ABSTRACT

A frequent need for re-ablations and limited overall success rates are still major limitations of catheter ablation procedures for the treatment of atrial fibrillation (AF). These limitations include not only the durability of the pulmonary vein isolation (PVI) lines, but also the pathophysiological understanding of the arrhythmia’s substrate. Long-term single procedure success rates in non-paroxysmal AF are disappointingly low for current stepwise ablation approaches adding the placement of linear lines and electrogram-based ablation after circumferential PVI isolation. In the future, substrate modification in AF ablation should move toward individualized patient-tailored ablation procedures. Magnetic resonance imaging could play a major role for noninvasively describing the localization and extent of fibrotic areas. Specific new strategies that could be used include precise localization and ablation of rotors that maintain the arrhythmia using multielectrode mapping during AF and box isolation of fibrotic areas guided by electroanatomic voltage mapping during sinus rhythm. (J Am Coll Cardiol 2015;65:196–206) © 2015 by the American College of Cardiology Foundation.

Percutaneous catheter ablation is widely used as an interventional tool for rhythm control in patients with atrial fibrillation (AF) (1). Circumferential pulmonary vein isolation (PVI), with confirmation of the entrance block, anchors this procedure. However, this intervention produces a frequent need for re-ablations and has limited overall success rates. This is caused by limitations not only in the durability of PVI lines, but also in our current understanding of the pathophysiology, especially of the arrhythmia’s substrate.

A better understanding of the human atrial substrate that maintains AF has led to the concept of pre-existing specific fibrotic atrial cardiomyopathy (FACM), in which AF manifests from an individually localized substrate (2,3). This may help explain why circumferential PVI is effective in many, but not all, patients with paroxysmal AF, and is also effective in some patients with long-standing, persistent AF. In addition, the extent and localization of an individual patient’s AF substrate must be understood to find effective ablation targets in the relatively small group of people with paroxysmal AF who experience AF recurrences despite durable PVI, as well as in the larger group of patients with persistent AF who obviously need more than PVI.

HUMAN AF SUBSTRATE

In a substantial subgroup of patients, evidence suggests that there is a genetic predisposition for development of AF based on the identification of multiple genes and genetic loci that appear to affect AF susceptibility (4). Although familial AF may be a monogenetic disorder, nonfamilial AF may be a multigenetic disease in which genetic factors interact with environmental variables. We are beginning to see research that focuses on primary fibrotic atrial changes. A recent study described a rare autosomal recessive atrial cardiomyopathy that clinically presented with atrial arrhythmias, including AF, bi-atrial dilatation, and potential electrical standstill over...
Fibrotic atrial structural remodeling has been consistently described in AF patients in histological and autopsy studies (6–8) (Figure 1). The presence of (micro)fibrosis leading to changes in cellular coupling results in spatial “nonuniform anisotropic” impulse propagation, which is a potential cause of atrial activation abnormalities underlying the initiation and perpetuation of re-entrant arrhythmias like AF (9,10). Recent clinical research has highlighted the presence of atrial tissue fibrosis using delayed-enhancement magnetic resonance imaging (DE-MRI) and electroanatomic voltage mapping (EAVM) (11–14). Importantly, fibrotic atrial changes vary in localization and extent, and are principally bi-atrial findings. A higher mean value of fibrosis was detected in patients with persistent AF versus paroxysmal AF; however, variability in the extent of fibrosis among patients with AF is very high (7). In addition, patients with so-called “lone” AF may exhibit a substantial fibrotic substrate before and/or at the clinical advent of AF, whereas other patients with a decades-long history of AF do not develop a significant fibrotic substrate (3). The most frequent manifestation combination of bi-atrial FACM was described as bradycardia/tachycardia syndrome with sick sinus node plus paroxysmal AF (2) (Figure 2). Importantly, the extent of the fibrotic atrial substrate is variable and has been classified as FACM 0 to 3 (2,3) (Figure 3), which corresponds to the DE-MRI study Utah classification of 1 to 4 (12). Furthermore, the regional distribution of patchy fibrotic atrial areas varies significantly from patient to patient (Figures 4 and 5).

In other patients, the fibrotic atrial substrate leading to increased AF susceptibility may result from severe underlying structural heart disease (e.g., mitral stenosis or hypertrophic obstructive cardiomyopathy). An EAVM study in patients with rheumatic mitral stenosis who underwent commissurotomy and who did not have a history of AF described a significantly reduced bi-atrial voltage (15). Conversely, in an EAVM series of patients with systemic hypertension plus left ventricular hypertrophy, but no history of AF, the mean right atrial voltage was identical in the hypertension and control groups (16). In general, the impact of “classic comorbidities” among patients undergoing catheter ablation of AF seems to be overestimated, as is the role of age on the fibrotic substrate (3). In an MRI study that compared left atrial (LA) structural changes in patients with lone AF versus those with classic comorbidities, the substrate was independent of comorbidities (17). This corresponds well with a recent autopsy study in which negligibly low amounts of fibrosis were found in older patients with a high CHA2DS2-VASc score (4.3), but who did not have a history of AF; patient age was not correlated with an increase in the extent of atrial fibrosis (8).

In addition to “substrate makers” like FACM or mitral stenosis, “modulators” influence the susceptibility of AF occurrence (e.g., obesity and/or cardiometabolic syndrome, infections and/or inflammation, surgery, and cancer). Weight reduction with intensive risk factor management substantially changed these modulators in 1 study, and reduced AF symptom burden and severity. Changing these modulators was also beneficial for cardiac remodeling (18). With respect to surgery, pre-operatively elevated serum markers of collagen synthesis were associated with postsurgical AF in patients without a history of AF (19). Importantly, pre-existing LA fibrosis was significantly higher in patients who developed post-surgical AF compared with those who stayed in sinus rhythm (19), which indicates toward the modulating effects of cardiac surgery on previously subclinical LA fibrosis and/or FACM.

**Atrial Substrate Modification Strategies**

**Circumferential PV Isolation.** Within the evolution of AF catheter ablation, circumferential PVI
extends the ablation sites to more proximal areas away from focal ablation sites within the veins and from distal sites of segmental PV disconnection (1). Such proximal PVI isolates triggers within the PVs and within the funnel-shaped left atrium–PV transition area, and also affects the substrate necessary for maintaining the arrhythmia. This may reflect a substantial atrial mass reduction, but it may also be related to the specific nonuniform anisotropic arrangement of the longitudinally- and spirally-oriented atrial myocardial muscle sleeves fanning out into the PVs. These muscle sleeves facilitate re-entry, fibrillatory wavelets, or rotors, and move into the anatomical barriers of the PV ostia, thus facilitating re-entry around these ostia (Central Illustration). In a randomized clinical study, large isolation areas were significantly more effective compared with small isolation areas around the PVs (20). In some cases, the isolated PV areas could even sustain AF themselves (Figure 6). Clearly, many patients with AF recurrences after PVI have PV re-connection at the time of re-ablation (21). However, the substrate modification aspect of circumferential PVI is supported by the observation that a substantial portion of patients had no further AF episodes after (acute) PVI despite re-connected PVs found at a repeat study during follow-up (22).

**LINEAR LINES.** Linear line placement has been investigated since the very first days of AF catheter ablation procedures 20 years ago. Forming contiguous lesion lines within the left atrium, which is aimed at complete conduction block, was quickly...
found to be technically challenging (23). However, surgically applied linear lesion line concepts confirmed the potential value of the placement of strategic linear lines connecting the PVs, including the 2 most frequently applied LA lines in AF percutaneous catheter ablation, the “roof line” and the “mitral isthmus line,” even without PVI (24). Both of these show an additive effect compared with PVI alone, even in patients with paroxysmal AF (25,26).

One of the issues related to long linear line placement remains the difficulty in achieving durable complete conduction block across the lines; incomplete block due to gap development may not only result in recurrence of AF, but may also lead to sustained episodes of gap-related LA flutter (27). Such a proarrhythmic effect of a noncomplete line may lead to secondary arrhythmias. One further limitation—and, strategy wise, an even more important one—is that placement of these empirical and purely anatomically defined lines does not address individual localization of the fibrotic substrate.

**ABLATION BASED ON ELECTROGRAM CHARACTERISTICS DURING AF MAPPING.** Clinical mapping studies have shown that the recording of complex fractionated atrial electrograms (CFAEs) during AF are correlated with slowed conduction and pivot points of wavelets (28). These findings were then tested as target sites for catheter ablation (29). These CFAEs, which were recorded during AF, found to be bi-atrial phenomena, and had a propensity for localization at the interatrial septum, the PVs, the LA roof, the left posteroseptal mitral annulus, and the coronary sinus ostium (29). The definition of the CFAEs included fractionated electrograms with \( \geq 2 \) deflections, continuous deflections of a prolonged activation complex over a 10-s recording period, and electrograms with a short cycle length (\( \leq 120 \text{ ms} \)) averaged over a 10-s recording period (29). Procedural endpoints included eliminating CFAE sites, converting AF to sinus rhythm in patients with paroxysmal and persistent AF, and noninducibility of AF in patients with paroxysmal AF.

In a prospective, randomized multicenter study in patients with a high burden of paroxysmal or persistent AF, combining PVI and CFAE ablation resulted in a significantly higher freedom from AF compared with either technique alone (30).

The potential limitations of CFAE mapping include the unclear specificity of these different types of electrograms, variable definition, temporal and spatial resolution of CFAE site mapping, an extensive...
amount of ablation, and the potential proarrhythmic effect of multiple single-point ablations.

COMBINATION OF PVI, CFAE ABLATION, AND LINEAR ABLATION. In clinical practice, different combinations of these strategies are often applied in AF ablation procedures. For example, a stepwise approach, including a combination of PVI followed by electrogram-based ablation and linear lines, has been suggested for patients with persistent and long-standing persistent AF (31). However, success rates with a single procedure remain very limited, even when applying stepwise ablation to these different targets (31,32). The frequent necessity for multiple ablation procedures has done little to enhance long-term success rates in patients with persistent and long-standing persistent AF; however, this approach has led to additive overall procedure and/or fluoroscopy times, additive complications per patient, and more ablated tissue, highlighting the need for new ablation strategies.

NOVEL ABLATION STRATEGIES

VOLTAGE MAP-GUIDED SUBSTRATE MODIFICATION: BOX ISOLATION OF FIBROTIC AREAS. The regional localization and the extent of the fibrotic LA substrate can be visualized during the intervention in sinus rhythm applying EAVM; this allows the use of a new patient-tailored ablation strategy, box isolation of fibrotic areas (BIFAs), for the circumferential isolation of the significantly affected fibrotic areas (e.g., <0.5 mV). We originally tested this strategy in patients with paroxysmal AF who had recurrence of AF despite durable PVI. EAVM identified 2 substantial fibrotic areas in the patient shown in Figure 7. The anteroseptal fibrotic area was circumferentially isolated with a connection to the right PVI line, the posteroseptal fibrotic area was isolated using a roof line plus a posterior line, and then both lines were connected to the previous circumferential PVI lines.

After observing good clinical response, we extended this strategy to patients with persistent or long-standing persistent AF. In these patients, we isolated low-voltage areas even in the initial ablation procedure. The PVs were isolated as the initial step. After spontaneous or electrical cardioversion, a voltage map was recorded during sinus rhythm; the low-voltage areas were identified and subsequently isolated according to individual localization and extent. These BIFA ablation lines should, in general, be connected to the initial PVI lines to prevent the production of small channels and their potential proarrhythmic effects.
Circumferential PVI is the only initial ablation strategy used by our group in patients with persistent and long-standing persistent AF, but who are without substantial low-voltage areas, and it was shown to be successful in preventing further AF episodes. In the relatively conservative “Hamburg sequential ablation strategy” for patients with long-standing persistent AF, 43% of patients remained in sinus rhythm after circumferential PVI was used as the sole ablative strategy (33). With additional CFAE ablation, left linear lesions, and superior caval vein isolation, the overall short-term success rate was reported to be 68%. During a 5-year follow-up, single and multiple ablation procedural successes were 20% and 45%, respectively. Importantly, one-half of the successes were still achieved in patients who underwent circumferential PVI alone (34).

In contrast, an individualized substrate modification using BIFAs may be added to circumferential PVI in patients with paroxysmal AF, but who also have very substantial regional LA fibrosis detected in the first ablation session (Figure 8). Finally, in patients with massive fibrosis (the “strawberry” in Figure 3D), failure of the initial ablation is likely regardless of the applied ablation concept, and further ablation procedures should be discouraged and avoided.

Some years ago, posterior box isolation at the level of the PVs was introduced (35). After placing lines at the anterior aspect of the ipsilateral PVs, lines at the LA roof and posterior left atrium were added to completely isolate that area. Because of the variable extent and localization of the fibrotic areas, this anatomically defined substrate modification did not address the substrate’s individuality. For example, such a posterior box isolation would have isolated the posterior fibrotic area of one patient (Figure 4A); however, this procedure would have isolated a completely normal posterior wall in another patient (Figure 4C). This and other examples highlight the substantial limitations of purely anatomically defined linear line placement in contrast to the individualized BIFA substrate modification.

THE ROLE OF MRI FOR SUBSTRATE DESCRIPTION AND MODIFICATION. Recently, DE-MRI was introduced for detecting, quantifying, and localizing atrial fibrosis, including the 4 Utah stages of structural changes (11,12,17). In contrast to invasive EAVM, DE-MRI seems to be an attractive noninvasive, repeatable diagnostic tool. The tissue characterization of the LA wall on DE-MRI was correlated with EAVM (11) and with the histology from surgical biopsy specimens (12). Currently, this modality requires extensive MRI experience, and its reproducibility is still under investigation in other groups. Normalization of DE-MRI by mean blood pool intensity is currently being tested to overcome the necessity of operator judgment to define the level of enhancement assigned to fibrosis (36,37).

Identification and acute targeting of gaps in atrial ablation lesions sets have also been investigated using a real-time MRI system (38). In a swine model, ablation lines with an intentional gap were created, and the gap area was identified and ablated using real-time MRI catheter navigation and visualization (38). However, DE-MRI recently demonstrated insufficient accuracy to reliably identify ablation lesions or to determine lesion distribution (39). The quantification and localization of atrial fibrosis might be used to guide individually tailored substrate elimination compared with EAVM-guided substrate modification. Finally, tissue visualization before, during, and directly after radiofrequency catheter ablation is the target for introducing real-time MRI into the clinical electrophysiological laboratory.

![Figure 5](image_url)
**ROTOR MAPPING.** Narayan et al. tested the hypothesis that human AF is sustained by localized “sources” whose specific elimination might improve outcome after ablation (Figure 9) (40). With this strategy, which is called focal impulse and rotor modulation (FIRM), a 64-pole basket catheter is advanced into the left and right atria, and a computational approach maps the AF. In an extended follow-up study, patients who underwent FIRM-guided ablation maintained higher freedom from AF versus those who underwent conventional ablation (41). Overall, FIRM mapping revealed AF rotors or focal sources in 98% of the patients, for 1.9 ± 1.1 concurrent sources per patient, 67% of which were in the left atrium and 33% in the right atrium (41). Importantly, AF sources were analyzed to be coincidentally ablated in 45% of conventional cases (e.g., at the LA roof or near the PVs) (42) (Central Illustration). These data might help explain why wide area PVI is more effective than more distal PVI, and especially, why patients might remain free of AF recurrences despite PV re-connection. The encouraging results obtained by elimination of patient-specific rotors were recently confirmed in a multicenter study (43).

This promising and novel technique is currently limited by the relatively low number of 64 basket electrodes and the nonuniform distribution of electrodes with stable contact to the atrial wall. The mapping data require propriety computational software, and the results have yet to be reproduced by others.

**NONINVASIVE MAPPING OF AF.** Data from simultaneous bi-atrial epicardial activation sequences during AF using noninvasive electrocardiographic imaging were published a few years ago (44). In that study, 256 electrodes were applied to the patient’s torso and connected to a mapping system; patients then underwent computed tomography (CT) imaging. AF complexity increased with a longer clinical history of AF, but the complexity of nonparoxysmal AF varied widely. Recently, high-resolution images of the bi-atrial geometry were described using an array of 252 body surface electrodes and thoracic CT (45). A specific signal-analysis process combined filtering, wavelet transformation, and phase mapping using surface unipolar electrograms acquired during AF. Using this technology, PV discharges, meandering rotors, and their mutual interplay were detected, as well as drifting rotors that were not stationary for more than 2 rotations. Thus, noninvasive AF mapping may identify active sources like (stable or unstable) rotors and may help identify a patient-specific ablation strategy.
LIMITATIONS OF TECHNIQUES AND TECHNOLOGIES FOR SUBSTRATE MODIFICATION. Durability of the isolating lesions and/or lesion lines clearly remains an issue, and the “true” success rate of pure circumferential PVI for paroxysmal and persistent AF is unknown. The same issue of durability of ablation points and/or lines holds true for BIFA lines for substrate modification guided by EAVM. Recent technology improvements of point-by-point catheter approaches (e.g., contact force-sensing catheters) can further pave the way. However, achieving the proposed strategies for BIFA substrate modification described herein will require extensive operator manual skills and experience. Therefore, new catheter and/or array technologies for simultaneous multielectrode contact mapping plus ablation may be helpful, and are currently under investigation (46).

Methods to describe the fibrotic substrate are also being evaluated, but these methods face several limitations. Voltage maps using point-by-point mapping not only take time, but the measured voltage also depends on the rhythm (sinus rhythm vs. extrasystole or AF), the electrode contact with tissue, the atrial myocardium thickness, and other variables. Therefore, clear limits or definitions for a normal voltage (e.g., >1.5 mV, >2.0 mV) and a highly abnormal voltage (e.g., <0.5 mV) are nonexistent. Also, there is no clear voltage mapping limit for seemingly “complete scar” because electrograms of <0.1 mV may have small deflections that indicate few surviving atrial myocardial fibers. Moreover, substantial voltages can be recorded in often patchy fibrotic areas due to far-field recording with current 3.5-mm tip electrodes; however, the overall spatial mapping resolution needed is unclear. Limitations at this early stage of rotor mapping also exist. The reproducibility of individual patient maps over time, the duration of AF mapping required to capture all potential sources, the role of epicardial dissociation, and necessary spatial mapping resolution are all under investigation.

A 61-year-old patient with “lone” AF presented with recurrent AF 1-year post-PVI. Mapping during the re-do procedure showed durable isolation of all PVs but substantial areas of low voltage at the anteroseptal (A) and posterior (B) left atrium. Anterior and posterior box isolation were performed (C) with connection to the previous PVI lines; the box isolations were also confirmed with a circular mapping catheter. Abbreviations as in Figure 1.
Evidence is increasing with regard to the development and progression of an atrial substrate independent of AF, whether due to a primary FACM, some other substrate makers and/or modulators, or some combination of both. This may explain AF recurrence following a period of stable sinus rhythm after ablation with durable PVI. Such progression is seen with other substrate-based arrhythmias (e.g., ventricular tachycardia in ischemic or nonischemic ventricular cardiomyopathy), in which remodeling of the substrate after an initially successful ablation may lead to new tachycardias. Furthermore, although many patients with AF present with individually localized and/or patchy fibrotic areas that ablation may specifically target, other patients present with diffuse, massive fibrosis (the “strawberry” in Figure 3D). In these patients, there is no apparent curative ablation approach, and multiple ablation sessions may even be discouraged. Some of these patients may eventually end up in atrial standstill, a loss of all electric and mechanical activity (5). In parallel with technological developments, the role of the right atrium in AF ablation must also be re-addressed in some of these AF patients (40).

CONCLUSIONS AND OUTLOOK: THE PRESENT AND FUTURE

At present, for patients with persistent and/or long-standing persistent AF, the success rate of stepwise approaches that add anatomically defined linear lines and electrogram-based ablation after circumferential PVI is disappointingly low, with a single-procedure success rate of <25% at 5 years. We must develop completely new strategies for substrate modification, with development toward patient-tailored individualization of AF ablation. In contrast to purely anatomically defined (blind) lines, new substrate modification concepts target the individual location and extent of the substrate. One specific strategy in this direction is the precise localization and ablation of rotors that maintain the
arrhythmia using multielectrode mapping during AF. The question that needs to be answered is if a specific microarchitecture of the fibrosis patterns determines rotor location. Another useful strategy targets the significantly affected fibrotic areas with EAVM together with BIFAs, and uses a circular mapping catheter for confirmation. Finally, these 2 strategies may be combined. In the future, individualized substrate modification may be added to circumferential PVI even in some patients with paroxysmal AF who have substantial regional LA fibrosis, whereas circumferential PVI may remain the sole ablation target in other patients with persistent AF and who do not have substantial LA fibrosis.

These new concepts will be supported in the future by further refinements in catheter technology using point-by-point mapping and new catheter and/or multielectrode arrays that allow simultaneous multi-site contact mapping plus ablation. Obviously, we are far from having solved the substrate modification target, but prospective randomized multicenter studies investigating these new strategies will answer these questions.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Hans Kottkamp, Hirslanden Hospital, Department of Electrophysiology, Witellikerstrasse 40, 8032 Zurich, Switzerland. E-mail: hans.kottkamp@hirslanden.ch.

**REFERENCES**


27. Sawhney N, Anousheh R, Chen W, Feld GK. Circumferential pulmonary vein ablation with additional linear ablation results in an increased incidence of left atrial flutter compared with segmental pulmonary vein isolation as an initial approach to ablation of paroxysmal atrial fibrillation. Circ Arrhythm Electrophysiol 2010;3:243-8.
38. Ranjan R, Kholmovski EG, Blauer J, et al. Identification and acute targeting of gaps in atrial fibrillation lesions sets using a real-time magnetic resonance imaging system. Circ Arrhythm Electrophysiol 2012;5:1130-5.