JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 64, NO. 8, 2014

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2014.06.1172

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Atrial Fibrillation Ablation

Translating Basic Mechanistic Insights to the Patient

Kunihiro Nishida, MD,*† Tomás Datino, MD,‡ Laurent Macle, MD,* Stanley Nattel, MD*

ABSTRACT

Atrial fibrillation (AF) ablation is widely performed and is progressively supplanting drug therapy. Catheter-based AF ablation modalities have evolved progressively in parallel to our understanding of underlying mechanisms. Initial attempts to mimic the surgical maze procedure, which were based on the multiple wavelet model, failed because of adverse outcomes and insufficient effectiveness. A major advance was the targeting of pulmonary veins, which is highly effective for paroxysmal AF. Active research on the underlying mechanisms continues. The main challenge is reconnection, but procedures to minimize this are being developed. Ablation procedures for persistent AF are presently limited by suboptimal success rates and long-term disease progression that causes recurrences. Basic research into the underlying mechanisms has led to promising driver mechanism-directed clinical approaches along with pathways toward the prevention of atrial remodeling. Here, we review the role of basic research in the development of presently used AF-ablation procedures and look toward future contributions in improving outcomes. (J Am Coll Cardiol 2014;64:823–31) © 2014 by the American College of Cardiology Foundation.

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, has complex underlying mechanisms (1). The incidence and prevalence of AF are increasing as the population ages (2). By the mid-1990s, ablation had revolutionized the therapy of most cardiac arrhythmias, with the notable exceptions of AF and ventricular tachycardias (3). The subsequent development of successful AF ablation procedures has dramatically changed AF management, but many limitations remain (4). The evolution of AF ablation has been marked by dynamic feedback between basic science concepts and clinical observations, each at various times contributing to advances in the other (Fig. 1). This paper reviews the fundamental science related to AF ablation, discussing the basic knowledge that led to advances in ablation procedures, findings emanating from clinical observations that forced a return to the bench to reconsider basic mechanisms, and present challenges to ablation success that require further improvements in our understanding of underlying mechanisms (Central Illustration).

BASIC RESEARCH AND THE EARLIEST AF ABLATION PROCEDURES

Multiple basic mechanisms (Fig. 2) were recognized as potential contributors to AF in the early 20th century (1,5). However, following Gordon Moe's classic work (6), the multiple wavelet hypothesis (Fig. 2A) predominated. The multiple wavelet hypothesis provided a quantitative framework for Garrey's much earlier idea (5) that the persistence of fibrillation depends on a critical mass of tissue large enough to support multiple re-entrant waves that prevent simultaneous termination of all underlying re-entrant activity. Translation of this paradigm (Fig. 1A) to humans led to the development of the surgical maze

From the *Research Center, Montreal Heart Institute and Université de Montréal, Montreal, Quebec, Canada; †Second Department of Internal Medicine, University of Toyama, Toyama, Japan; and the ‡Department of Cardiology, Hospital General Universitario Gregorio Marañón, Madrid, Spain. Funding for this work was provided by the Canadian Institutes of Health Research (grant 6957) and Heart and Stroke Foundation of Canada. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Nishida and Datino contributed equally to this work.

Manuscript received May 27, 2014; revised manuscript received June 26, 2014, accepted June 27, 2014.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CFAE = complex fractionated atrial electrogram

DF = dominant frequency (of fast-Fourier transformed signals)

ERP = effective refractory period

GP = ganglionated plexus

LA = left atrium/atrial

PV = pulmonary vein

PVI = pulmonary vein isolation

procedure (7) (**Fig. 1B**), arguably the single most successful nonpharmacological approach to sinus rhythm maintenance for AF ("arguably" because the quoted success rates for the maze procedure are on the basis of symptomatic recurrences, and many AF recurrences are asymptomatic). The first catheter-based ablation approaches for AF (**Fig. 1C**) were designed to mimic the surgical cut-and-sew maze procedure (8–10). This first phase of AF ablation largely failed because right atrial-directed ablations were generally insufficient to control the arrhythmia, transmural linear lesions proved very difficult to achieve, and left atrial (LA) procedures were associated with an unacceptable risk of major complications, particularly stroke (10).

THE ROLE OF PULMONARY VEINS AND OTHER KEY ANATOMICAL STRUCTURES

A key discovery in the development of AF ablation was the recognition by Haissaguerre et al. (11) of the role of pulmonary vein (PV) cardiomyocyte sleeves in AF, which led to a variety of PV-directed ablation approaches (**Fig. 1D**). Because the mechanisms for PV participation in AF were unclear, investigators began to address them (**Fig. 1E**). Initially, the role of the PVs was attributed to well-localized, spontaneous focal ectopic driver activity, which was supported by observations of dramatic resolution of AF with local radiofrequency (RF) energy application in a PV. However, it soon became apparent that AF tended to recur because other sources in the same and other PVs emerged, and pulmonary vein isolation (PVI) rapidly replaced focal ablation (12). Basic studies had identified spontaneous PV activity in the early 1980s, but the firing rate was slow and unlikely to contribute to AF (13).

Following the report by Haissaguerre et al. (11), basic scientists noted rapid arrhythmic activity in rabbit PVs (14) and provided evidence of Ca^{2+} mishandling in canine PVs (15). However, other observations in dogs failed to support the idea that normal PV sleeve cardiomyocytes spontaneously generate rapid focal activity (16–18). Moreover, PV cardiomyocytes displayed action potential (AP) properties (short AP duration and decreased phase 0 upstroke velocity) that reduce refractoriness and conduction velocity, potentially promoting re-entry (17). In addition, structural properties of PV cardiomyocyte sleeves, including longitudinal dissociation and abrupt shifts in fiber orientation, also favored local conduction slowing, block, and re-entry (19,20). A mathematical model incorporating realistic PV cellular electrophysiology and coupling properties suggested that there was enhanced vulnerability to local re-entry (21). This model was recently corroborated in the clinical electrophysiology laboratory (22). Present evidence suggests that multiple features of the PV cardiomyocyte sleeve predispose it to either focal or re-entrant activity, with discrete roles in AF initiation and maintenance in specific patient populations (23).

PVI was soon noted to be much more effective for paroxysmal than persistent AF (24). Subsequent work showed that non-PV sources become more important as AF becomes more persistent (25). Similarly, in animal models of persistent AF, the PVs play a limited role in AF maintenance (26). To deal more effectively with persistent AF, investigators sought other key anatomical structures and mechanisms involved in AF maintenance. Multiple linear lesions were found to suppress AF induced by vagal stimulation (27) and long-term rapid atrial pacing, with (28) or without (29) associated mitral regurgitation in dogs.

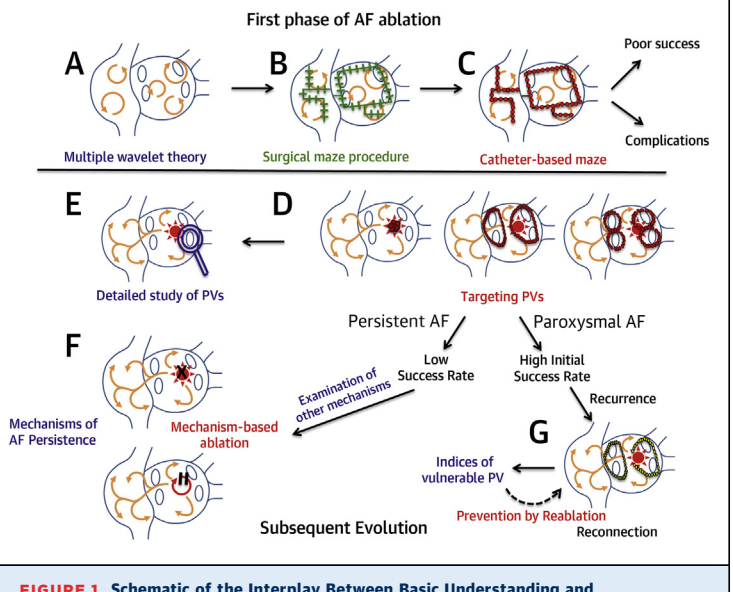
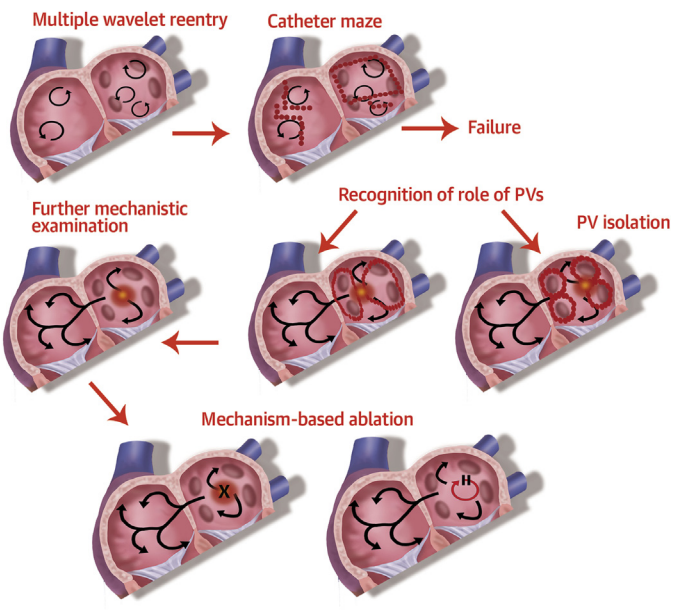


FIGURE 1 Schematic of the Interplay Between Basic Understanding and Clinical Approaches

The multiple wavelet theory of atrial fibrillation (AF) **(A)** led to the highly-successful surgical maze procedure **(B)**. However, attempts at mimicking the surgical maze by catheter ablation largely failed **(C)**. Clinical identification of the key role played by the pulmonary veins (PVs) led to the first truly successful ablation procedures for AF **(D)** and to basic studies of the underlying mechanisms **(E)**. Limited success of PV ablation for persistent AF led to a detailed examination of other mechanisms and mechanism-targeted procedures **(F)**. Clinical ablation procedures are labeled in **red**, basic research contributions are in **blue**.

A variety of anatomical structures have been specifically targeted in clinical approaches to persistent AF (**Fig. 3**). Stepwise ablation, in which discrete areas are targeted sequentially to an AF maintenance endpoint, such as AF termination (30), is a common paradigm. The LA posterior wall and roof regions have unique characteristics that contribute to AF maintenance. Shorter cycle lengths are found in the posterior LA during persistent AF in a canine model; cryoablation of this region suppresses AF (31). Experimental ablation of the LA roof suppresses AF perpetuation by interrupting LA re-entry circuits (26); however, macrore-entry atrial tachycardias sometimes result. Macrore-entry tachycardias also plague clinical AF procedures, particularly stepwise approaches involving multiple linear lesions (32). Other important atrial structures have also been identified in animal studies, including the atrial septum (33), Bachmann's bundle (33), and the ligament of Marshall (34). The stepwise approach to functionally-important atrial structures produced some improvement in persistent AF ablation, but failure rates and iatrogenic arrhythmias continue to be problems.



CENTRAL ILLUSTRATION **Pathophysiology Schema of Atrial Fibrillation**

This schematic illustrates the interactions between basic science concepts and clinical catheter-based AF-ablation techniques. The prevailing mechanistic hypothesis used to explain AF until the late 1990s was multiple circuit re-entry. The successful surgical maze procedure was based on this concept, and led to the catheter-based maze procedure, which failed because of complications and inadequate efficacy. The first successful AF ablation procedures resulted from a clinical recognition of the role of the PVs in AF. This observation led to a return to the bench to address the basic mechanisms by which the PVs contribute to AF occurrence, as well as a broader range of related fundamental mechanisms. Advances in the basic mechanistic understanding of AF have led to a variety of ablation approaches that target underlying mechanisms and promise to greatly improve the success of AF ablation. PV = pulmonary vein.

THE ROLE OF AUTONOMIC NERVOUS SYSTEM STRUCTURES

It has long been recognized that the autonomic nervous system plays an important role in governing AF susceptibility (35). Cervical vagal-nerve stimulation promotes long-lasting AF by abbreviating the atrial effective refractory period in a spatially heterogeneous manner (36,37). Cholinergic stimulation stabilizes AF-maintaining rotors (38). Depending on tissue properties and geometry, vagal AF may be maintained by single rotors or complex functional multicircuit re-entry (39). Adrenergic stimulation promotes AF by enhancing triggered activity (40). In some pathological contexts, adrenergic activation is essential for the emergence of atrial ectopic activity (41). Autonomic neural activity induces Ca^{2+}-dependent atrial tachyarrhythmias in canine models (42–44), and stellate-ganglion cryoablation delays tachyarrhythmia development (44). Cardiac autonomic inputs pass through epicardial fat pads to form ganglionated plexuses (GPs), containing both sympathetic and parasympathetic components (40,45). Ablation of cardiac GPs suppresses vagal AF (46,47). The effectiveness of GP ablation in other AF models is model-specific: atrial tachycardia remodeling produces autonomic hyperinnervation, and GP ablation has substantial anti-AF effects in tachycardia-remodeled dogs; however, experimental heart failure causes denervation, and GP ablation has no effect on AF associated with heart failure (48). Experimental sleep apnea induces spontaneous AF following increased GP firing, and GP ablation suppresses apnea-related AF inducibility (49).

Because most of the important GPs are situated near the PV ostia, autonomic denervation may contribute to the efficacy of PVI procedures (47), as evidenced by lower recurrence rates with PVI producing autonomic denervation (50). A controlled clinical study suggested that combining GP ablation with circumferential PVI prevents paroxysmal AF recurrence (51); however, it is uncertain whether the benefit was truly due to autonomic denervation or simply to more extensive lesion sets. One limitation to autonomic denervation approaches is spontaneous reinnervation, occurring over months in animal models (52,53) and apparently in humans (50). If GP ablation is to provide long-term benefit, ways to

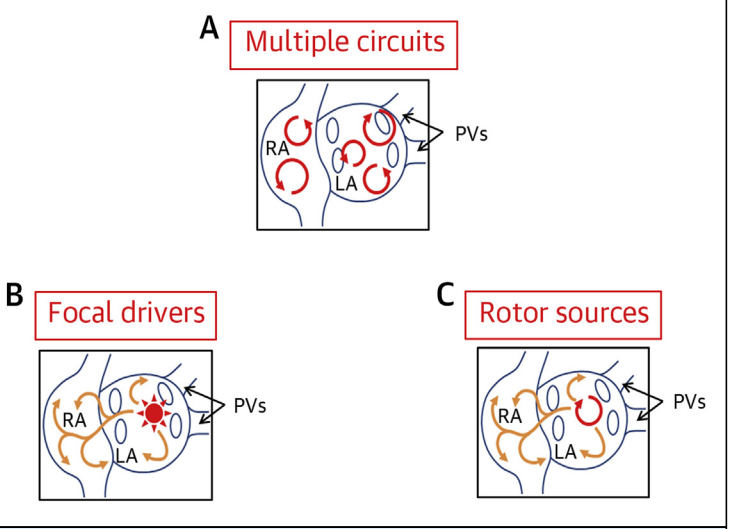


FIGURE 2 Three Major Candidate Mechanisms for AF

This figure schematically illustrates 3 basic concepts of the mechanism maintaining AF. Each concept is based on a primary "driver" mechanism, shown in red in each panel. Interestingly, the basic concepts represented were first put forward in the early 20th century (for discussion see reference 1). **(A)** Multiple circuit re-entry. **(B)** Focal-ectopic drivers. **(C)** Rotor sources. Driver mechanisms are shown in **red.** LA = left atrium; PV = pulmonary vein; RA = right atrium.

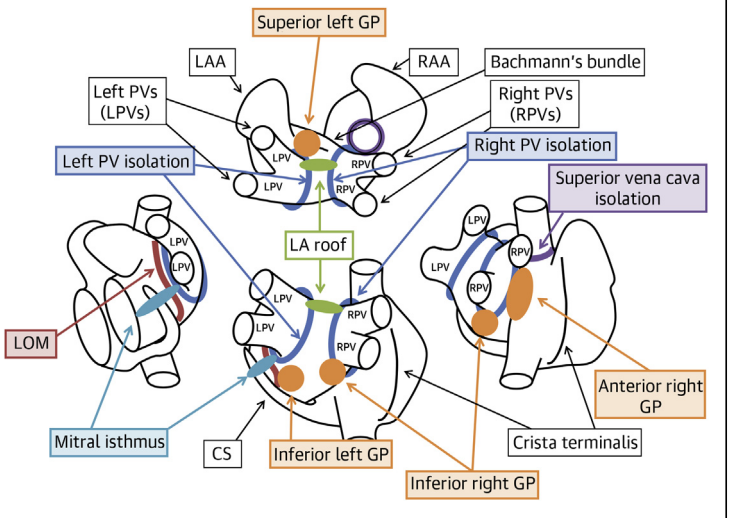


FIGURE 3 Key Anatomical Structures and Common AF Ablation Sites

This schematic illustrates various key anatomical structures that have been shown to play significant roles in AF, and have been targeted for ablation. Principal sites that have been included in AF ablation procedures are shown in color. The orange boxes indicate regions that have been targeted for cardiac autonomic innervation (ganglionated plexus) ablation. For more detailed discussion see text. CS = coronary sinus; GP = ganglionated plexus; LA = left atrial; LAA = left atrial appendage; LOM = ligament of Marshall; LPV = left pulmonary vein; PV = pulmonary vein; RAA = right atrial appendage; RPV = right pulmonary vein.

prevent reinnervation may need to be developed. A recent study showed that PVI plus GP ablation provided modestly (but statistically-significantly) improved sinus rhythm maintenance over PVI plus linear ablation (54).

Renal sympathetic denervation has generated considerable excitement as an approach for managing resistant hypertension (55). Both clinical studies (56) and experimental data (57,58) have suggested that there is AF protection following renal sympathetic denervation. However, the carefully conducted, sham denervation-controlled, SIMPLICITY HTN-3 trial failed to document any benefit from renal denervation in resistant hypertension (59), raising doubts about the procedure.

DYNAMICAL PROPERTIES OF ATRIAL ACTIVITY AND ABLATION TARGETS

The term *dynamical* is often applied to describe time-dependent properties, in particular those that concern the relationship between each event in a series and the preceding event. Atrial dynamical properties that relate to the development and maintenance of atrial tachyarrhythmias have been exploited to guide AF ablation (**Fig. 4**).

PROPERTIES OF LOCAL ATRIAL ELECTRICAL ACTIVITY AS GUIDES TO AF ABLATION

The targeting of sites with complex fractionated atrial electrograms (CFAEs) (**Fig. 4A**) was initially reported to produce very high success rates in clinical AF (60). Extensive subsequent work was performed to understand the mechanisms underlying CFAEs, their relationship to the AF substrate, and the precise value of CFAE targeting. CFAEs may relate to fibrosis-associated focal conduction delays at rotor anchoring-points (61) or wave fractionation caused by rotor meandering (62). Noncontact mapping in dogs suggests that, rather than emerging from true arrhythmia driver sites, most CFAE activity may result from wave front collision (63). Autonomic mechanisms may also be involved (64). The available basic research suggests that CFAEs are produced by a variety of mechanisms, with more or less direct relationships to the primary AF-maintaining substrate. Very few centers presently target CFAEs only, although many include CFAE targeting in persistent AF ablation protocols. A recent meta-analysis suggested that adding CFAE-targeted lesions to PVI reduces AF recurrence by about one-third in persistent AF without marginal benefit in paroxysmal AF, at the expense of longer procedures and increased risks of post-ablation atrial tachycardias (65).

DOMINANT-FREQUENCY ANALYSIS

An early experimental study introduced the concept of AF *drivers*: rapidly-firing regions that maintain the arrhythmia (31). Mechanistically, either focal ectopic sources (Fig. 2B) or rapid local re-entry (Fig. 2C) might underlie driver activity. Dominant frequency (DF) analysis (Fig. 4B) was introduced to identify rapidly-discharging periodic sources showing maximum DFs (DF_{max}) that might be AF drivers (66). Left-to-right atrial DF gradients are consistent with a primary role of the LA in AF maintenance (67,68), and studies of tissues from AF patients have provided insights into potential ionic mechanisms (69). One study showed that DF_{max}-targeted ablation improved outcomes when significant reductions in DFs and left-to-right atrial DF gradient were achieved (70), but a subsequent study (71) showed little benefit from DF targeting and limited correlations between DF_{max} and CFAE sites. A recent detailed analysis showed that focal DF_{max} areas are less common in persistent versus paroxysmal AF, are spatially unstable, and, in many cases, cannot be identified with localized drivers (72).

RESTITUTION PROPERTIES AND ROTORS

Dynamical properties, such as the response of the AP to premature activation and increased activation rates (Fig. 4C), contribute to AF vulnerability (73,74). Abnormalities in Ca^{2+} handling are important in abnormal rate adaptation (73). Steep AP duration restitution favors the initiation of re-entrant arrhythmias (74), and may help to identify appropriate sites for intervention (75). Electrical restitution properties of atrial tissue (76) were recently incorporated in computational algorithms to identify AF driver mechanisms in patients (77).

The concept of "spiral-wave re-entry" (Fig. 5) has significant implications for AF. Initially developed by Winfree (78,79), spiral-wave re-entry differs in some important ways from the "leading circle" paradigm initially developed by Allessie et al. (80). *Rotor* is a descriptive term for a spiral-wave re-entry generator. Rotors can be long lasting and stable, or transient and enduring as briefly as a single rotation.

NOVEL MAPPING-METHODS AND MECHANISM-DIRECTED ABLATION

Arguably, one of the greatest contributions of basic research to AF ablation is the recent development of mechanism-directed approaches (Fig. 1F). The idea of targeting the patient-specific substrate underlying AF emerged from basic research over a decade ago (81), but only recently have tools been developed to apply this concept clinically.

The notion that surface electrocardiographic events can be related to their intracardiac source has

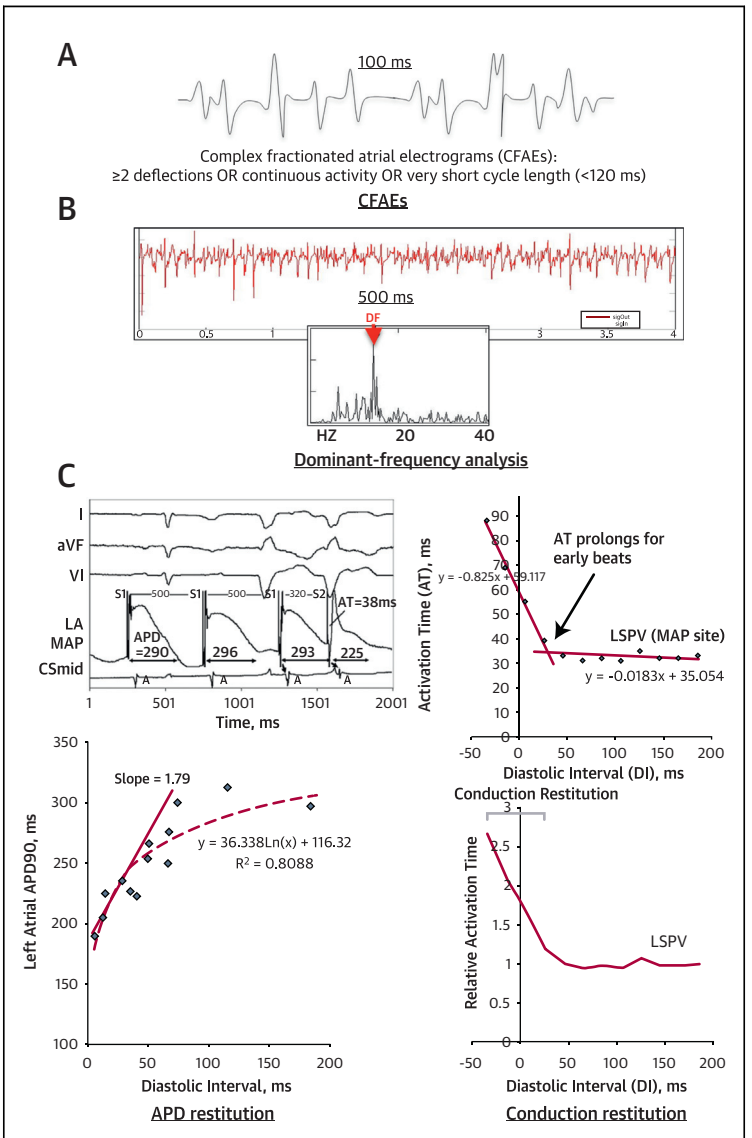


FIGURE 4 Dynamical Atrial Tissue Electrophysiological Properties Relevant to AF Ablation

(A) Complex fractionated atrial electrograms (CFAEs) are often targeted in ablation procedures for persistent AF. **(B)** Atrial electrogram activity and corresponding fast-Fourier transformation with dominant frequency (DF) indicated. Zones with the greatest DF values are targeted with the assumption that they are driver regions. **(C)** Restitution properties. **(Left)** Action potential duration (APD) restitution. When the slope of the relationship between APD and the preceding diastolic interval (DI) exceeds 1, the APD change resulting from a change in DI will be greater than the change in DI, causing progressive amplification in changes, instability, and arrhythmia initiation. **(Right)** Conduction restitution. Reprinted with permission from Narayan et al. (76). A = atrial electrogram; AT = activation time; CSmid = coronary sinus electrogram; DF = dominant frequency; LSPV = left superior pulmonary vein; MAP = monophasic action potential; PV = pulmonary vein; S1 = basic stimulus; S2 = extrastimulus.

existed for almost 50 years (82). Computing and theory have advanced to the point that patient-specific AF-maintaining mechanisms can be identified in detail via noninvasive body-surface mapping by electrocardiographic imaging (83). Recently, electrocardiographic imaging has been applied to target ablation for persistent AF, resulting in abbreviated ablation procedures with increased efficiency compared with stepwise ablation (84).

Another approach to mechanism-targeted ablation uses biatrial basket-catheter mapping, in combination with algorithms based on restitution data, to identify focal sources and stable (for >10 min) AF-maintaining rotors (77). The mean number of concurrent sources per patient averages about 2, with the number of sources increasing with AF-promoting factors such as obstructive sleep apnea, LA enlargement, and left ventricular dysfunction (85). A randomized multicenter trial has shown superior sinus rhythm maintenance with this mechanism-based approach compared with conventional AF ablation (77).

PREVENTION OF RECURRENCE AND PROGRESSION

Recurrence of atrial tachyarrhythmia is a major problem limiting the effectiveness of AF ablation. A recent meta-analysis indicated an AF recurrence rate of 31.2% after a mean follow-up of almost 2 years post-ablation (86). The mechanisms of arrhythmia recurrence vary. For paroxysmal AF, the single most important factor (particularly within the first year post-ablation) is PV reconnection, a return of PV conduction after an initially successful PVI (**Fig. 1G**) (87). Later recurrences appear to be related to progression of the AF substrate (24,87).

Pharmacological maneuvers have been developed to identify (during the initial PVI procedure) "dormant" veins at risk of reconnecting, and to guide additional ablation to prevent subsequent reconnection (**Fig. 1G**). Intravenous adenosine is widely used to identify dormant conduction. RF ablation depolarizes the resting membrane potential to levels at which Na^+-channels are inactivated, producing inexcitability. Adenosine hyperpolarizes PV cells by increasing the background K^+ current (88). PVs that recover excitability have less severe membrane depolarization, and adenosine-induced hyperpolarization is sufficient to restore excitability and conduction. In contrast, veins with more severe RF-induced depolarization do not regain conduction with adenosine (88). Adenosine hyperpolarizes PVs more effectively than isoproterenol, and is more likely to reveal dormant conduction (89). Adenosine-guided ablation for drug-resistant paroxysmal AF has been tested in a multicenter randomized controlled trial (90). The preliminary results indicate that post-PVI dormant PV conduction is associated with a greater atrial tachyarrhythmia recurrence rate, and eliminating dormant PV conduction by additional targeted ablation reduces atrial tachyarrhythmia recurrence by >50% (91).

The problem of substrate progression is multifactorial and challenging. Progression of atrial damage due to underlying heart disease is a major factor (24). Most risk factors affect AF by causing structural remodeling (2). Recent work suggests that AF recurrence can be prevented by effectively managing risk factors such as obstructive sleep apnea and obesity, presumably by curtailing further damage and/or reversing existing abnormalities (92–94).

Conversely, AF itself can cause progression of the substrate (95). In addition to complex ion-channel remodeling that accelerates repolarization and alters conduction properties (95), rapid activation of atrial cardiomyocytes causes profibrotic changes in fibroblast function and promotes atrial fibrosis (96). Recent work points to Ca^{2+} signaling as a key mechanism in AF progression (97).

The well-established therapeutic resistance of longstanding AF appears to result from structural alterations that greatly magnify the complexity of underlying mechanisms and make it almost impossible to successfully restore and maintain sinus

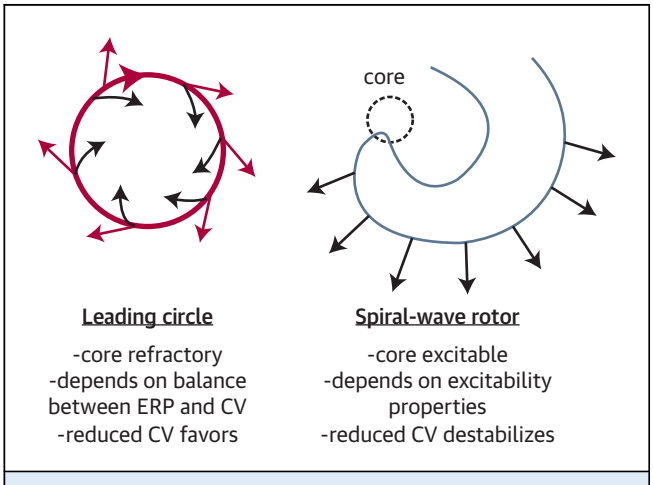


FIGURE 5 Comparison of Leading Circle and Spiral Wave Concepts of Re-Entry

Whereas leading-circle re-entry should establish itself in smaller circuits with Na^+-channel blockade, favoring AF, spiral-wave theory predicts rotor destabilization, more consistent with clinical observations. CV = conduction velocity; ERP = effective refractory period.

rhythm (84,98). Early and aggressive sinus rhythm maintenance may forestall such changes (99). Interesting recent data suggest that effective mechanism-directed ablation might prevent long-term recurrence (100). Alternatively or additionally, work is needed to develop safe, effective upstream pharmacological therapies to suppress mechanisms leading to AF progression. To date, despite success in well-defined animal models (101), effective upstream therapy has yet to be convincingly applied in humans (102). Extensive additional basic and clinical research is clearly needed before upstream therapy can become a practical reality.

LIMITATIONS OF BASIC RESEARCH

It is important to recognize that all experimental models, by their nature, are simplified paradigms that interrogate specific questions in the absence of clinical AF's complexity. Thus, the results of experimental studies need careful consideration, and their predictions must be confirmed by appropriate clinical research. Experimental models of atrial ectopic activity, as may occur with both PV and non-PV drivers (103), are very limited, and only recently have insights into the mechanisms underlying such ectopic activity been obtained (104–106).

CONCLUSIONS

The development of successful AF ablation procedures has been marked by dynamic interplay between basic research and astute clinical application/observation. Despite great progress to date, more work is needed to ensure effective and enduring management of AF in the broad and complex AF population.

ACKNOWLEDGMENT The authors thank France Thériault for excellent secretarial assistance.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Stanley Nattel, Montreal Heart Institute, Université de Montréal, 5000 Belanger Street East, Montreal, Quebec H1T 1C8, Canada. E-mail: stanley.nattel@icm-mhi.org.

REFERENCES

1. Nattel S. New ideas about atrial fibrillation 50 years on. Nature 2002;415:219–26.

2. Andrade J, Khairy P, Dobrev D, et al. The clinical profile and pathophysiology of atrial fibrillation: relationships among clinical features, epidemiology, and mechanisms. Circ Res 2014;114:1453–68.

3. Zipes DP. Radiofrequency ablation—what is left? Eur Heart J 1995;16 Suppl G:24–7.

4. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Heart Rhythm 2012;9:632–96.e21.

5. Garrey WE. The nature of fibrillary contraction of the heart: its relation to tissue mass and form. Am J Physiol 1914;33:397–414.

6. Moe GK, Rheinboldt WC, Abildskov JA. A computer model of atrial fibrillation. Am Heart J 1964;67:200–20.

7. Cox JL, Schuessler RB, D'Agostino HJ Jr., et al. The surgical treatment of atrial fibrillation. III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 1991;101:569–83.

8. Schwartzman D, Kuck KH. Anatomy-guided linear atrial lesions for radiofrequency catheter ablation of atrial fibrillation. Pacing Clin Electrophysiol 1998;21:1959–78.

9. Calkins H, Hall J, Ellenbogen K, et al. A new system for catheter ablation of atrial fibrillation. Am J Cardiol 1999;83:227D–36D.

10. Jaïs P, Shah DC, Haïssaguerre M, et al. Efficacy and safety of septal and left-atrial linear ablation for atrial fibrillation. Am J Cardiol 1999;84:139R–46R.

11. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 1998;339:659–66.

12. Jaïs P, Weerasooriya R, Shah DC, et al. Ablation therapy for atrial fibrillation (AF): past, present and future. Cardiovasc Res 2002;54:337–46.

13. Cheung DW. Electrical activity of the pulmonary vein and its interaction with the right atrium in the guinea-pig. J Physiol 1981;314:445–56.

14. Chen YJ, Chen SA, Chen YC, et al. Effects of rapid atrial pacing on the arrhythmogenic activity of single cardiomyocytes from pulmonary veins: implication in initiation of atrial fibrillation. Circulation 2001;104:2849–54.

15. Honjo H, Boyett MR, Niwa R, et al. Pacing-induced spontaneous activity in myocardial sleeves of pulmonary veins after treatment with ryanodine. Circulation 2003;107:1937–43.

16. Coutu P, Chartier D, Nattel S. Comparison of Ca2+-handling properties of canine pulmonary vein and left atrial cardiomyocytes. Am J Physiol Heart Circ Physiol 2006;291:H2290–300.

17. Ehrlich JR, Cha TJ, Zhang L, et al. Cellular electrophysiology of canine pulmonary vein cardiomyocytes: action potential and ionic current properties. J Physiol 2003;551:801–13.

18. Cha TJ, Ehrlich JR, Zhang L, et al. Atrial tachycardia remodeling of pulmonary vein cardiomyocytes: comparison with left atrium and potential relation to arrhythmogenesis. Circulation 2005;111:728–35.

19. Hocini M, Ho SY, Kawara T, et al. Electrical conduction in canine pulmonary veins: electrophysiological and anatomic correlation. Circulation 2002;105:2442–8.

20. Verheule S, Wilson EE, Arora R, et al. Tissue structure and connexin expression of canine pulmonary veins. Cardiovasc Res 2002;55:727–38.

21. Cherry EM, Ehrlich JR, Nattel S, et al. Pulmonary vein reentry—properties and size matter: insights from a computational analysis. Heart Rhythm 2007;4:1553–62.

22. Lee G, Spence S, Teh A, et al. High-density epicardial mapping of the pulmonary vein-left atrial junction in humans: insights into mechanisms of pulmonary vein arrhythmogenesis. Heart Rhythm 2012;9:258–64.

23. Nattel S. Paroxysmal atrial fibrillation and pulmonary veins: relationships between clinical forms and automatic versus re-entrant mechanisms. Can J Cardiol 2013;29:1147–9.

24. Oral H, Knight BP, Tada H, et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. Circulation 2002;105:1077–81.

25. Kurotobi T, Iwakura K, Inoue K, et al. Multiple arrhythmogenic foci associated with the development of perpetuation of atrial fibrillation. Circ Arrhythm Electrophysiol 2010 Feb;3:39–45.

26. Nishida K, Sarrazin JF, Fujiki A, et al. Roles of the left atrial roof and pulmonary veins in the anatomic substrate for persistent atrial fibrillation

and ablation in a canine model. J Am Coll Cardiol 2010;56:1728–36.

27. Elvan A, Pride HP, Eble JN, et al. Radiofrequency catheter ablation of the atria reduces inducibility and duration of atrial fibrillation in dogs. Circulation 1995;91:2235–44.

28. Mitchell MA, McRury ID, Haines DE. Linear atrial ablations in a canine model of chronic atrial fibrillation: morphological and electrophysiological observations. Circulation 1998;97:1176–85.

29. Elvan A, Huang XD, Pressler ML, et al. Radiofrequency catheter ablation of the atria eliminates pacing-induced sustained atrial fibrillation and reduces connexin 43 in dogs. Circulation 1997;96:1675–85.

30. Takahashi Y, O'Neill MD, Hocini M, et al. Effects of stepwise ablation of chronic atrial fibrillation on atrial electrical and mechanical properties. J Am Coll Cardiol 2007;49:1306–14.

31. Morillo CA, Klein GJ, Jones DL, et al. Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 1995;91:1588–95.

32. Zheng L, Yao Y, Zhang S, et al. Organized left atrial tachyarrhythmia during stepwise linear ablation for atrial fibrillation. J Cardiovasc Electrophysiol 2009;20:499–506.

33. Kumagai K, Uno K, Khrestian C, et al. Single site radiofrequency catheter ablation of atrial fibrillation: studies guided by simultaneous multisite mapping in the canine sterile pericarditis model. J Am Coll Cardiol 2000;36:917–23.

34. Doshi RN, Wu TJ, Yashima M, et al. Relation between ligament of Marshall and adrenergic atrial tachyarrhythmia. Circulation 1999;100:876–83.

35. Coumel P, Attuel P, Lavallee J, et al. The atrial arrhythmia syndrome of vagal origin. Arch Mal Coeur Vaiss 1978;71:645–56.

36. Liu L, Nattel S. Differing sympathetic and vagal effects on atrial fibrillation in dogs: role of refractoriness heterogeneity. Am J Physiol 1997;273:H805–16.

37. Nishida K, Michael G, Dobrev D, et al. Animal models for atrial fibrillation: clinical insights and scientific opportunities. Europace 2010;12:160–72.

38. Kneller J, Zou R, Vigmond EJ, et al. Cholinergic atrial fibrillation in a computer model of a two-dimensional sheet of canine atrial cells with realistic ionic properties. Circ Res 2002;90:E73–87.

39. Zou R, Kneller J, Leon LJ, et al. Substrate size as a determinant of fibrillatory activity maintenance in a mathematical model of canine atrium. Am J Physiol Heart Circ Physiol 2005;289:H1002–12.

40. Chen PS, Chen LS, Fishbein MC, et al. Role of the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res 2014;114:1500–15.

41. Nishida K, Qi XY, Wakili R, et al. Mechanisms of atrial tachyarrhythmias associated with coronary artery occlusion in a chronic canine model. Circulation 2011;123:137–46.

42. Chou CC, Nguyen BL, Tan AY, et al. Intracellular calcium dynamics and acetylcholine-induced triggered activity in the pulmonary veins of dogs with pacing-induced heart failure. Heart Rhythm 2008;5:1170–7.

43. Choi EK, Shen MJ, Han S, et al. Intrinsic cardiac nerve activity and paroxysmal atrial tachyarrhythmia in ambulatory dogs. Circulation 2010;121:2615–23.

44. Tan AY, Zhou S, Ogawa M, et al. Neural mechanisms of paroxysmal atrial fibrillation and paroxysmal atrial tachycardia in ambulatory canines. Circulation 2008;118:916–25.

45. Armour JA, Murphy DA, Yuan BX, et al. Gross and microscopic anatomy of the human intrinsic cardiac nervous system. Anat Rec 1997;247:289–98.

46. Schauerte P, Scherlag BJ, Pitha J, et al. Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. Circulation 2000;102:2774–80.

47. Lemola K, Chartier D, Yeh YH, et al. Pulmonary vein region ablation in experimental vagal atrial fibrillation: role of pulmonary veins versus autonomic ganglia. Circulation 2008;117:470–7.

48. Nishida K, Maguy A, Sakabe M, et al. The role of pulmonary veins vs. autonomic ganglia in different experimental substrates of canine atrial fibrillation. Cardiovasc Res 2011;89:825–33.

49. Ghias M, Scherlag BJ, Lu Z, et al. The role of ganglionated plexi in apnea-related atrial fibrillation. J Am Coll Cardiol 2009;54:2075–83.

50. Pappone C, Santinelli V, Manguso F, et al. Pulmonary vein denervation enhances long-term benefit after circumferential ablation for paroxysmal atrial fibrillation. Circulation 2004;109:327–34.

51. Katritsis DG, Pokushalov E, Romanov A, et al. Autonomic denervation added to pulmonary vein isolation for paroxysmal atrial fibrillation: a randomized clinical trial. J Am Coll Cardiol 2013;62:2318–25.

52. Oh S, Zhang Y, Bibevski S, et al. Vagal denervation and atrial fibrillation inducibility: epicardial fat pad ablation does not have long-term effects. Heart Rhythm 2006;3:701–8.

53. Sakamoto S, Schuessler RB, Lee AM, et al. Vagal denervation and reinnervation after ablation of ganglionated plexi. J Thorac Cardiovasc Surg 2010;139:444–52.

54. Pokushalov E, Romanov A, Katritsis DG, et al. Ganglionated plexus ablation vs linear ablation in patients undergoing pulmonary vein isolation for persistent/long-standing persistent atrial fibrillation: a randomized comparison. Heart Rhythm 2013;10:1280–6.

55. Froeschl M, Hadziomerovic A, Ruzicka M. Renal sympathetic denervation for resistant hypertension. Can J Cardiol 2013;29:636–8.

56. Pokushalov E, Romanov A, Corbucci G, et al. A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol 2012;60:1163–70.

57. Zhao Q, Yu S, Zou M, et al. Effect of renal sympathetic denervation on the inducibility of atrial fibrillation during rapid atrial pacing. J Interv Card Electrophysiol 2012;35:119–25.

58. Linz D, Mahfoud F, Schotten U, et al. Renal sympathetic denervation provides ventricular rate control but does not prevent atrial electrical remodeling during atrial fibrillation. Hypertension 2013;61:225–31.

59. Bhatt DL, Kandzari DE, O'Neill WW, et al., SYMPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014;370:1393–401.

60. Nademanee K, McKenzie J, Kosar E, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 2004;43:2044–53.

61. Tanaka K, Zlochiver S, Vikstrom KL, et al. Spatial distribution of fibrosis governs fibrillation wave dynamics in the posterior left atrium during heart failure. Circ Res 2007;101:839–47.

62. Zlochiver S, Yamazaki M, Kalifa J, et al. Rotor meandering contributes to irregularity in electrograms during atrial fibrillation. Heart Rhythm 2008;5:846–54.

63. Gerstenfeld EP, Lavi N, Bazan V, et al. Mechanism of complex fractionated electrograms recorded during atrial fibrillation in a canine model. Pacing Clin Electrophysiol 2011;34:844–57.

64. Lin J, Scherlag BJ, Zhou J, et al. Autonomic mechanism to explain complex fractionated atrial electrograms (CFAE). J Cardiovasc Electrophysiol 2007;18:1197–205.

65. Wu SH, Jiang WF, Gu J, et al. Benefits and risks of additional ablation of complex fractionated atrial electrograms for patients with atrial fibrillation: a systematic review and meta-analysis. Int J Cardiol 2013;169:35–43.

66. Skanes AC, Mandapati R, Berenfeld O, et al. Spatiotemporal periodicity during atrial fibrillation in the isolated sheep heart. Circulation 1998;98:1236–48.

67. Mansour M, Mandapati R, Berenfeld O, et al. Left-to-right gradient of atrial frequencies during acute atrial fibrillation in the isolated sheep heart. Circulation 2001;103:2631–6.

68. Lazar S, Dixit S, Marchlinski FE, et al. Presence of left-to-right atrial frequency gradient in paroxysmal but not persistent atrial fibrillation in humans. Circulation 2004;110:3181–6.

69. Voigt N, Trausch A, Knaut M, et al. Left-to-right atrial inward rectifier potassium current gradients in patients with paroxysmal versus chronic atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:472–80.

70. 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;6:33–40.

71. Verma A, Lakkireddy D, Wulffhart Z, et al. Relationship between complex fractionated electrograms (CFE) and dominant frequency (DF) sites and prospective assessment of adding DF-guided ablation to pulmonary vein isolation in persistent

atrial fibrillation (AF). J Cardiovasc Electrophysiol 2011;22:1309–16.

72. Jarman JW, Wong T, Kojodjojo P, et al. Spatiotemporal behavior of high dominant frequency during paroxysmal and persistent atrial fibrillation in the human left atrium. Circ Arrhythm Electrophysiol 2012;5:650–8.

73. Kneller J, Sun H, Leblanc N, et al. Remodeling of Ca2+-handling by atrial tachycardia: evidence for a role in loss of rate-adaptation. Cardiovasc Res 2002;54:416–26.

74. Weiss JN, Qu Z, Chen PS, et al. The dynamics of cardiac fibrillation. Circulation 2005; 112:1232–40.

75. Krummen DE, Bayer JD, Ho J, et al. Mechanisms of human atrial fibrillation initiation: clinical and computational studies of repolarization restitution and activation latency. Circ Arrhythm Electrophysiol 2012;5:1149–59.

76. Narayan SM, Kazi D, Krummen DE, et al. Repolarization and activation restitution near human pulmonary veins and atrial fibrillation initiation: a mechanism for the initiation of atrial fibrillation by premature beats. J Am Coll Cardiol 2008;52:1222–30.

77. Narayan SM, Krummen DE, Shivkumar K, et al. Treatment of atrial fibrillation by the ablation of localized sources: CONFIRM (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial. J Am Coll Cardiol 2012;60:628–36.

78. Winfree AT. Spiral waves of chemical activity. Science 1972;175:634–6.

79. Winfree AT. Sudden cardiac death: a problem in topology. Sci Am 1983;248:144–9, 152–7, 160–1.

80. 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;41:9–18.

81. Nattel S. Therapeutic implications of atrial fibrillation mechanisms: can mechanistic insights be used to improve AF management? Cardiovasc Res 2002;54:347–60.

82. Plonsey R. Limitations on the equivalent cardiac generator. Biophys J 1966;6:163–73.

83. Cuculich PS, Wang Y, Lindsay BD, et al. Noninvasive characterization of epicardial activation in humans with diverse atrial fibrillation patterns. Circulation 2010;122:1364–72.

84. Haïssaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. Circulation 2014 Jul 15 [E-pub ahead of print].

85. Baykaner T, Clopton P, Lalani GG, et al., CONFIRM Investigators. Targeted ablation at stable atrial fibrillation sources improves success over conventional ablation in high-risk patients: a substudy of the CONFIRM Trial. Can J Cardiol 2013;29:1218–26.

86. D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. Int J Cardiol 2013;167:1984–9.

87. Sotomi Y, Inoue K, Ito N, et al. Cause of very late recurrence of atrial fibrillation or flutter after catheter ablation for atrial fibrillation. Am J Cardiol 2013;111:552–6.

88. Datino T, Macle L, Qi XY, et al. Mechanisms by which adenosine restores conduction in dormant canine pulmonary veins. Circulation 2010;121:963–72.

89. Datino T, Macle L, Chartier D, et al. Differential effectiveness of pharmacological strategies to reveal dormant pulmonary vein conduction: a clinical-experimental correlation. Heart Rhythm 2011;8:1426–33.

90. Macle L, Khairy P, Verma A, et al. Adenosine following pulmonary vein isolation to target dormant conduction elimination (ADVICE): methods and rationale. Can J Cardiol 2012;28: 184–90.

91. Macle L, Khairy P, Weerasooriya R, et al. Adenosine-guided pulmonary vein isolation for the treatment of atrial fibrillation: results of the prospective randomized ADVICE trial. LB01-02. Paper presented at: HeartRhythm 2014; May 8, 2014; San Francisco, CA.

92. Naruse Y, Tada H, Satoh M, et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm 2013;10:331–7.

93. Fein AS, Shvilkin A, Shah D, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. J Am Coll Cardiol 2013;62:300–5.

94. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. JAMA 2013;310:2050–60.

95. Wakili R, Voigt N, Kääb S, et al. Recent advances in the molecular pathophysiology of atrial fibrillation. J Clin Invest 2011;121:2955–68.

96. Yue L, Xie J, Nattel S. Molecular determinants of cardiac fibroblast electrical function and therapeutic implications for atrial fibrillation. Cardiovasc Res 2011;89:744–53.

97. Li N, Chiang DY, Wang S, et al. Ryanodine receptor-mediated calcium leak drives progressive development of an atrial fibrillation substrate in a transgenic mouse model. Circulation 2014;129: 1276–85.

98. Allessie MA, de Groot NM, Houben RP, et al. Electropathological substrate of long-standing persistent atrial fibrillation in patients with structural heart disease: longitudinal dissociation. Circ Arrhythm Electrophysiol 2010;3:606–15.

99. Kirchhof P, Breithardt G, Camm AJ, et al. Improving outcomes in patients with atrial fibrillation: rationale and design of the early treatment of atrial fibrillation for stroke prevention trial. Am Heart J 2013;166:442–8.

100. Narayan SM, Baykaner T, Clopton P, et al. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: extended follow-up of the CONFIRM trial (Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation). J Am Coll Cardiol 2014;63:1761–8.

101. Woods CE, Olgin J. Atrial fibrillation therapy now and in the future: drugs, biologicals, and ablation. Circ Res 2014;114:1532–46.

102. Camm AJ, Al-Khatib SM, Calkins H, et al. A proposal for new clinical concepts in the management of atrial fibrillation. Am Heart J 2012; 164:292–302.

103. Lin D, Frankel DS, Zado ES, et al. Pulmonary vein antral isolation and nonpulmonary vein trigger ablation without additional substrate modification for treating longstanding persistent atrial fibrillation. J Cardiovasc Electrophysiol 2012;23:806–13.

104. Yeh Y-H, Wakili R, Qi XY, et al. Calcium handling abnormalities underlying atrial arrhythmogenesis and contractile dysfunction in dogs with congestive heart failure. Circulation: Arrhythmia and Electrophysiology 2008;1:93–102.

105. Voigt N, Li N, Wang Q, et al. Enhanced sarcoplasmic reticulum Ca2+ leak and increased Na+-Ca2+ exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. Circulation 2012;125:2059–70.

106. Voigt N, Heijman J, Wang Q, et al. Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. Circulation 2014;129:145–56.

KEY WORDS atrial fibrillation, ectopic focus, ganglionated plexus, pulmonary vein ablation, re-entry, rotors