WJ. Clinical mapping approach to diagnose electrical rotors and focal impulse sources for human atrial fibrillation. J Cardiovasc Electrophysiol. 2012;23(5):447-454.
9. Laugnner J, Shome S, Child N, et al. Practical considerations of mapping persistent atrial fibrillation with whole-chamber basket catheters. JACC: Clinical Electrophysiology. 2016;2(1):55-65.
10. Issa Z, Miller J, Zipes D. Clinical arrhythmology and electrophysiology: a companion to Braunwald’s heart disease. Philadelphia, PA, Elsevier; 2012.
11. Oesterlein T, Frisch D, Loewe A, et al. Basket-type catheters: diagnostic pitfalls caused by deformation and limited coverage. BioMed Res Int. 2016;5340574:1-13.
12. Roney CH, Cantwell CD, Bayer JD, et al. Spatial resolution requirements for accurate identification of drivers of atrial fibrillation. Circ Arrhythm Electrophysiol. 2017;10(5):e004899.
13. Nygren A, Fiset C, Firek L, et al. Mathematical model of an adult human atrial cell the role of k+ currents in repolarization. Circ Res. 1998;82(1):63-81.
14. Cherry EM, Evans SJ. Properties of two human atrial cell models in tissue: restitution, memory, propagation, and reentry. J Theor Biol. 2008;254(3):674-690.
15. Meo M, Pambrun T, Derval N, et al. Noninvasive assessment of atrial fibrillation complexity in relation to ablation characteristics and outcome. Front Physiol. 2018;9:1-19.
16. Haissaguerre M, Shah AJ, Cochet H, et al. Intermittent drivers anchoring to structural heterogeneities as a major pathophysiological mechanism of human persistent atrial fibrillation. J Physiol. 2016;594(9):2387-2398.
17. Berenfeld O. The major role of I K1 in mechanisms of rotor drift in the atria: a computational study. Clin Med Insights Cardiol. 2016;10:71-79.
18. Plonsey R, Barr R. Bioelectricity: a quantitative approach. New York, NY, Springer Science & Business Media; 2007.
19. Gima K, Rudy Y. Ionic current basis of electrocardiographic waveforms: a model study. Circ Res. 2002;90(8):889-896.
20. Lee S, Sahadevan J, Khrestian CM, Durand DM, Waldo AL. High density mapping of atrial fibrillation during vagal nerve stimulation in the canine heart: restudying the Moe hypothesis. J Cardiovasc Electrophysiol. 2013;24(3):328-335.
21. Konings KTS, Smeets JLRM, Penn OC, Wellsen HJJ, Allessie MA. Configuration of unipolar atrial electrograms during electrically induced atrial fibrillation in humans. Circulation. 1997;95(5):1231-1241.
22. Hunter R, Liu Y, Lu Y, Wang W, Schilling R. Left atrial wall stress distribution and its relationship to electrophysiologic remodeling in persistent atrial fibrillation clinical perspective. Circ Arrhythm Electrophysiol. 2012;5(2):51-360.
23. Pandit SV, Jalife J. Rotors and the dynamics of cardiac fibrillation. Circ Res. 2013;112(5):849-862.
24. Allessie MA, Bonke FI, Schopman FJ. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The ”leading circle” concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ Res. 1977;41(1):9-18.
25. Ghoraani B, Dalvi R, Gizurarson S, et al. Localized rotational activation in the left atrium during human atrial fibrillation: relationship to complex fractionated atrial electrograms and low-voltage zones. Heart Rhythm. 2013;10(12):1830-1838.
26. Sibson R. Interpolating multivariate data: Chapter 2: A Brief description of natural neighbor interpolation. New York: John Wiley & Sons; 1981.
27. Hansen BJ, Zhao J, Csepe TA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. Eur Heart J. 2015;36(35):2390-2401.
28. Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysologic substrate. J Am Coll Cardiol. 2004;43(11):2044-2053.
29. Atienza F, Almendral J, Jalife J, et al. Real-time dominant frequency mapping and ablation of dominant frequency sites in atrial fibrillation with left-to-right frequency gradients predicts long-term maintenance of sinus rhythm. Heart Rhythm. 2009;6(1):33-40.
30. Jadidi AS, Lehrmann H, Keyl C, et al. Ablation of persistent atrial fibrillation targeting low-voltage areas with selective activation characteristics. Circ Arrhythm Electrophysiol. 2016;9(3):e002962.
31. Atienza F, Almendral J, Ormaetxe JM, et al. Comparison of radiofrequency catheter ablation of drivers and circumferential pulmonary
vein isolation in atrial fibrillation: a noninferiority randomized multi-center RADAR-AF trial. J Am Coll Cardiol. 2014;64(23):2455-2467.
32. Wong K, Paisey J, Sopher M, et al. No benefit of complex fractionated atrial electrogram (CFAE) ablation in addition to circumferential pulmonary vein ablation and linear ablation: BOCA study. Circ Arrhythm Electrophysiol. 2015;8(6):1316-1324.
33. Frontera A, Takigawa M, Martin R, et al. Electrogram signature of specific activation patterns: analysis of atrial tachycardias at high-density endocardial mapping. Heart Rhythm. 2018;15(1):28-37.
34. King B, Porta-Sánchez A, Massé S, et al. Effect of spatial resolution and filtering on mapping cardiac fibrillation. Heart Rhythm. 2017;14(4):608-615.
35. Buch E, Share M, Tung R, et al. Long-term clinical outcomes of focal impulse and rotor modulation for treatment of atrial fibrillation: a multicenter experience. Heart Rhythm. 2016;13(3):636-641.
36. Roney CH, Cantwell CD, Qureshi NA, et al. Rotor tracking using phase of electrograms recorded during atrial fibrillation. Ann Biomed Eng. 2017;45(4):910-923.
37. Weber FM, Schilling C, Seemann G, et al. Wave-direction and conduction-velocity analysis from intracardiac electrograms-a single-shot technique. IEEE TBME. 2010;57(10):2394-2401.
38. de Groot N, van der Does L, Yaksh A, et al. Direct proof of endo-epicardial asynchrony of the atrial wall during atrial fibrillation in humans. Circ Arrhythm Electrophysiol. 2016;9(5):e003648.
39. Gharaviri A, Verheule S, Eckstein J, et al. How disruption of endo-epicardial electrical connections enhances endo-epicardial conduction during atrial fibrillation. EP Europace. 2016;19(2):308-318.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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