Mechanisms for the Termination of Atrial Fibrillation by Localized Ablation
Computational and Clinical Studies

Wouter-Jan Rappel, PhD; Junaid A.B. Zaman, MA, BMBCh; Sanjiv M. Narayan, MD, PhD

Background—Human atrial fibrillation (AF) can terminate after ablating localized regions, which supports the existence of localized rotors (spiral waves) or focal drivers. However, it is unclear why ablation near a spiral wave tip would terminate AF and not anchor reentry. We addressed this question by analyzing competing mechanisms for AF termination in numeric simulations, referenced to clinical observations.

Methods and Results—Spiral wave reentry was simulated in monodomain 2-dimensional myocyte sheets using clinically realistic rate-dependent values for repolarization and conduction. Heterogeneous models were created by introduction of parameterized variations in tissue excitability. Ablation lesions were applied as nonconducting circular regions. Models confirmed that localized ablation may anchor spiral wave reentry, producing organized tachycardias. Several mechanisms referenced to clinical observations explained termination of AF to sinus rhythm. First, lesions may create an excitable gap vulnerable to invasion by fibrillatory waves. Second, ablation of rotors in regions of low-excitability (from remodeling) produced re-entry in more excitable tissue allowing collision of wavefront and back. Conversely, ablation of rotors in high-excitability regions migrated spiral waves to less excitable tissue, where they detached to collide with nonconducting boundaries. Third, ablation may connect rotors to nonconducting anatomic orifices. Fourth, reentry through slow-conducting channels may terminate if ablation closes these channels.

Conclusions—Limited ablation can terminate AF by several mechanisms. These data shed light on how clinical AF may be sustained in patients’ atria, emphasizing heterogeneities in tissue excitability, slow-conducting channels, and obstacles that are increasingly detectable in patients and should be the focus of future translational studies. (Circ Arrhythm Electrophysiol. 2015;8:1325-1333. DOI: 10.1161/CIRCEP.115.002956.)

Key Words: ablation techniques ▪ atrial fibrillation ▪ computational modeling ▪ rotor ▪ therapeutics
WHAT IS KNOWN

- Spiral waves (rotors) and focal sources may drive atrial fibrillation (AF) as recently shown in humans. Limited ablation may disrupt anchor spiral waves, converting AF into atrial tachycardia (AT), but should not terminate AF to sinus rhythm with extensive, linear ablation.
- However, targeted ablation is well known to terminate clinical micro-reentrant AT to sinus rhythm, and has been shown to terminate AF rotors to sinus rhythm in recent clinical studies.

WHAT THE STUDY ADDS

- Using computational models incorporating recognized heterogeneities in repolarization or excitability, limited ablation was able to terminate spiral wave re-entry by creation of an excitable gap, dislodgement or closing of critical isthmuses.
- As predicted, targeted ablation can also anchor a spiral wave to atrial tachycardia and linear ablation from a spiral tip to anatomic or functional barriers can also terminate re-entry.
- These computational mechanisms were consistent with clinical cases employing focal impulse and rotor modulation (FIRM) guided ablation at sites of proven AF termination.

In this study, we numerically investigated the effects of ablation lesions on spiral wave reentry, incorporating increasingly appreciated nonuniformities in atrial physiology that may enable ablation to terminate AF, using clinical results to corroborate numeric findings.

Methods

Simulations

Simulations were performed in isotropic 2-dimensional (2D) sheets using the monodomain equation:

$$\frac{dV}{dt} = \nabla \cdot D \nabla V - \frac{I_{m}}{C_{m}}$$ (1)

Here, $V$ is the membrane voltage, $C_{m}=1 \ \mu F/cm^{2}$ represents the membrane capacitance, $D$ the diffusion tensor with diagonal entries of $D=0.001 \ \text{cm}^{2}/\text{ms}$, and $I_{m}$ the membrane currents. Membrane currents were implemented by the Fenton–Karma (FK) model. Parameter values for the FK model were chosen from set 3 and excitability was modified through the parameter $\tau_{D}$. As demonstrated, this set and variations in $\tau_{D}$ can capture different spiral wave dynamics, including nonmeandering and meandering spiral tips as well as spiral wave breakup. Notably, other parameter sets or detailed electrophysiological models give similar dynamics, and termination mechanisms discussed are not unique to a specific parameter set or model.

Equation 1 was simulated on a square grid using a standard finite difference scheme with spatial discretization of 0.025 cm and time-step of 0.05 ms. These values of spatial and temporal discretization ensured conduction velocity (CV) and action potential durations (APDs) were <3% of their converged values with resulting activation waves qualitatively unchanged. During 1000-ms cycle length pacing, CV and APD for the parameter set were 42.5 cm/s and 270 ms, respectively. These values can be adjusted arbitrarily by multiplying all time constants and the diffusion coefficient with a constant. Computational details are detailed in Table.

Ablation lesions were modeled as circular regions of radius $R_{abl}$ with zero conductivity, rendering the tissue inexcitable. $R_{abl}$ was varied in steps of 0.05 cm (range, 0.2–1.0 cm). To account for zero-flux boundary conditions at the edge of the disk-like region, we use the phase-field method, which is well suited to model appropriate boundary conditions on curved interfaces while using a finite difference grid. The edges of the computational domain are assumed to have zero-flux boundary conditions unless otherwise specified.

Cardiac tissue can exhibit significant nonuniformities as a result of local differences in APD restitution, conduction or fibrosis. In our model, heterogeneity of tissue excitability was introduced by spatially varying $\tau_{D}$ parameter of the FK model, $\tau_{D}$. Low values correspond to highly excitable tissue, whereas large values indicate reduced excitability. To vary this parameter in tissue, we defined 2 circles with radii $R_{1}$ and $R_{2}$, centered in the computational domain. The value of the excitability parameter was varied in a linear and radial fashion from $\tau_{D1}$ to $\tau_{D2}$:

$$\tau_{D} = \tau_{D1} + \left( \frac{\tau_{D2} - \tau}{\tau_{D2} - \tau_{D1}} \right) \left( R_{2} - \tau \right) / \left( R_{2} - \tau_{D1} \right)$$

where $r$ is location in the computational domain relative to its center.

Reentry arose from either cross-stimulation or using a broken wave as initial conditions. Several perturbations were then introduced as described in Results section of this article. Typical simulation times ranged from 1 to 7 min on a workstation equipped with a dual 2.4 GHz quad-core Intel Xeon processor. Spiral tip trajectories were computed using a standard tracking algorithm.

Clinical Studies

An institutional review committee approved all clinical studies, and subjects gave informed consent. The approach to mapping human AF and ablating localized sources has been detailed by our group and others. We studied patients referred for ablation of symptomatic paroxysmal or persistent AF for standard indications. After discontinuation of antiarrhythmic medications, AF was recorded from biatrial multipolar contact catheters. Recordings were analyzed using methods described to interpret electrograms based on human repolarization and conduction dynamics.

Electric rotors were defined as phase singularities that radiate electric waves into surrounding tissue at high rate causing wavebreak into fibrillation, whereas focal impulses showed centrifugal activation from an origin. AF sources identified using contact mapping procedures to map the inverse solution also occur in reproducible and limited areas for long periods of time, whereas drivers mapped by the inverse solution also occur in reproducible and limited regions for days.

Ablation of each AF source involved application of radiofrequency energy to the $\approx 2$ to 3 cm$^{2}$ ablation area. This process (FIRM) was repeated for each source (2.1±1.1 per patient). Subsequent clinical care included conventional ablation. In this report, we focus only on the impact of limited FIRM-guided ablation to acutely terminate AF. We illustrate modeling-predicted mechanisms of AF termination with examples from our experience of FIRM-guided ablation.

Results

Computational simulations revealed several mechanisms by which limited ablation interfered with spiral wave reentry, converting AF to organized tachycardias, or terminating AF to sinus rhythm. These mechanisms were consistent with several observed clinical cases of rotor targeted (FIRM guided) ablation.

Conversion of AF to AT

Targeted ablation (a nonconducting obstacle) may pin a spiral wave to fixed reentry around the obstacle. Figure 1A shows a numeric example of a spiral wave with meander (green
line, shown for ≈900 ms) causing AF in surrounding tissue. An ablation lesion (blue disk) alters tip trajectory (red line), and after ≈1200 ms, the spiral tip is stably anchored at the lesion. This spiral wave produces regular AT with cycle length 210 ms. As reported in other computational studies, simulations using τ and domain sizes display the same termination mechanism. For example, creating sufficiently large ablation lesions (τd=0.3 to τd=0.42, with corresponding CVs of 36.7 and 26.3 cm/s, respectively). Ablating the heterogeneous high-excitability domain results in a nonconducting zone (radius, 0.8 cm), detachment of the spiral wave, consequent migration and collision with anatomic obstacles (modeled as no-flux boundaries). This resulted in termination of the rotor and AF (Movie II in the Data Supplement). Varying ablation radius in steps of 0.05 cm revealed minimum ablation radius as 0.65 cm for the parameters in Figure 3A. We have verified other combinations of τd, τg, Rg, and R≈, which result in successful termination as well. For example, creating sufficiently large ablation lesions when changing either τd to (0.25) or R≈ to (0.6 cm) only causes spiral wave termination. Clearly, minimum ablation size will depend on precise parameter values, but the qualitative termination behavior of Figure 3 is insensitive to parameter choices.

### Table. Numeric Details

<table>
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<th>Figures</th>
<th>Domain Size, cm</th>
<th>Boundary Conditions</th>
<th>τg</th>
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<td>Nonconducting in all directions (A)</td>
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<tr>
<td></td>
<td></td>
<td>10×5 (B and C)</td>
<td>Nonconducting in vertical and periodic in horizontal direction (B and C)</td>
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<td></td>
<td></td>
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<td>0.35–0.25 (C–E)</td>
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</table>

### Elimination of Reentry by Creation of an Excitable Gap

First, we studied the impact of ablation creating an excitable gap near the rotor core. Figure 2A shows a snapshot of simulations in which the excitability parameter τ produced multiple spiral waves, τg=0.34. Creating a lesion (Figure 2B) anchored 1 spiral wave leaving a small excitable gap (Figure 2C). Activation from surrounding fibrillatory waves invaded this excitable gap, with a stochastic likelihood of wave collision causing block and terminating reentry (Figure 2D; Movie I in the Data Supplement). We verified that other values of τg and domain sizes display the same termination mechanism. For example, simulations using τg=0.32 in a 5×5-cm domain and τg=0.36 in a 7.5×7.5 cm result in spiral wave dislodgment by surrounding waves, followed by termination.

### Elimination of Reentry Related to Gradients in Tissue Excitability

To address mechanisms based on spatial heterogeneities in tissue, we varied the FK model excitability parameter, τg, in a radial fashion (Methods section of this study). Initially, we created a spiral wave stably attached to a nonconducting zone with a radius of 0.4 cm (Figure 3) and investigated 2 scenarios: one in which excitability increased with distance from the nonconducting zone and another in which it decreased. An ablation lesion introduced over the initial nonconducting zone but of larger radius was able to unpin the anchored spiral in both scenarios.

Figure 3A and 3B illustrates the first scenario, with excitability higher within the dashed circle than in surrounding tissue (τg=0.3 to τg=0.42, with corresponding CVs of 36.7 and 26.3 cm/s, respectively). Ablating the heterogeneous high-excitability domain results in a nonconducting zone (radius, 0.8 cm), detachment of the spiral wave, consequent migration and collision with anatomic obstacles (modeled as no-flux boundaries). This resulted in termination of the rotor and AF (Movie II in the Data Supplement). Varying ablation radius in steps of 0.05 cm revealed minimum ablation radius as 0.65 cm for the parameters in Figure 3A. We have verified other combinations of τg, τg, Rg, and R≈, which result in successful termination as well. For example, creating sufficiently large ablation lesions when changing either τg to (0.25) or R≈ to (0.6 cm) only causes spiral wave termination. Clearly, minimum ablation size will depend on precise parameter values, but the qualitative termination behavior of Figure 3 is insensitive to parameter choices.

**Figure 1.** Conversion of atrial fibrillation (AF) to atrial tachycardia (AT). A, Snapshot of anchoring of a counter clockwise spiral wave (white arrow) by introduction of a nonconducting ablation lesion. Activation is shown using a gray scale with white indicating activated tissue and black indicating unpowered tissue. The spiral tip trajectory before the introduction of the lesion is shown in green and meanders, resulting in AF-like activation. The creation of a lesion (blue disk) progressively anchors the trajectory (shown as the red trajectory) that converges to a regular AT (counterclockwise red arrows). The tissue has size 5×5 cm, and R≈=0.4 cm. The direction of the tip trajectories is indicated by arrows. B and C, Snapshots before (B) and after (C) the introduction of a circular lesion (blue, R≈=1 cm) in a larger computational domain (10×5 cm) with period boundary conditions in the horizontal direction. Before the introduction of the lesion (B), the domain harbors 3 spirals with tip trajectories indicated in green and direction by arrows. After the lesion (C), a single activation front is stably anchored at the lesion, resulting in regular activation. Scale bars, 1 cm.
Figure 2. An excitable gap created by ablation is invaded by fibrillatory waves to rapidly terminate spiral wave reentry. A, Multiple spiral waves exist before ablation. B, The abrupt creation of an ablation lesion (blue disk, nonconducting zone, $R_2=0.6$ cm) leads to an activation front that rotates around the zone in a counterclockwise fashion (indicated by red arrows) and an incoming wave (indicated by green arrows). C, The distance between the front and the back of the wave is large enough that an incoming wave can excite the tissue. This results in a wave collision and dislodgement of reentry (D). Domain size 5×5 cm, periodic boundary conditions in the horizontal direction. Scale bar, 1 cm.

Figure 3C to 3E illustrates the second scenario when ablation may terminate a spiral wave whose tip is located in a region of low excitability ($R_1=0.4$ cm, $\tau_1=0.35$, and CV=33.0 cm/s) surrounded by higher excitability ($\tau_2=0.25$ and CV=42.6 cm/s). Initially, the activation front is anchored at a small, circular nonconducting obstacle. Creating an ablation lesion of larger radius results in the activation front propagating in tissue with higher excitability and correspondingly higher wave speed, allowing activation front and back to eventually meet, leading to block (Figure 3E, double bars). This results in detachment of the wavefront and termination of reentry (Movie III in the Data Supplement). As in the first scenario, this mechanism is insensitive to precise parameter values. Using different values of $\tau_1$, $\tau_2$, $R_1$, and $R_2$ (eg, $\tau_1=0.40$, $\tau_2=0.20$, $R_1=0.4$ cm, and $R_2=2.0$ cm or $\tau_1=0.40$, $\tau_2=0.20$, $R_1=0.3$ cm, and $R_2=1.5$ cm) can result in the termination mechanisms of Figure 3C to 3E.

Terminating Reentry by Creating a Barrier to Nonconducted Obstacles

Targeted ablation could also terminate spiral waves if lesions connect to a large nonconducting obstacle (eg, an anatomic orifice or a large scar). Figure 4A shows a spiral wave with tip trajectory close to a nonconducting zone (the lower boundary of the simulation domain). Targeted ablation connecting the spiral wave core to this obstacle terminates reentry. This is shown in the snapshots displayed in Figure 4B and 4C, where we highlight wave block occurring in the gaps between lesions. The lesions prevent the wave from rotating (Figure 4B) and push it toward the nonconducting boundary where it extinguishes (Figure 4C). Note that ablation lesions need not overlap because isthmuses require a minimum size to support wave propagation, $\approx 0.05$ cm in our simulation.

Terminating Reentry by Ablation of an Isthmus for Reentry

In computational models, AF often exhibits paired spiral waves of opposite chirality, with 1 spiral extinguishing. We modeled a scenario whereby reentry is supported by a slow-conducting isthmus between nonconducting zones (hatched regions in Figure 5). The isthmus region has a linear gradient in diffusion constant ranging from $D=0.0002$ cm$^2$/ms (left side) to $D=0.00005$ cm$^2$/ms (right side). This $\approx10$-fold lower diffusion constant results in a CV $\approx4\times$ smaller than surrounding tissue (9.4 versus 36.6 cm/s for $D=0.0001$ cm$^2$/ms, $\tau_1=0.30$). The mismatch in CV between isthmus and surrounding tissue creates figure-of-eight reentry (Figure 5D, green arrows; Movie IV in the Data Supplement). In this scenario, ablating the slow conduction zone blocks the reentry pathway, terminating reentry.

Clinical Cases Illustrating Various Mechanisms of AF Termination

Observations in several patients support the modeling-predicted mechanisms of AF termination. Figure 6 shows atrial propagation in a 67-year-old man with left atrial diameter 62
Figure 4. Termination of spiral wave reentry by ablation connecting to a nonconducting boundary. A, Snapshot of a spiral wave before ablation, with the tip trajectory in green. On creating lesions (blue) placed on a line connecting the spiral tip domain to a nonconducting boundary, the spiral wave is blocked (B and C, indicated by the double bar), collides with the boundary and terminates (C). $R_m=0.4$ cm, and domain size 5×5 cm with no-flux boundary conditions. Note that lesions do not have to overlap to block the wave and terminate reentry. Scale bar, 1 cm.

Figure 5. Ablation of a slow-conducting isthmus can terminate spiral wave pairs. A, The hatched zones are nonconduction regions that sandwich an area of slow conduction, modeled as reduced cell-to-cell coupling that could biologically represent remodeled atrial tissue or patchy fibrosis. The mismatch in conduction velocity in this channel and the surrounding tissue creates a figure-of-eight reentry pattern, indicated by the green arrows in D. Domain size 5×5 cm, D varies linearly in the isthmus from $D=0.0002$ cm/ms (left) to $D=0.00005$ cm/ms (right). Scale bar, 1 cm.

Discussion

This work provides a novel theoretical foundation for AF, illustrating for the first time how limited ablation targeted to the site(s) of localized sources can terminate AF to sinus rhythm or organized AT. Although the clinical literature is replete with cases where limited ablation terminates AF, there has previously been no theoretical foundation explaining this phenomenon—using either nonhierarchical (ie, multiwavelet reentry) or hierarchical (ie, source) models of AF. The present study illustrates how increasingly recognized structural heterogeneities and functional nonuniformities in remodeled human atria may enable ablation to terminate AF, by nonuniform excitability, conduction, repolarization, and nonconducting obstacles. Clinically, these data may help to guide improved ablation strategies and, mechanistically, suggest specific approaches to modify AF substrates by ionic, antifibrotic, or regenerative therapies.

Disorganized or Localized Mechanisms Sustaining AF: A Fundamental Dilemma

Whether AF is maintained by nonhierarchical self-sustaining disorganization or is hierarchical such that localized regions drive disorganization remains a central mechanistic debate. Answers to this question will affect decision making in AF therapy.

Disorganized sustaining mechanisms are supported by surgical studies demonstrating reentry without hierarchy using recording plaques. However, these studies have limitations as clinical AF signals may reflect nonlocal activation, complex signals are often ignored and plaques only simultaneously map small regions (<10%-20% of both atria). This mechanism also cannot reconcile how AF is modulated by limited ablation, why outcomes are worse when performing more ablation (ie, undergoing greater mass reduction), and data directly challenging the critical mass concept.

Localized sources for fibrillation were demonstrated directly by the pioneering work of Pandit and Jalife in the early 1990s and by recent optical mapping studies in human AF. Sources readily explain modulation of AF by ablation, insufficient to limit critical mass, AF termination by localized intervention, and increasing data showing stability of propagation. A hierarchical model also explains success during extensive ablation if it coincidentally modifies sources. One major question for the source hypothesis is how localized ablation at rotors can abolish AF. The present study provides the first potential answers to that question.
Figure 6. Conversion of human atrial fibrillation (AF) to atrial tachycardia (AT) by localized ablation in left atrium (LA). A, Electrograms show abrupt conversion. B, Pretermination (focal impulse and rotor mapping) FIRM map shows counter clockwise AF rotor, as indicated by the arrow, with peripheral disorganization (fibrillatory conduction) in this chamber. C, Post-termination FIRM map shows AT at this location. Note cycle length prolongation and regular activation sequence in postablation AT.

Figure 7. Termination of atrial fibrillation (AF) to sinus rhythm by ablation that detaches AF rotor enabling its collision with nearby anatomic structures (mitral annulus or left inferior pulmonary vein [PV] orifice). A, Intracardiac. B, Clockwise rotor that processes in a limited region of low left atrium (LA) before ablation. C, Ablation destabilizes the rotor precession locus, causing AF to terminate to sinus rhythm. D, Proximity of rotor to the mitral annulus, in particular, may have enabled rapid AF termination.
Reconciling Our Studies With Previous Work

First, the present study confirms previous computational31,32,38,39 and in vitro40–42 studies where limited ablation converted an AF rotor to anatomic reentry. This is consistent with clinical cases (Figure 6) using FIRM2 or an ECG-based inverse solution,43 supporting the localized source hypothesis. Studies are required to exclude ablation modulating high densities of multiple wavelets although this would not explain why the unablated lower density wavelets do not perpetuate AF.

Second, this study provides the first set of mechanisms to explain how limited ablation terminates AF directly to sinus rhythm. Most numeric simulations studied anchoring of spiral waves to obstacles in uniform tissue,31,32,38,39,43 revealing how both low and high excitability limit the minimum obstacle size around which reentry is stable. In tissue with uniformly low excitability, spiral tips cannot follow trajectories with high curvature.44 Thus, stable attachment to a circular obstacle requires a minimum radius—if smaller, spiral waves will detach. In tissue with uniformly high excitability, the CV determines the minimum size of an anchoring obstacle. The CV is large (small) for high (low) excitability and, accordingly, highly excit able tissue can only support activation if the path around the obstacle has a minimum size—if smaller, activating head meets tail, detaching wavefronts. Thus, in uniform tissue, it is unlikely that limited ablation can dislodge an anchored spiral wave.

However, our study shows that incorporating well-recognized nonuniformities in atrial tissue reveals several mechanisms whereby limited targeted ablation can terminate AF rotors. Nonuniformities in atrial tissue are ubiquitous and possibly reflect regional variations in APD restitution, conduction,3–4 fibrosis,4 or fiber architecture.8 In the scenarios studied (Figure 3), the initial condition consists of an activation front rotating around a small obstacle. The tissue properties close to this obstacle were chosen to differ from those further away. Note that this initial condition is stable because of this spatial heterogeneity: choosing uniform excitability equal to the excitability far from the obstacle would result in detachment in both cases. In the first scenario (Figure 3A and 3B), stable reentry around an obstacle in tissue with an excitability equal to that of the tissue further from the initial obstacle (τc=0.42) requires a minimum obstacle radius of R=1.9 cm, much larger than a single ablation lesion (typical size 0.5–0.7 cm). Tissue with excitability corresponding to the parameter value at the periphery of Figure 3C and 3E (τc=0.25) requires a minimum radius of R=1.2 cm, again larger than a lesion. This may explain how hyperkalemia terminates fibrillatory rotors.45

Validating Results From This Modeling Study With Clinical Observations

Ablation may lengthen wavepath around lesions, analogous to microreentrant AT.46 A rapid microreentrant source driving AF with fibrillatory conduction may terminate if the excitable gap is invaded by fibrillatory waves. The effects of pacing on spiral tips have been studied before,47 and we recently demonstrated in a case study of AF propagation using patient-specific geometries that fibrillatory waves can invade an excitable gap.48 This model agrees with clinical observation, where even if AF is inducible, it may be shorter lived, with recurrence relating to ATs depending on the extent of ablated tissue.3,4,14 Studies are needed to further define our description of conduction properties at sites of rotors and surrounding tissue7 to identify patients in which gradients of excitability may operate.

The proposed mechanism of joining the rotor site to a nonconducting obstacle or eliminating a nonconducting channel both require direct clinical validation. However, Figure 8 illustrates rotors whose location would easily enable targeted ablation to connect to nonconducting boundaries including functional boundaries. Figure 1 in the Data Supplement shows figure-of-eight activation through slow-conducting channels, which may occur in relation to fibrosis or other forms of atrial remodeling, awaiting clinical mapping validation.

Limitations

There are several limitations of this study. First, it was performed in computational grids not accounting for geometric curvature, which may provide additional mechanisms for ablation to terminate AF. Second, we used the FK model for computational efficiency, so our study was not designed to explore effects of derangements in specific ion channels or drugs on AF. Third, simulations were performed in isotropic domains, whereas fiber anisotropy can affect spiral tip...
dynamics. Fourth, ablation lesions were modeled as discrete obstacles to activation and conduction, while in practice the necrotic core of an ablation lesion is surrounded by a penumbra of inflammation that may short out APD and alter wave dynamics. Additional studies should attempt to quantify such inflammation so that it may be incorporated. Fifth, simulations were performed in 2D sheets that did not include transmural components. Indeed, epicardial and endocardial differences in cellular and fiber properties were recently shown in optical mapping of human AF. The study found stable rotors (~1 cm² precession areas on the endocardium), terminated by localized ablation, but less stability on the epicardium, where they appeared as focal breakthroughs. It remains to be seen whether this transmural difference is consistent. We did not model the impact of ablation on potential focal sources for AF because this is mechanically straightforward. Clinically, we were unable to directly register clinical cases with computational models. While rotors have been questioned, many studies either had signal processing issues such cycle lengths of 250–500 ms in patients ostensibly with AF or use of bipolar analyses on unipolar signals or mapped small atrial areas. Although FIRM-based mapping is sufficient to map human AF at the resolution required for ablation, it is insufficient to map the dynamics of the rotor core during ablation. In the present study, clinical data illustrate model predictions and are not used to present a definitive mechanistic proof or a relationship to the long-term results of rotor ablation as shown by others and for which randomized trials are ongoing.

Conclusions
This study proposes novel mechanisms by which limited ablation can terminate human AF. These data illustrate for the first time how targeted ablation may interact dynamically with the anatomic locations of rotors and with tissue characteristics of nonuniform excitability, slow conduction, and nonconducting boundaries. Future translational studies should focus on mapping and quantifying these tissue heterogeneities in remodeled atria in individual patients to improve therapy.

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Supplementary Figure 1. Paired clockwise and counterclockwise spiral waves during AF. (A). Electrograms of AF. (B) Isochronal map of both atria during AF, showing paired spirals in the right atrium.
Movie 1. Elimination of re-entry due to excitable gap formation after ablation. This gap was invaded by surrounding fibrillatory waves and caused wavefront collision, thus terminating AF. See figure 2 and text for further details.

Movie 2. Elimination of re-entry due to ablation of a high excitability domain. This results in detachment of the spiral wave from the obstacle and migration outside of domain to a non-conducting boundary. See figure 3A-B for more details.

Movie 3. Elimination of re-entry due to ablation of a low excitability domain. This creates an activation front that propagates with higher wave speed and causes wavefront/tail collision and block, ultimately causing detachment and termination of re-entry. See figure 3C-E in text.

Movie 4. Terminating re-entry by ablation of an isthmus. The isthmus between the red bars has a linear gradient in diffusion constant. The mismatch in resulting CV between isthmus and surrounding tissue creates figure-of-eight reentry. See figure 5 and section V of results for further details.