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.
ABBRiEvATiONS AND ACRONYMS

AF = atrial fibrillation  
CFAE = complex fractionated atrial electrogram  
DF = dominant frequency (of fast-Fourier transformed signals)  
ERP = effective refractory period  
GP = ganglionic plexus  
LA = left atrium/atrial  
PV = pulmonary vein  
PVI = pulmonary vein isolation

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.
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, macro-re-entry atrial tachycardias sometimes result. Macro-re-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.

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
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 (DFmax) 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 DFmax-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 DFmax and CFAE sites. A recent detailed analysis showed that focal DFmax 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 Ca²⁺ 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...
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 Ca2+ 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...
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.

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REFERENCES


71. Verma A, Lalikireddy D, Woffhart 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


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