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Rotor mapping and ablation to treat atrial fibrillation

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Abstract

Purpose of review—Rotors have long been postulated to drive atrial fibrillation, but evidence has been limited to animal models. This changed recently with the demonstration using focal impulse and rotor modulation (FIRM) mapping that rotors act as human atrial fibrillation sources. This mechanistic approach to diagnosing the causes of atrial fibrillation in individual patients has been supported by substantially improved outcomes from FIRM-guided ablation, resulting in increased attention to rotors as therapeutic targets.

Recent findings—In this review, we outline the pathophysiology of rotors in animal and in-silico studies of fibrillation, and how this motivated FIRM mapping in humans. We highlight the characteristics of rotors in human atrial fibrillation, now validated by several techniques, with discussion on similar and discrepant findings between techniques. The interventional approaches to eliminate atrial fibrillation rotors are explained and the ablation results in latest studies using FIRM are discussed.

Summary—We propose that mapping localized sources for human atrial fibrillation, specifically rotors, is moving the field towards a unifying hypothesis that explains several otherwise contradictory observations in atrial fibrillation management. We conclude by suggesting areas of potential research that may reveal more about these critical sites and how these may lead to better and novel treatments for atrial fibrillation.

Keywords

ablation; atrial fibrillation; focal impulse and rotor modulation; rotors

INTRODUCTION

The mechanisms that sustain human atrial fibrillation remain unclear despite more than a century of research. This uncertainty has profoundly limited our therapy for this highly prevalent disease, and has created an urgency to combine physiology, clinical ablation studies, pharmacology, bioengineering, and other disciplines to substantially advance our

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understanding and hence patient outcomes. There are essentially two schools of mechanistic thought: one proposing localized sources and the other distributed mechanisms.

There is no question that atrial fibrillation is disorganized, but whether disorganization results from organized sources or whether disorganization is the primary driver of atrial fibrillation has been debated for decades [1]. We will consider clinical evidence that is readily explained by localized sources, yet difficult to explain by primarily disorganized mechanisms. This includes the presence of stable frequency gradients between and within the atria [2], the presence of consistent and reproducible directions of propagation in atrial fibrillation within the atria in many patients [3], the ability of ablation to modulate atrial fibrillation before trigger sites are isolated or lines are complete [4], and the mere existence of preferred anatomical sites including the pulmonary vein antra, roof or other regions in either atrium. Conversely, data suggesting that atrial fibrillation requires a ‘critical mass’ of tissue [5,6] favor spatially disorganized mechanisms in which no particular area is critical to sustain atrial fibrillation.

Although this dichotomy of opinion at first appears difficult to rationalize, scrutiny of the literature increasingly suggests that it may largely reflect differences in approaches to map ping atrial fibrillation. It is important to question whether traditional techniques to map arrhythmias, such as atrial flutter, are still reliable in the face of disorganized, complex, and varying activity in atrial fibrillation. In animals, techniques to map fibrillation were developed to minimize far field noise and reliably indicate local activation. One approach, voltage potential mapping (optical mapping), consistently shows that atrial fibrillation may be caused by localized sources [7■■], but these findings were until recently not translated to human studies. Clinical studies are a necessary compromise between maximizing field of view and spatial resolution with safe and atraumatic data collection. Studies that maximize field of view increasingly demonstrate localized sources [8,9■], whereas those that maximize spatial resolution, often in a small viewing field, typically report disorganized mechanisms [10].

Rotors were first reported to drive human atrial fibrillation in 2011 in the Conventional ablation with or without focal impulse and rotor modulation (CONFIRM) trial [8], and were previously considered not to exist in humans [11]. Since 2011, there have been extensive developments in mapping, with studies to define the mechanistic role of rotors, and studies to define their importance as ablation targets. As many groups now report rotors in atrial fibrillation using many techniques, the debate has largely shifted to defining the dynamic properties of rotors and ascertaining through clinical trials whether ablation at rotor sites substantially improves the success of ablation compared with conventional anatomically based ablation.

We will review the current state-of-the-art thinking in human atrial fibrillation, grounded on two basic questions that must be answered to advance the field. First, does the new mechanistic hypothesis explain why ablation focused on the pulmonary veins is suboptimal in many patients yet successful in others even if the veins reconnect to the atria? Second, how can we reconcile the divergent data supporting localized sources and the impact of spatially widespread mechanisms?

What is a rotor?

Spiral waves were described in cardiac fibrillation in the early 1990s using optical mapping in animal tissue [12], and demonstrated to cause the characteristic ECG changes seen in ventricular fibrillation [13]. Since then, their role in causing atrial and ventricular fibrillation in animal studies has become well established [14]. Initial attempts by these investigators to use isochronal (activation) mapping did not detect stable rotational circuits in sheep atrial fibrillation [15] until they developed and applied complex signal analysis known as phase mapping [16]. These principles likely apply to human atrial fibrillation.

Several types of reentry exist (Fig. 1 [7■■]). Spiral waves represent a specific form of reentry that has been hypothesized and now demonstrated to cause human fibrillation (Fig. 1c–f). The central core from which the spiral waves emanate – the reentrant singularity – is termed a 'rotor' and meanders (precesses) as it pivots around 'unexcited but eminently excitable tissue' [7■■]. Critical to the definition of rotors is extreme wavefront curvature, which increases as conduction slows towards the 'core' and the small (curved) excitable gap that exists between head and tail of the wavefront eluding standard entrainment maneuvers [17,18]. Rotors are thus defined using three key characteristics (see Fig. 1e):

1. Extreme wavefront curvature at the core in which head meets tail.
2. An excitable and precessing core.
3. A highly variable reentrant wavelength, with an often-undetectable excitable gap.

Contrasting rotors with other rotational circuits

Electrical activation around a fixed obstacle, such as scar, is classical reentry, with a minimum path length determined by local conduction velocity and refractory period such that reentry terminates if the head meets the tail (Fig. 1a). Such reentry exhibits an excitable gap during which electrical stimuli can modify (entrain) the circuit. This underpins many common arrhythmias, such as atrial flutter or ventricular tachycardia, and therapy is designed either to interrupt the circuit by ablation or to increase wavelength with drugs. However, there is little evidence that atrial fibrillation is caused by excitable gap reentry.

Leading circle reentry is a distinct mechanism in which reentrant circuits surround a functionally inexcitable (partially excitable) core, which is depolarized by centripetal penetration of the wavefront [19] (Figs. 1b [7] and 2 [20,21]). Despite being superficially similar to a rotor, this circuit is fundamentally different – the central core is totally or partially inexcitable, making the reentry circuit spatially stable and preventing spatial precession, and the wavelength is stable, as opposed to rotors whose wavelength changes dynamically.

These features distinguish leading circle reentry from the three criteria outlined for rotors (see Fig. 1e) as reviewed elsewhere [22]. These fundamental differences made rotors undetectable in animals until novel mapping approaches were developed. These combined phase mapping, which plots a signal against a time shifted version to display the different stages within one cycle, and optical mapping of hearts using voltage sensitive dyes. These avoid some of the limitations of clinical electrograms as fluorescent changes reflect those of

membrane potential and allow optical action potentials to be calculated for each pixel. In combination, these two techniques offered a new tool for analyzing cardiac fibrillation. Analogous limitations likely hampered the detection of rotors in human fibrillation, which have been rarely detected by traditional activation or entrainment mapping.

FOCAL IMPULSE AND ROTOR MODULATION

To optimize the detection of rotors in human atrial fibrillation, we designed approaches to map broadly, as human atrial electrophysiology and structure are spatially nonuniform, to use phase analysis, and to identify signals best representing local activity as opposed to 'far-field' signals from other atrial regions [8,23–26]. These approaches led to focal impulse and rotor modulation (FIRM), which in the CONFIRM trial [27,28] showed that rotors and focal sources are present in the vast majority of patients with atrial fibrillation (Fig. 3 [29]), and their elimination can acutely modify atrial fibrillation and substantially improve outcomes from ablation on long-term follow-up [30■■]. Other groups have now used this approach to demonstrate rotors in human atrial fibrillation [31■,32■].

COMPARISONS WITH ATRIAL FIBRILLATION ROTATIONAL CIRCUITS DEMONSTRATED BY OTHER TECHNIQUES

Since the CONFIRM trial, several groups have used diverse methods to report rotors in human atrial fibrillation. Each study has revealed rotors that are analogous to those detected by FIRM, with differences that likely reflect each specific technique. A panoramic approach using body surface mapping has recently shown rotors in persistent atrial fibrillation [9■] that cluster in patient-specific atrial regions over dayswitha right or left atrial distribution (30/70%, respectively) akin to that in CONFIRM (Fig. 4 [30■■]). Nonpanoramic methods have demonstrated rotors using activation mapping using endocardial Lasso catheters [33■], epicardial high-density plaques [34■■] and point-by-point mapping [35■]. These methods reported unstable rotors, although stable enough for limited ablation [9■,35■] with similar spatial distributions. Studies are thus required to determine the extent to which rotor stability is impacted by a small mapping field (which cannot track rotors that precess outside this field), by amplified precession on projection to the body surface [36■], by endocardial–epicardial differences [37] or by other factors. Most importantly, validation studies are needed to compare clinical outcomes from ablation of rotors detected by each technique.

USE OF ROTOR MAPPING TO IMPROVE ATRIAL FIBRILLATION ABLATION OUTCOMES

To prove its mechanistic role, an identified rotor must be eliminated by intervention (ablation), remapped to show that it is abolished, then the patient followed to demonstrate freedom from atrial fibrillation in the long term. Studies of FIRM were designed with this paradigm in mind – to establish the mechanistic basis of rotors and use this as the basis for multicenter trials [38]. Mapping studies that have not followed this paradigm are necessarily more descriptive, particularly if they did not ablate proposed mechanisms. There are two recognized approaches to prevent rotors from driving atrial fibrillation: first, rotor elimination and second, rotor modification.

Elimination by direct targeted ablation

From the classical studies of Pandit and Jalife [7■,39,40■], the rotor core is the mechanism of fibrillation, and so the goal of therapy is to eliminate these functional elements. The CONFIRM trial [30■■] demonstrated superior single procedure efficacy by adding ablation based on targeting atrial fibrillation sources revealed by FIRM mapping compared with conventional ablation alone (82.4 versus 44.9%). Lesion sets typically required 5–10 lesions to eliminate the precession locus of rotors. This approach may be considered analogous to the elimination of microreentrant atrial tachycardia by localized ablation. Experimentally, studies now show that ablation of precession loci can eliminate rotors [41], possibly by increasing meander until they encounter an anatomic obstacle. In CONFIRM, when atrial fibrillation terminated, it was often to sinus rhythm, whereas other more extensive approaches terminate mostly to atrial tachycardia. Clinically, if repeat FIRM maps after ablation show rotor or source elimination in atrial fibrillation, there is no requirement to draw lines or perform extensive atrial ablation.

Elimination by coincidental lines

An on-treatment analysis of CONFIRM examined whether empirical lesions, such as ‘lines’ at the roof or elsewhere in left or right atria, confer greater freedom from atrial fibrillation if they coincidentally bisect rotor areas than if they do not. In this analysis, clinical success was highest when all sources were eliminated, intermediate when some were eliminated, and lowest when all sources were missed [42]. This suggests that rotor elimination alone may be sufficient to eliminate atrial fibrillation: a hypothesis that is being tested prospectively in multicenter studies of FIRM guided ablation alone vs. standard techniques including pulmonary vein isolation (PVI). Preliminary results from precise rotor elimination without concomitant pulmonary vein isolation for the successful elimination of paroxysmal atrial fibrillation showed that FIRM-only ablation provided more than 80% elimination of paroxysmal atrial fibrillation [43]. This may explain how ablation strategies may be successful even before completion of a lesion set and why even persistent atrial fibrillation can be modulated or may terminate at specific critical sites. These observations are readily explained by rotor or source mechanisms, but are otherwise difficult to rationalize with multiple meandering wavelets or other hypotheses. Lines currently used for wide area circumferential ablation or roof lines may inadvertently transect rotor core precession loci, and clustering of rotor sites near pulmonary vein antra in some patients may also explain the success of PVI even if the pulmonary veins reconnect [44,45].

Modification

Rotors can be modified in either of the two following ways.

Elbow room argument—Lesions sets may compartmentalize the left atrium sufficiently to create less space, or ‘elbow room’, for a rotor to stabilize [7■■,46■,47■■]. Computational studies confirm that the boundary length of iatrogenic and anatomical lesions is a major determinant in reducing the frequency and longevity of reentrant circuits in atrial fibrillation [48]. This increases the chance that empirical lesions will modulate a rotor – that would only have to lie within some distance of rotors (defined as one interelectrode spacing

in the on-treatment analysis) rather than bisect them. This 'topological' approach to intervention may also be exemplified by the Cox-Maze procedure, which renders the compartmentalized atrium unable to hold sufficient path length to accommodate reentry. This approach would fit equally with localized rotors being the specific form of reentry whose precession is curtailed by atrial compartmentalization.

Modulation of 'fibrillatory conduction'—Modification of the atrial substrate may impact on its capability to support fibrillatory conduction secondary to a localized source or, potentially, as a modulator of multiwavelet reentry. Distal cycle length prolongation at a site remote from that being ablated or pharmacologically modified has been suggested to support the role of the neural autonomic network in supporting atrial fibrillation, which is well characterized in animal studies using acetylcholine to maintain atrial fibrillation [49]. The coexistence of multiple mechanisms in atrial fibrillation (focal, multiwavelet, rotor) has been demonstrated in a canine preparation, with propafenone and ablation having mechanism-specific effects on termination [50]. Such pleiotropy of mechanisms may exist in human atrial fibrillation, and sufficient modification of the substrate may render it incapable of supporting fibrillatory conduction. Future studies are needed to define how to target complex substrates such as endo-epicardial or longitudinal dissociation to prove their role as drivers.

RELEVANCE TO HUMAN ATRIAL FIBRILLATION

One fundamental observation causes the rotor and focal source hypothesis to stand out – how can focal ablation in a persistent atrial fibrillation, and hence globally remodelled substrate, ever modulate atrial fibrillation? This would seemingly make multiple wavelets not the primary driver of persistent atrial fibrillation and hence a 'downstream' manifestation of the substrate, rather than the source itself – at least in those patients.

The demonstration of rotors driving human atrial fibrillation suggests a unifying mechanistic paradigm with insights into the translational gap that has existed between animal and human studies to date. Looking for structural correlates with rotor sites is a vital step in furthering the rotor paradigm and offers a bridge across the translational gap. Although ionic gradients and tissue fibrosis have been proven to anchor rotors in animal [51] and computer modeling studies [52■], such data are still remarkably lacking for the human rotors discovered to date.

Electrogram markers

Work is needed to identify electrogram markers that may predict rotor site formation. The electrogram represents the raw data of clinical electrophysiology and is the principal window through which we infer information about local electroarchitecture and global panorama. It is remarkable that we still simply binarize electrograms with qualitative terms such as simple, double, or complex when they seem so rich in content. Theories surrounding fractionated electrograms require a coherent cell to tissue-level mechanistic understanding to find their true distinction.

Stabilizing mechanisms

Recent work in ovine paroxysmal and persistent atrial fibrillation has demonstrated that the dominant frequency gradients persist and progress with disease progression, on the basis of molecular and ionic remodeling [53]. These dominant frequency sites have been ablated in human atrial fibrillation [2], as have other measures of spatial stability based on dominant frequency, such as organizational index [54]. Data from dominant frequency spatiotemporal stability studies are conflicting [55■], which may be because of technical aspects of dominant frequency analysis and the presence of fractionated electrograms, which limit their applicability [56].

Autonomic ganglia

Autonomic ganglia are also coincident with sites of current ablation lesions and it has been demonstrated that functional interrogation of these can help identify additional end points of ablation and improve targeting above anatomical approaches alone [57]. These are best identified functionally using high-frequency stimulation, which unmasks gradients in the atrium responsible for maintaining fibrillatory conduction [58]. However, their overlap with FIRM-identified atrial fibrillation sources remains to be determined.

Imaging

FIRM source correlation with other markers of disease recurrence, such as extensive atrial fibrosis on late gadolinium-enhanced (LGE) MRI [59■], also may offer insight into the role imaging techniques have to offer in further refining patient-specific therapies, and may offer prognostic value after atrial fibrillation ablation [60]. Beyond this global level, point-by-point correlation [61] is vital to understand the substrate using LGE-MRI and the role fibrosis may play in humans as a stabilizing mechanism.

Understanding atrial fiber orientation is vital to help understand the anisotropic propagation that may lead to spiral wave reentry and rotor initiation. Correlation with post-mortem tissue has shown characteristic activation patterns in the human left atrium [62], but proving similar patterns *in vivo* remains a challenge, despite computer modeling studies confirming feasibility [63].

Imaging will also be the key to understanding whether two-dimensional rotors, as detected by FIRM and noninvasive mapping, are actually but one manifestation of more complex transmural reentry as scroll waves [64]. This offers a putative link between the elegant high-resolution observations of distributed theorists [11] and the mechanistic validation of focal sources by ablation outcomes [65■].

Clinical outcomes

Efficacy even from repeat catheter ablation procedures plateaus at 50–60% for paroxysmal atrial fibrillation and may be as low as 40% in persistent atrial fibrillation [66]. How we select the patients we perform ablation on, which strategies we use and what to do if atrial fibrillation recurs are still poorly defined and reflected in the suboptimal long-term efficacy.

In contrast, the CONFIRM trials suggest that results from a single procedure based on rotor or source ablation may be maintained at up to 3 years' follow-up. As these results are validated by external groups [38], this supports the mechanistic hypothesis that, when atrial fibrillation substrates are eliminated (by FIRM), residual triggers, such as from reconnected pulmonary veins, may be rendered impotent. This is being tested in ongoing trials. Higher success from substrate-based ablation may also be explained by the one-third of patients with right atrial sources, who are routinely targeted by FIRM yet may underlie the more than 33% recurrence of atrial fibrillation in patients undergoing left-sided conventional ablation.

CONCLUSION

To improve atrial fibrillation outcomes, mechanistic understanding must be improved. Some of the major technical difficulties in mapping human atrial fibrillation have been addressed by FIRM, which has shown that atrial fibrillation is tractable in many patients and sustained by focal sources and rotors. Although the 'hierarchical' nature of atrial fibrillation organization is revealed by global mapping, it is at the microscopic level that these clinical observations must be explained and that a significant translational – and hence truly mechanistic – gap exists.

Clinical evidence by several groups that rotors and focal sources can be targets for direct ablation that may improve atrial fibrillation ablation success provides a mechanistic foundation for future improvements. For instance, coincidental ablation or modification of rotors may explain how conventional ablation can be successful even if ablated tissue reconnects. The widespread bi-atrial location of rotors and sources readily explains why left-atrial focused ablation may have limited efficacy, and provides an alternative to widespread atrial ablation to achieve higher success rates.

Further work is required to identify electrogram markers that may predict rotor site formation. The impact of molecular, cellular and tissue-level remodeling on atrial fibrillation sources, as revealed by FIRM, is also an area requiring further study, as are explanations for why recurrences occur.

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KEY POINTS

- Current theories for atrial fibrillation do not explain key observations during ablation procedures.
- There is significant basic science supporting localized mechanisms in the form of rotors, which are distinct from other forms of reentry.
- Rotors are demonstrable in human atrial fibrillation by FIRM and numerous other approaches.
- Ablation results from CONFIRM have been reproduced in multicenter studies and extend up to 3 years.
- Further work to investigate the cellular and structural changes responsible for rotors is vital to truly further understanding human atrial fibrillation maintenance.

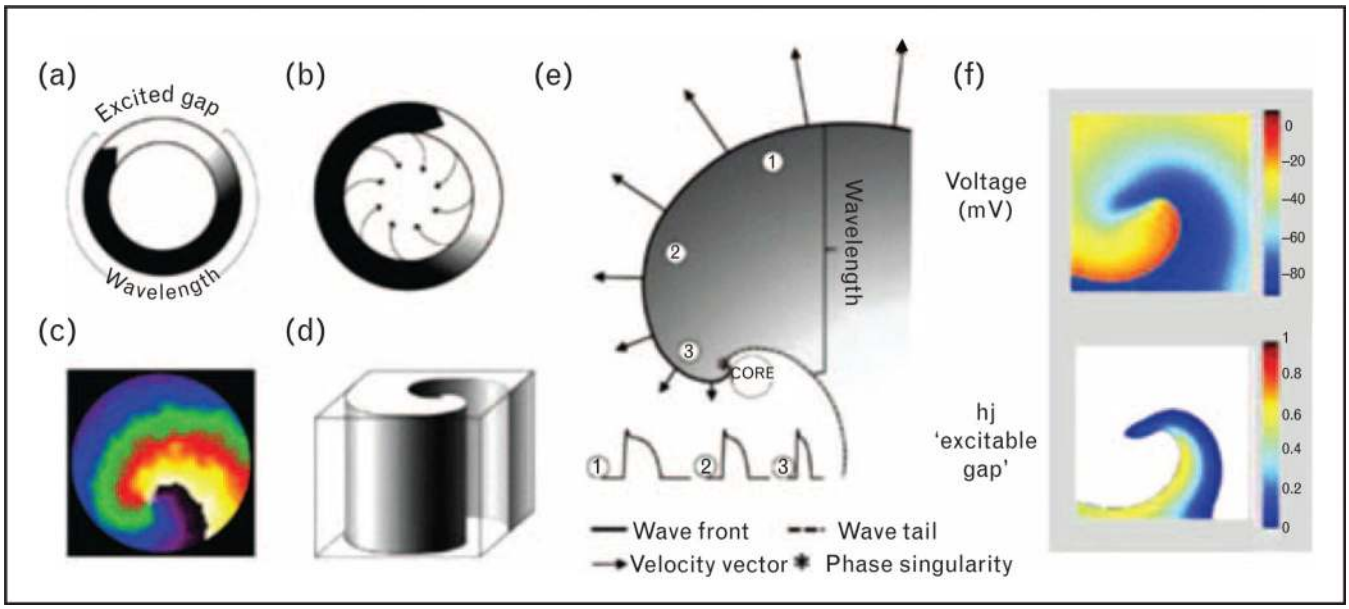

FIGURE 1.

Types of reentry. (a) Reentry around a fixed anatomic obstacle. The wavelength (black) is shorter than the path length around the obstacle, enabling the activation wave front to encounter fully excitable tissue (excitable gap, white). (b) Leading circle reentry, in which activation propagates around a functionally refractory core. (c) Color phase map of a two-dimensional (2D) spiral wave which, as in a pinwheel, spins around a singular point in the center, that is, in which all phases converge. (d) A 3-dimensional scroll wave emanating from a filament. (e) Features of a rotor. Near the core conduction velocity falls (see shorter vectors, arrowed) and action potential duration shortens (examples from positions 1, 2, and 3), thus shortening wavelength [distance from the wavefront (black line) to the wave tail (dashed line)]. Wavefront curvature becomes more pronounced near the rotor, which is a phase singularity at the point in which the wavefront and the wave tail meet (*). (f) Snapshots of trans-membrane voltage distribution during simulated reentry in AF in a 2D sheet incorporating human atrial ionic models. Bottom panel shows complex excitable gap morphology. Adapted from [7■■].

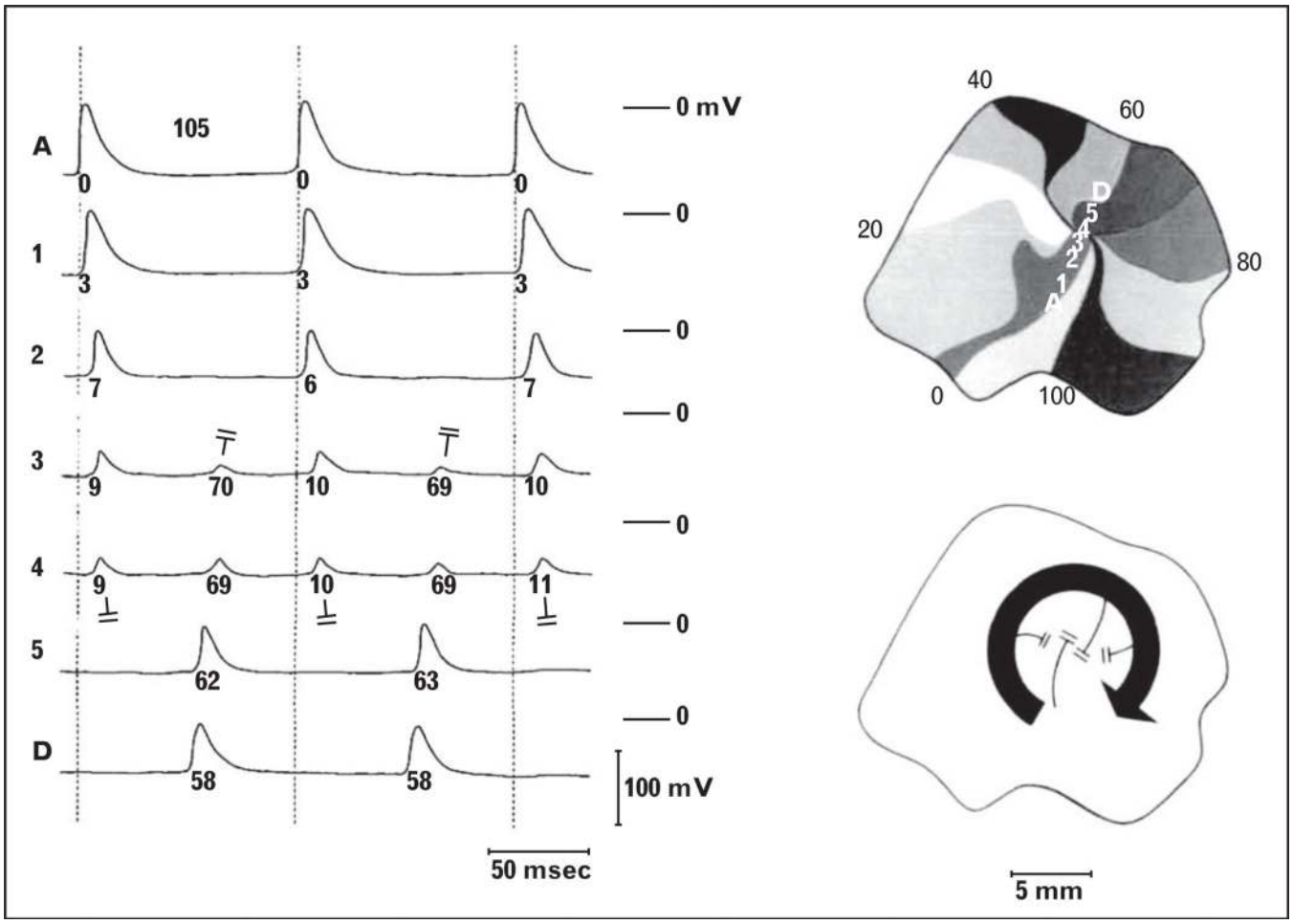

FIGURE 2.

Detail of leading circle reentry in rabbit atrial muscle. The membrane potentials of seven fibers (marked A, D, and 1–5) located on a straight line through the center of the circus movement are shown. Fibers in the central point of the circuit (fibers 3 and 4) show double responses of subnormal amplitude unable to propagate beyond the center, thus preventing the impulse from traversing the circuit. Below the map, the activation pattern is given schematically. It shows the leading circuit with the converging wavelets in the center. Block is indicated by double bars. Adapted from [20,21].

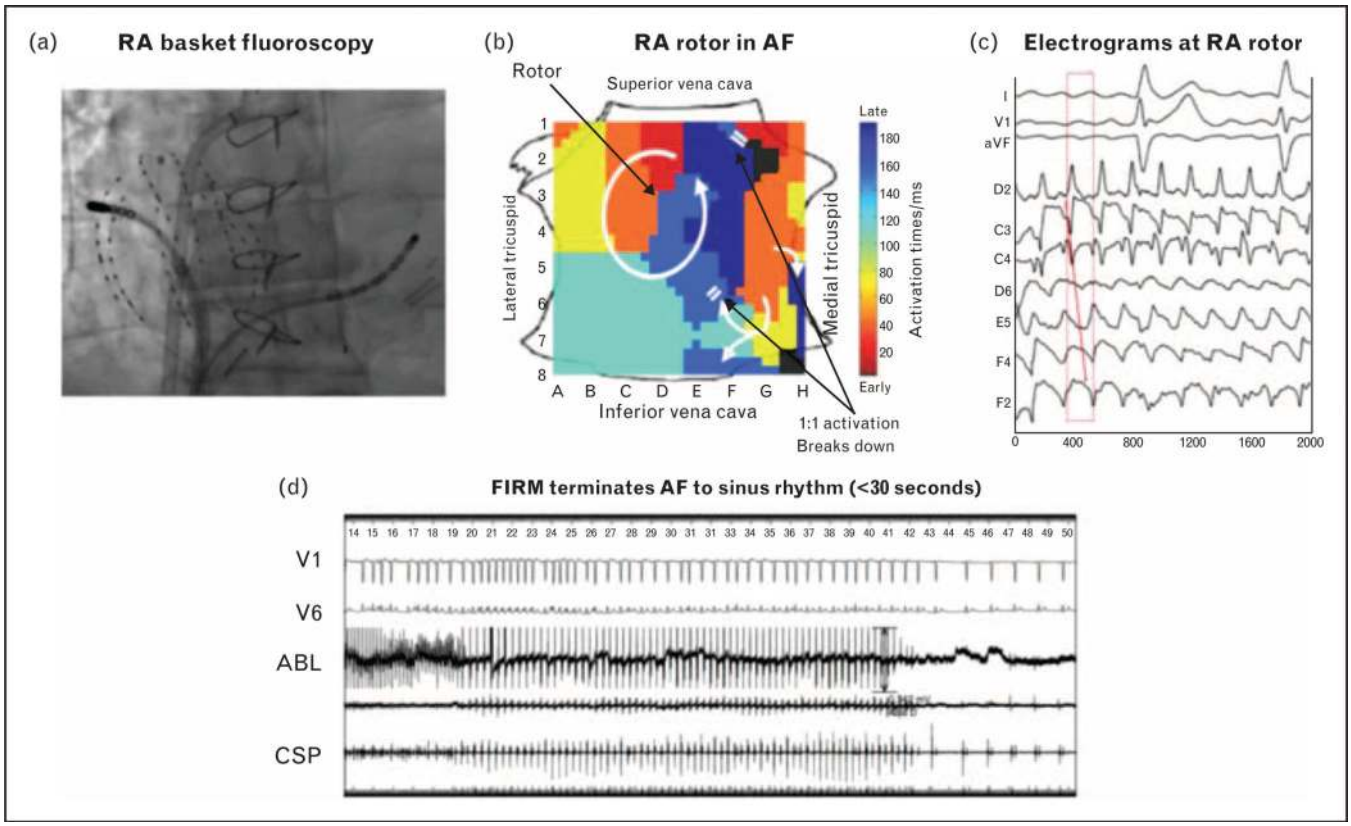

FIGURE 3.

Focal impulse and rotor modulation mapping demonstrates right atrial rotor. (a) Basket and ablation catheters in the right atrium. (b) Counterclockwise rotor in the posterolateral right atrium (centered at electrode C3), with collision beyond the spiral arms (double lines). (c) Electrograms around the right atrial rotor site, indicating counterclockwise rotation that precesses at cycle length ≈ 177 ms. (d) FIRM ablation at right atrial rotors alone terminates atrial fibrillation to sinus rhythm within 30 s. ABL, ablation electrogram; AF, atrial fibrillation; CL, cycle length; CSP, proximal coronary sinus; FIRM, focal impulse and rotor modulation; RA, right atrial. Adapted from [29].

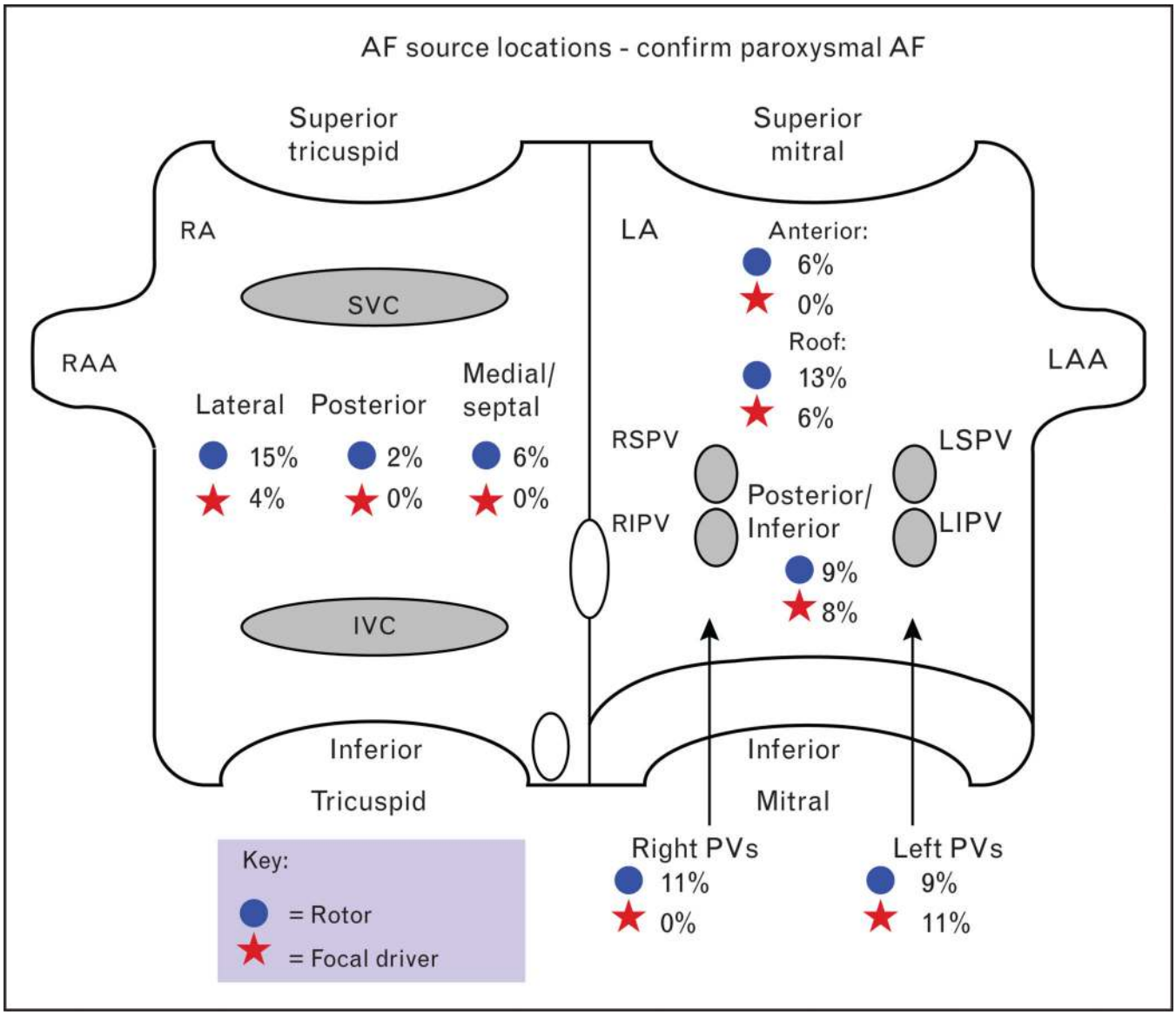

FIGURE 4.

Locations of focal sources as percentage of all sources in persistent atrial fibrillation revealed by FIRM mapping in the CONFIRM study. CONFIRM, conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation; IVC, inferior vena cava; LAA, left atrial appendage; LIPV, left inferior pulmonary vein; LSPV, left superior pulmonary vein; RAA, right atrial appendages; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava. Adapted from [42].