Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with associated deterioration of atrial mechanical function. It is the most common cardiac arrhythmia, becomes more prevalent with age, and is associated with an increased long-term risk of stroke, heart failure, and all-cause mortality. AF can occur in the absence of underlying heart disease but is more frequent in connection with mitral valve disease, heart failure, ischemic heart disease, and hypertension. The most frequent pathological observations in AF are atrial fibrosis and loss of atrial muscle mass. Although the severity of fibrosis reflects the duration of preexisting AF, fibrosis can also occur in association with inflammation in the absence of other cardiac pathology and may contribute to the onset of AF. Molecular, ionic, and genetic influences have all been implicated in AF and are reviewed in detail elsewhere. It is likely that most AF occurs primarily in the context of an interplay between left atrial (LA) electrical and mechanical dysfunction and later becomes self-perpetuating by promoting further electromechanical change during ongoing fibrillation.

AF: Mechanisms and Consequences

A simple and clinically relevant consensus classification recognizes 3 patterns of AF: paroxysmal (lasting <7 days and self-terminating), persistent (lasting >7 days and requiring electrical or pharmacological cardioversion), and permanent (cardioversion failed or not attempted). Although useful, this arbitrary classification does not account for all presentations of AF and is not clearly related to any specific pathophysiology or mechanism of arrhythmogenesis.

Focal activity, multiple reentrant wavelets, and macroreentrant activity have all been implicated in AF, perhaps under the further influence of the autonomic nervous system. The focal source hypothesis, incorporating automaticity and/or local reentry, is consistent with a dominant role for the LA in human AF. AF can be initiated by ectopic beats originating from the pulmonary veins (PVs) and elsewhere, and experimental work has shown that a high-frequency source is capable of maintaining AF. An alternative theory of AF proposes the presence of macroreentrant loops and/or multiple reentrant wavelets meandering throughout the atria seeking nonrefractory tissue, the number of which is related to atrial refractory period, mass, and conduction velocity. This hypothesis provides the rationale for ablation procedures that compartmentalize the LA area available for conduction and therefore reentry. A further intriguing hypothesis is that rather than individual structures, it is the interaction between the LA and its appended structures (PVs, coronary sinus, and LA appendage) that is critical for perpetuation of AF.

The shorter the duration, the more easily AF can be terminated either pharmacologically or by DC cardioversion. In animal models, sustained AF is associated with shortening of the atrial effective refractory period, an increase in LA size, and facilitated induction of AF. In contrast to the rapid recovery of these electrical parameters after restoration of sinus rhythm, recovery of atrial size and transport function occurs more slowly, is often preceded by a period of atrial stunning, and is related to the duration of the preceding AF. ACE inhibitors reduce the incidence of AF in patients with left ventricular dysfunction after acute myocardial infarction. Similarly, pharmacological interruption of the intracellular signaling pathways crucial to remodeling may have important consequences for patient management after restoration of sinus rhythm.

Rapid and irregular ventricular rates during AF may result in left ventricular impairment, which may be wholly or partially reversible with control of the ventricular rate or restoration of sinus rhythm. Atrial remodeling also occurs due to congestive heart failure and is characterized by structural changes, abnormalities of conduction, sinus node dysfunction, and increased refractoriness, all of which may increase the propensity to AF. An ablative approach to achieve sinus rhythm in many patients with heart failure may be warranted whether or not AF is overtly symptomatic.

Patient Selection

Catheter ablation has emerged as a realistic treatment strategy to target pulmonary venous triggers that initiate AF. The feasibility of catheter ablation, with a variety of ablation techniques, has been demonstrated for patients across the entire spectrum of AF from paroxysmal to permanent. There are recent data to support the extension of ablation as a treatment option to patients previously deemed unsuitable, i.e., those with persistent and permanent

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AF refractory to medical therapy is approached with catheter ablation. Drug-refractory paroxysmal AF is the predominant type of persistent and permanent AF, and predictors of AF recurrence include left atrial and left ventricular structural factors, and the degree of atrial electrical remodeling. In this section, we review the current literature on catheter ablation for AF. We begin with a summary of current practice guidelines, then consider approaches to drug-refractory paroxysmal AF, including atrial fibrillation ablation lesions sets, approaches to atrial flutter, and left atrial and appendage targeting, before considering the present role of ablation in persistent and permanent AF.

###Drug-Refractory Paroxysmal AF

The greatest body of data supporting catheter ablation exists for patients with paroxysmal AF. This is recognized in the most recent American College of Cardiology/American Heart Association/European Society of Cardiology guidelines on management of patients with AF, in which catheter ablation should be considered after failure of antiarrhythmic medication for recurrent paroxysmal AF. Three trials have demonstrated the superiority of catheter ablation either in combination or in direct comparison with antiarrhythmic medication in patients with drug-refractory paroxysmal AF. In the absence of any large, randomized trial of catheter ablation as a first-line therapy for AF in either symptomatic or asymptomatic patients, a history of symptoms despite therapeutic doses of antiarrhythmic medication (type 1A, 1C, or III according to the Vaughan Williams classification) is widely accepted as the minimum qualifying criterion for catheter ablation. Ablation is performed using one or more of the following techniques: linear ablation, high-density mapping, and radiofrequency lesion sets. Ablation is performed on an outpatient basis or within 24 hours of admission to an acute care facility, and the ablation lesions sets are performed with an ablation catheter. The greatest body of data supporting catheter ablation exists for patients with persistent or permanent AF, with medium-term (1 to 2 years) success rates of 70% to 95% with an acceptable procedural risk. At present, the extensive procedures required, coupled with the shortcomings of current energy-delivery systems (non-transmurality of lesions, tissue recovery), represent significant limitations to effective ablation in this patient group. As the long-term follow-up data are gathered and tools and techniques improve, the role of catheter ablation will become more clearly defined. In the meantime, published guidelines recommend catheter ablation for recurrent persistent AF only after failure of at least 1 antiarrhythmic medication and severe symptoms despite rate control.

###Preinterventional Diagnostic Modalities

Electrocardiography, both static and ambulatory, remains the primary tool for diagnosis and quantification of AF, with the optimal preinterventional diagnostic evaluation still evolving. Transthoracic echocardiography to assess cardiac structure and function is required in all patients. Preprocedural transesophageal echocardiography is widely practiced to exclude the presence of intra-atrial thrombus before transseptal puncture and catheter manipulation within the LA. Electroanatomic mapping can localize a given electrode position in 3D space and thereby enable the construction of a representation of atrial anatomy while simultaneously gathering activation timing and voltage-amplitude data. Magnetic resonance or tomographic cardiac images acquired before the ablation procedure give detailed anatomic information that can be useful to plan the procedure. These images can be imported or “merged” into the electroanatomic platform and integrated with the mapping-acquired anatomy to aid catheter manipulation during the ablation procedure. Such techniques are now widely available, can reduce intra-
procedural radiation exposure, and may improve procedural outcomes.

Techniques for Ablation of AF

The clinical presentation may provide clues to the mechanism of AF and assist in planning an ablation procedure. Paroxysmal AF, especially of short duration, is frequently a purely trigger-dependent phenomenon, whereas persistent AF and permanent AF are generally mechanistically complex, implicating a more diffuse abnormality of the atrial substrate. Elimination of the influence of triggers of AF in an individual patient requires spontaneous firing to be readily identifiable during an ablation procedure. Although this is unpredictable, the PVs are well established as the dominant sources of triggers in paroxysmal AF, in addition to their contribution to maintenance of AF. On the other hand, there is limited knowledge of how to identify, map, and ablate the culprit atrial substrate in an individual patient, because AF is generally associated with locally complex electrograms of indefinable timing and sequence. Mapping is possible, however, after AF organization (consistent activation sequence) either spontaneously, pharmacologically, or by prior ablation. This heterogeneity of substrate may explain why no single predetermined ablation schema is effective for all patients across the entire spectrum of AF. At present, there are 3 principal techniques for catheter ablation of AF: PV isolation, LA linear ablation, and ablation of LA electrophysiological targets. Each of these has been implicated in modification of the triggers and/or substrate of AF.

PV Isolation

Ablation targeting the PV-LA junction is effective in isolating the LA from proarhythmic PV activity. PV or pulmonary antral isolation confirmed by absence or dissociation of PV potentials is easily demonstrated, objective, and an effective end point for treatment of most patients with paroxysmal AF. After PV isolation alone, success rates of 60% to 85% have been reported in patients with paroxysmal AF, who were free of antiarrhythmic drug use at follow-up. Because AF frequently coexists with atrial flutter, additional cavotricuspid ablation has also been shown to improve outcome in patients with typical atrial flutter documented either before or during the procedure. Recurrences of arrhythmia after successful PV isolation are generally related to recovered conducting tissue at the pulmonary venous ostia.

LA Linear Ablation

PV isolation alone is insufficient for restoration and maintenance of sinus rhythm in most patients with persistent AF. In these patients, additional linear lesions at the roof and mitral isthmus are intended to eliminate more arrhythmogenic substrate and specifically to prevent large atrial reentrant circuits potentially involved in perpetuation of AF. Complete linear lesions have been shown to improve outcomes. Even if incomplete, they may be effective merely by incorporating other abnormal arrhythmic substrate within their trajectory. PV isolation plus ablation at the roof and mitral isthmus achieved sinus rhythm in 69% of patients with persistent AF compared with only 20% of patients who underwent PV isolation alone. The incremental benefit of mitral isthmus ablation in addition to PV isolation was greater for patients with persistent AF than for those with paroxysmal AF. Circumferential PV ablation and adjunctive roof and mitral isthmus ablation significantly reduced the AF burden at 12-month follow-up as measured by 7-day Holter monitoring. At 18-month follow-up, 91% of patients with paroxysmal AF were free of arrhythmia when adjunctive linear ablation was performed, guided by the presence of persisting or inducible AF after PV isolation. Linear ablation in addition to PV isolation was demonstrated to be effective in preventing atrial tachycardia after circumferential PV ablation for paroxysmal AF, whereas macroreentrant arrhythmias that occur during follow-up are frequently related to gaps in previous linear lesions.

LA Electrophysiological Targets

Fractionated potentials are high-frequency, cycle-length-dependent signals, the precise mechanism and significance of which are unclear but likely to be multifactorial, including local areas of slow or anisotropic conduction, continuously reentering impulses, and temporal overlap of different activation waves. Nademanee et al demonstrated that ablation solely targeting areas of complex fractionated electrical activity was effective in treating both chronic and paroxysmal AF. Further studies are needed to improve our interpretation of the mechanistic significance of these electrograms and to differentiate those sites perpetuating AF from those activated passively.

Constant or intermittent sources of rapid activity (with or without 1:1 conduction to surrounding atrium) have been demonstrated to drive AF. With the use of conventional recording techniques in humans, such sources can be identified as (1) sites with the most rapid regional atrial activity or (2) rapid centrifugal atrial activation emanating from a single point source or a small (≈ 1 to 2 cm in diameter) local reentrant circuit. Ablation at such sites has been shown to prolong AF cycle length and/or change activation sequence and terminate AF organized by prior ablation (Figure 1).

Combination of Ablation Techniques

No single ablation strategy is uniformly effective in all patients with AF. The heterogeneous individual mechanisms at work in AF are targeted to greater or lesser degrees by each of the techniques outlined above. Many groups have now incorporated elements of all of the above techniques to optimize the outcome of catheter ablation of AF.

Ablation of complex electrograms in patients with paroxysmal AF undergoing PV isolation resulted in freedom from AF in 77% of patients (not taking antiarrhythmic medication). In patients with persistent AF who were taking amiodarone, ablation in the LA roof, septum, anterior wall, mitral isthmus, and atrial aspect of the mitral annulus restored sinus rhythm in 68% of patients not taking drugs. With a stepwise approach that combined all of the aforementioned targets, termination of long-lasting persistent AF by ablation alone can be achieved in 87% of patients, with freedom from AF achieved in 95% of patients.
Safety of Catheter Ablation Techniques

Catheter ablation is not without risk, with a major complication being reported in up to 6% of procedures performed worldwide. Complications may arise as a result of direct injury to cardiac structures, thermal injury to adjacent extracardiac structures, or thromboembolism.

Cardiac tamponade has been reported in 2.2% of cases from high-volume centers that perform AF ablation. Reduction of the power used for radiofrequency ablation has reduced this to 1%. Injury to the phrenic nerve, the right substantially more often than the left, is observed in 0.5% of cases, with complete or partial recovery in the majority. Gastric hypomotility has been described as a result of injury to periesophageal vagal plexus in 4 of 367 patients undergoing AF ablation and may have implications for evolving ablation strategies that target the cardiac vagal plexi. Anecdotal reports exist for injuries to other extracardiac structures, including the recurrent laryngeal nerve and bronchi.

The most significant complication of LA catheter ablation is atrioesophageal fistula formation, with a reported incidence of between 0.05% and 1% and an associated mortality rate in excess of 50%. The position of the esophagus relative to the LA varies considerably between patients and varies even in a single patient during an ablation procedure. Ablation can result in a temperature rise in the esophageal lumen, which may, in turn, be related to an increased risk of fistula formation. Although rare, this devastating complication warrants attention, with possible solutions including development of real-time esophageal location, temperature monitoring, the use of lower-power or alternative energy sources when ablation near the esophagus is necessary, and improved early detection of esophageal injury.

PV stenosis remains an important complication, with reports suggesting an incidence of between 1% and 10% in those undergoing ablation for AF. The incidence may be decreased by a more proximal ablation position when targeting the LA-PV junction, a reduction in power delivery when engaging the anterior aspect of the left PVs, and increased operator experience.

Radiofrequency ablation disrupts the cardiac endothelial surface, activates the extrinsic coagulation cascade, and leads to char and thrombus formation, which in turn may lead to systemic thromboembolism. Intracardiac echocardiography has identified a 10% incidence of LA thrombus during catheter ablation of AF. An increased intensity of heparin anticoagulation (activated clotting time >300 seconds) may prevent LA thrombus formation during radiofrequency ablation of the LA, whereas aggressive heparinization (activated clotting time 350 to 400 seconds) is associated with a reduction of periprocedural embolic events, albeit without affecting char formation. High-flow transseptal sheath perfusion (180 mL of heparinized saline per hour) may further reduce the risk of stroke during complex LA ablation procedures in addition to conventional systemic anticoagulation. As novel, potentially thrombogenic ablation tools are introduced to the LA for treatment of AF, for example, balloon-based therapies, mesh catheters, and noncontact arrays, we must maintain vigilance to minimize the potential for thromboembolic complications.

A recent study of 755 patients who underwent LA ablation for AF reported a thromboembolic complication after the procedure in 1.2%. Although the findings support the discontinuation of anticoagulation if sinus rhythm is maintained at 3 to 6 months after successful ablation, the advisability of discontinuation of anticoagulation in patients with known risk factors for stroke is not fully settled. The latter study did not extend to patients whose risk factors included age >65 years and previous history of stroke. In addition, the study was relatively small and nonrandomized, and the follow-up was relatively short for a potentially lifelong threat. Of note, three quarters of thromboembolic events in this study occurred within 30 days of the ablation procedure, which underscores the importance of strict therapeutic anticoagulation at least within this window while longer-term follow-up data are awaited.
Controversies in AF Ablation

Optimization of patient selection and development of improved ablation strategies leading to better patient outcomes can only come from a clearer understanding of the shortcomings of current practices. The greatest barrier to meaningful comparison of the current approaches between centers is the lack of standard definitions for technical, procedural, and clinical end points.

Technical End Points of Catheter Ablation

There is near consensus of electrical PV isolation as an end point of ablation targeting the LA-PV junction. Conduction block across linear lesions is associated with an improved outcome after catheter ablation for atrial flutter and fibrillation, whereas incomplete linear-ablation lesions are associated with recurrence of atrial arrhythmias. Conduction block at the mitral isthmus and LA roof can be readily assessed in a manner analogous to that used for the cavitricuspid isthmus and represents an unequivocal end point. Clear reporting of the presence or absence of PV isolation and conduction block for linear lesions is desirable to facilitate more meaningful comparisons between ablation strategies for AF and their outcomes.

Abolition of inducible vagal reflexes has been proposed as an end point of ablation on the basis of experimental data. In 1 series, vagal reflexes induced by radiofrequency energy were seen in up to one third of patients with paroxysmal AF undergoing circumferential PV ablation, and their elimination by further ablation was associated with 99% freedom from AF at 1-year follow-up. The latter finding remains to be verified by others.

End points for ablation at sites of complex fractionated electrograms are more ambiguous and include complete elimination of these activities or local slowing/organization. Furthermore, it is not known whether ablation of all such sites is necessary or if it is possible to target specific locations and thereby limit the extent of unnecessary ablation and resultant tissue damage.

Procedural End Points of Catheter Ablation

There are 3 principal procedural end points advocated for catheter ablation of AF, the applicability and relevance of which may depend on the type of AF: (1) completion of a predetermined lesion set, (2) termination of AF during ablation, and (3) noninducibility of AF after ablation. The clear electrophysiological and pathophysiological differences between trigger-dependent and substrate-dependent AF argue strongly against a single pret-a-porter ablation strategy for all forms of AF; however, certain generalizations can be made for paroxysmal versus persistent AF.

In paroxysmal AF, PV isolation is the basic ablation lesion and is effective alone in ~70% of patients. In the remainder for whom this is insufficient for a satisfactory outcome, whether determined by failure to terminate AF or by persistent inducibility, the precise role of supplementary electrogram-guided versus linear ablation is ill-defined and remains at the discretion of the operator. Although noninducibility is associated with an improved outcome in paroxysmal AF (~20% greater success), persistent inducibility may lead to further unnecessary ablation and associated LA tissue damage. Furthermore, neither the definition of inducibility nor the protocols used to assess it are uniform.

In patients with persistent and permanent AF, the procedural end point is less clear. Although restoration of sinus rhythm by ablation, without the use of antiarrhythmic drugs or DC cardioversion, appears an intuitively ideal end point, as of yet there are few data to support the widespread applicability of such an exacting end point. In the interim, completion of a predetermined lesion set that incorporates PV isolation and LA ablation remains the basic procedure.

Clinical End Points of Catheter Ablation

Freedom from AF, both symptomatic and asymptomatic, at specified intervals after ablation without the use of concomitant antiarrhythmic medication is the ideal clinical end point. Consensus is needed on what constitutes adequate monitoring and what is the minimum acceptable AF burden to satisfy this end point.

Although symptomatic improvement despite continuing AF is a valuable end point from the patient’s perspective, absence of symptoms is clearly not reliable proof of the absence of AF and therefore is of little use in determining future stroke risk and the need for continued anticoagulation. Definitions of freedom from AF include absence of AF, AF episodes lasting no more than 3 to 30 seconds, absence of symptomatic AF of any duration, and others. Many published studies have combined populations of patients with paroxysmal and persistent AF, which makes it confusing to
interpret results. Finally, success rates are not uniformly quoted for patients who have stopped taking all antiarrhythmic medication. After catheter ablation for AF, success rates within a single study differ depending on the duration of ECG monitoring.66 Examples of follow-up protocols reported in the literature include 3-monthly Holter, event monitor, and ECG recording64; event monitor for 1 year with 3-minute daily recordings, 5 days per week when asymptomatic and at any time when symptomatic65; continuous 7-day ECG recording at 3, 6, and 12 months after ablation66; and continuous inpatient telemetry for 3 to 5 days after ablation and at 1, 3, 6, and 12 months.77 As of yet, there are few truly long-term data (>5 years) available for corroboration of the short-term clinical efficacy of catheter ablation. Although continuous-loop recording with regular transtelephonic data transmission throughout a uniform period of follow-up would be the “gold standard” for assessment of cardiac rhythm, this is impractical, inconvenient, and expensive.73

Recurrences of AF and organized atrial arrhythmias are well described after all catheter ablation techniques for AF, the mechanisms of which include (1) recurrence of PV to LA conduction,61,97 (2) gaps in previous linear lesions (manifesting as roof-dependent or perimitral macroreentry),37,98 and (3) locally abnormal conduction at the site of previously ablated tissue or LA scar.99–101 Many investigators empirically incorporate a “blanking period” of 1 to 3 months after ablation, during which time antiarrhythmic medication may be continued or modified and DC cardioversion performed for early arrhythmia recurrences without resort to further catheter intervention. This strategy of watchful waiting may prevent unnecessary intervention in up to one third of patients in whom atrial tachycardia resolves spontaneously within 3 to 4 months of ablation.68 For those in whom tachycardia recurs after electrical or pharmacological cardioversion, repeat electrophysiological study and ablation are invariably recommended and are frequently successful.37,99,102

Future Directions
Ablation is more effective than medical therapy for the treatment of all forms of AF in selected groups of patients.35,38,40 and retrospective data are suggestive of a mortality benefit in favor of AF ablation over conventional treatment.103 Heart failure and AF coexist in up to 40% of patients with heart failure, and restoration of sinus rhythm by catheter ablation of AF in patients with congestive heart failure has been shown to improve cardiac function, symptoms, exercise capacity, and quality of life.31 Clearly, there is an urgent need for robust, prospective, long-term data to address 2 critical questions: (1) What is the role of ablation in the therapeutic arsenal across all AF patient groups? (2) Is there an associated mortality benefit? The answers would have immense implications for electrophysiology worldwide and are crucial for ablation therapy to be disseminated effectively and safely from the high-volume centers to those centers that wish to establish an AF ablation program. Future trials should include patients with chronic AF,35 elderly patients (>70 to 75 years), and patients with LA enlargement (parasternal dimension >55 to 65 mm), structural heart disease, and heart failure (left ventricular ejection fraction <30% to 35%). The design of future trials must aim for inclusion rather than exclusion to define appropriate patient selection criteria by incorporating these large patient groups who potentially have the most to gain by restoration of sinus rhythm if acceptable efficacy and safety can be demonstrated.

At a more fundamental level, the limited resolution of current mapping technologies is an obstacle to a more complete understanding of the underlying mechanisms in AF. Although great progress has been made in real-time tracking of catheter position within reconstructed and registered anatomy, interpretation of the significance of recorded activity requires greater development, with an emphasis on online global substrate mapping during AF. This may facilitate the development of an “AF fingerprint” for an individual patient, allow custom selection of ablation targets and tools to optimize the procedural and clinical outcome, and perhaps even thereby shorten the operator learning curve.

Recovery of conduction across previously ablated tissue is responsible for the vast majority of arrhythmia recurrences after catheter ablation for AF. Radiofrequency is the dominant energy source used but remains inadequate to ensure lesion continuity and permanence without an unacceptable increase in procedural time and complications. New, effective, and safe alternative energy sources are needed to achieve the ultimate goal of a single, widely applicable, curative procedure for all forms of AF.

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