The mechanisms of initiation and maintenance of atrial fibrillation
Implications for the success rate of catheter ablation

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This year marks 21 years since catheter ablation was first introduced into the armamentarium that physicians can use to treat atrial fibrillation\(^1,2\). The initial strategy used for persistent forms of catheter ablation was to attempt to reproduce the surgical maze operation pioneered by Cox\(^3,4\) and colleagues by creating lines of conduction block in both atria\(^2\). Although the initial experience with this catheter-based maze procedure reported that long-standing atrial fibrillation could be converted to sinus rhythm in approximately 70% of patients, there were significant complications and this level of success was considered suboptimal\(^2\). Following this, Haissaguerre and colleagues reported the seminal observation that paroxysmal atrial fibrillation is often induced by rapidly firing foci within the pulmonary veins and the strategy for ablation shifted to attempt to electrically isolate the pulmonary veins by blocking conduction into the left atrium\(^5\). Starting with the direct targeting of the focus\(^6\) and advancing to a segmental ostial approach to pulmonary vein isolation (Haissaguerre) and then towards a wide area circumferential technique\(^6\), some centers reported that catheter ablation could eliminate atrial fibrillation in over 90% of patients\(^7\). Subsequent experience has shown that pulmonary vein isolation strategies are effective in approximately 70% of patients with paroxysmal AF while being effective for less than 50% of patients with persistent or permanent AF\(^8,9\). The next “breakthrough” technique for ablation of AF to be reported was a strategy to eliminate complex fractionated electrograms within both atria\(^10\). Despite the initial enthusiasm generated by this report, this approach has not held up to widespread use\(^9,11\).

Another approach to AF ablation was the recognition that autonomic innervation was an important mechanism of AF initiation in some patients with paroxysmal AF, leading to a strategy to eliminate ganglionated plexi of the intrinsic cardiac nervous system\(^7,12\). The latest approach is the elimination of focal rotors that have been proposed to sustain AF\(^13\). And like these other “breakthrough” techniques that have shown such promise when initially reported, subsequent clinical experience has not been as encouraging when reported by others\(^14\).

All of these starts and stops with catheter ablation leave us with the sense that we still do not know how atrial fibrillation perpetuates itself. And while each of these observations is likely to be an important clue as to the mechanism of AF in some individuals, a basic mechanism common to all patients with atrial fibrillation has yet to be clearly de-
fined and may not exist. This review discusses what we presently know about AF and what needs to be understood if we are to consistently eliminate this arrhythmia in with catheter ablation.

**Atrial remodeling**

Atrial fibrosis is independently associated with increasing age, the presence of structural heart disease, and atrial fibrillation\(^ {10} \). Delayed enhancement in the left atrium detected by MRI has been noted in 24.7 ± 8.0% of patients with AF versus 15.5 ± 7.7% in patients who had no history of AF \((p < 0.0001)\)\(^ {10} \). In addition, the quantity of fibrosis increases with greater persistence of atrial fibrillation such that delayed enhancement was found in 22.9 ± 7.8% of patients with paroxysmal AF patients versus 27.8 ± 7.7% in patients with persistent AF \((p = 0.02)\) (Figure 1). The distribution of atrial fibrosis is greater in the posterior wall of the left atrium than in the septum, lateral, or anterior walls.

Atrial remodeling includes an increase in fibrosis and atrial dilatation as well as changes in conduction velocity and action potential shortening. Figure 2 illustrates how atrial remodeling promotes reentry within the atrium\(^ {10} \). An ectopic beat may encounter a region of atrial myocardium that is refractory to conduction in one direction while simultaneously able to conduct slowly through regions of atrial myocardium interspersed with fibrosis. In order for reentry to be sustained, the conduction time through the circuit (determined by circuit length / conduction velocity) must be longer than the longest refractory period in the circuit. If this conduction time exceeds the wavelength of the circuit (determined by refractory period X conduction velocity) then the circuit can perpetuate reentry.

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**Figure 1.** Delayed Enhancement MRI images and corresponding registered DE maps in 4 patients with different clinical characteristics. 1st Column represents raw delayed-enhancement images from patients with no structural heart disease and no AF (A), structural heart disease and no AF (B), paroxysmal AF (C), and persistent AF (D). Columns 2 and 3 represent posterior and anterior segmented DE maps registered on template. Yellow arrows indicate enhanced areas. DE: atrial delayed enhancement; SHD: structural heart disease; AF: atrial fibrillation. Reproduced with permission from (15)
The rapid atrial rate during atrial fibrillation shortens the atrial APD by a combination of reduced inward L-type Ca\(^{2+}\) current (\(I_{\text{Ca}^{2+}L}\)) and increased outward K\(^{+}\) currents \((17)\). Furthermore, atrial fibrillation reduces the excitatory inward Na\(^{+}\) current \((I_{\text{Na}^{+}})\) \((18)\).

Fibrotic atrial myocardium is characterized by reduced myocyte coupling with a reduction of connexin-40 gap junction protein expression, significantly contributing to slowing of conduction velocity\(^{19}\). In addition, the mechanical dilatation of the atrium that is typical of patients with atrial fibrillation allows a greater surface area for reentrant circuits to propagate. This allows multiple reentrant circuits to exist simultaneously and allows for the development of circuits that would be too long to propagate in normally sized atria. Taken together, atrial remodeling greatly favors the development of intra-atrial reentrant circuits which sustain atrial fibrillation.

**Basic mechanisms of atrial remodeling**

Several factors, including oxidative stress, atrial dilatation, programmed cell death and replacement of myocytes by myofibroblasts, calcium overload, inflammation, and modulation of protein expression by microRNAs are all thought to be important mechanisms by which AF induces atrial remodeling\(^{20}\) (Figure 3). The relative contribution of these factors and the time course over which they produce remodeling to maintain AF is unknown. However, these factors result in electrical remodeling with induction of triggered activity based on early and delayed afterdepolarizations due to increased cytosolic calcium and down regulation of the calcium-induced calcium release from the sarcoplasmic reticulum\(^{20}\). In addition, microRNAs produce downregulation of ionic channel protein expression leading to reduced \(I_{\text{KATP}}\) and reduced L-type calcium current \((I_{\text{Ca}^{2+}L})\)\(^{16,17}\). These alterations in ion channel expression lead to shortening of the atrial action potential duration (APD) and the atrial refractory period. The signaling pathways also contribute to structural changes in the atrium as inflammatory cells induce the programmed death of atrial myocytes and their replacement by myofibroblasts\(^{20}\). This leads to regions of slow conduction and localized conduction block conditions that likely contribute to the development of atrial reentry.
Reactive oxygen species, inflammation, and fibrosis

Atrial fibrillation is associated with circulating markers of oxidative stress. An important role for nicotinamide adenine dinucleotide diphosphate oxidases (NOX)2/4 has been demonstrated in fibrillating atria (21,22). The atrial mitochondria have been demonstrated to swell and release further reactive oxygen species such as nitric oxide synthase and mitochondria oxidase during atrial pacing induced AF (23). Pro-inflammatory cytokines IL-6, angiotensin-II, and tumor necrosis factor (TNF-α) released during AF are likely to lead to infiltration of the atrial myocardium by neutrophils and macrophages (24). These inflammatory cytokines and leukocytes are known causes of apoptosis and inducers of fibroblast differentiation into atrial myofibroblasts leading to atrial fibrosis. Fibroblasts themselves may further amplify the inflammatory response in the atria as they can release pro-inflammatory cytokines and attract immunoreactive cells to the fibrillating atrial myocardium (25). Transforming Growth Factor B1 (TGF-B1) and Angiotensin II are important promoters of fibroblast proliferation and increase in patients with CHF and AF, enhancing the development of myocyte hypertrophy and fibrosis (16,22). Since myofibroblasts are not electrically excitable, the accumulation of fibrotic tissue within the myocardium leads to regions of conduction delay or block, both of which promote the development of reentrant circuits. Combined with a reduction of gap junction protein expression supporting myocyte-to-myocyte conduction, atrial fibrosis greatly reduces conduction velocity and increases the likelihood of conduction block. Depending on the size of the inexcitable regions, either microreentrant or macroreentrant arrhythmias could be supported.

Calcium overload and APD shortening

The rapid atrial rates during AF result in increased intracellular Ca²⁺ which is potentially cytotoxic. In order to protect the cell from Ca²⁺ overload, L-type Ca²⁺ current is greatly reduced. In addition, intracellular Ca²⁺ handling is altered (Figure 4) (17,16,26). In addition to these alterations, the main inward rectifying current I_K1 increases, resulting in shortening of the APD (18). The vagal effects of shortening atrial APD are mediated by the inward rectifying current I_KACH (16). This current is greatly increased in atrial fibrillation and promotes atrial arrhythmias consistent with the proarrhythmic effects of vagal stimulation in the atrium (27,28). Atrial tachycardia remodeling also reduces the transient outward current (Ito) of atrial myocytes (16). Since Ito opposes inward Na⁺ current, this may contribute to ectopic focus generation.
The mechanisms of initiation and maintenance of atrial fibrillation

G. Neal Kay

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Spontaneous release of calcium into the atrial myocardial cytosol from Ryanodine receptors (RyR2) is a purported mechanism of intracellular calcium overload and triggered activity. The increased intracellular Ca\(^{2+}\) increases the Na\(^+-\)Ca\(^{2+}\) exchange pump, leading to extrusion of Ca\(^{2+}\) with increased depolarizing Na\(^+\) entry. This is a likely mechanism for triggering foci that induce atrial fibrillation. In addition, atrial fibrillation itself leads to a vicious cycle of intracellular Ca\(^{2+}\) overload, further shortening the atrial APD and refractoriness. The very rapid atrial rate during atrial fibrillation leads to increased L-type Ca\(^{2+}\) entry into the cell. As a consequence, the cytosolic Ca\(^{2+}\) concentration increases. In order to protect themselves from Ca\(^{2+}\) overload, isolated atrial remodeling occurs within 5 days of sustained tachycardia resulting in silencing of Ca\(^{2+}\) signaling through a reduction of subcellular propagated Ca\(^{2+}\) release\(^{20,30}\). Taken together, these observations regarding Ca\(^{2+}\) homeostasis suggest that these mechanisms may be different in paroxysmal AF than in persistent AF, changing from triggered activity to reduced Ca\(^{2+}\) signaling and shortening of the atrial APD.

Role of microRNAs in atrial fibrillation

MicroRNAs (miRNAs) are small RNA segments that, unlike messenger RNA (mRNA), do not code for proteins. MicroRNAs have a complementary base pair structure to mRNA. The role of miRNAs is to regulate mRNA levels by binding to them and reducing the level of proteins for which they encode. Thus, miRNAs serve to regulate protein synthesis and their concentrations are an important part of ion-channel protein production. Myofibroblasts secrete multiple miRNAs including miRNA-21 which increases atrial fibrosis and myocyte hypertrophy. Several different miRNAs (including miRNA-21) are significantly upregulated in patients with atrial fibrillation while others are downregulated\(^{31}\). Downregulation of some miRNAs results in (miRNA-29) increased collagen deposition in the atrium\(^{20}\). Overexpression of miRNA-328 reduces atrial APD and ICa\(^{2+}\) in dogs with induced atrial fibrillation. Other miRNAs increase the inward K\(^+\) current k\(_{IR}\) known to be important for perpetuating AF\(^{32,33}\). These studies provide further evidence of how gene expression is influenced by the atrial rhythm itself, upregulating some ionic currents and decreasing others.

Remodeling as a cause for ectopic triggers

It is highly probable that Ca\(^{2+}\) related triggered activity generated by abnormal Ca\(^{2+}\) handling is an important mechanism for triggering foci. Ca\(^{2+}\) enters the atrial myocyte through L-type Ca\(^{2+}\) channels. Intracellular Ca\(^{2+}\) causes the release of Ca\(^{2+}\) from the SR by activating ryanodine receptors, further augmenting intracellular Ca\(^{2+}\) which supports activation of contractile proteins. The free intracellular Ca\(^{2+}\) is then removed by active pumping back into the SR by SR-Ca\(^{2+}\) - ATPase (SERCA) as well as through the cell membrane by the Na\(^+\) - Ca\(^{2+}\) exchanger (NCX). Free intracellular Ca\(^{2+}\) is also bound by calsequestrin and any impairment of calsequestrin function by atrial remodeling would promote the development of DADs and triggered activity. The NCX mechanism extrudes one Ca\(^{2+}\) ion in exchange for the entry of 3 Na\(^+\) ions and is a net inward depolarizing current. Atrial fibrillation results in increased NCX expression and leads to DADs and triggered activity\(^{34,35}\). In addition, the hyperphosphorylation of RyRs and SERCA lead to their dysfunction and promote triggered activity\(^{36}\).
What do we know about the mechanisms of AF in patients undergoing ablation?

Clinical evidence for triggering foci initiating AF
The first report that paroxysmal atrial fibrillation could be eliminated by catheter ablation of a rapidly firing focus was by Haissaguerre and colleagues in 1994[4]. This report included 3 patients who had rapidly firing foci in a diverticulum located at the junction of the right atrium and the superior vena cava, in the mid right atrium, and near the ostium of the coronary sinus. However, the era of catheter ablation of atrial fibrillation was started with a report by Haissaguerre in 1998 that among 45 patients with paroxysmal atrial fibrillation, 69 triggering foci could be identified during electrophysiologic study, including 65 from the pulmonary veins[5]. The triggering focus was located 2-4 cm inside any of the 4 PVs and was identified by a sharp electrogram occurring an average of 104 msec prior to the ectopic P-wave. Direct catheter ablation of the focus abolished AF. Among the 38 patients with an initially successful ablation, 25 required a second procedure and 6 required 3 procedures. This report suggested that 28 of these 38 patients had no recurrence of atrial fibrillation over a mean follow-up interval of 8 months. Since localizing a pulmonary vein trigger took patience while waiting for a trigger to fire and the typical patient had triggers in more than one pulmonary vein, a strategy of PV isolation of all 4 veins was devised[57,30]. This technique initially used a segmental approach to ablation at the ostia of the PVs, though the long-term follow-up showed a moderate degree of success. In one multicenter study, arrhythmia-free survival rates after a single catheter ablation procedure were 40%, 37%, and 29% at 1, 2, and 5 years, respectively, with most recurrences over the first 6 months[39]. Arrhythmia-free survival following the last catheter ablation procedure was 87%, 81%, and 63% at 1, 2, and 5 years, respectively[30]. Subsequent reports suggested that a wider area, circumferential ablation strategy was more effective in preventing recurrence[6,8,40]. This approach has been adopted by many laboratories around the world as the standard technique for catheter ablation of AF. Nevertheless, PVI when used for paroxysmal AF is effective in preventing recurrences of AF in <70% of patients independent of the energy source that is used[39,40]. Recurrences of AF after PVI are usually related to PV reconnection suggesting that the strategy is not flawed, rather its implementation[41,42]. Other sites of triggering foci include the superior vena cava, theligament of Marshall, the coronary sinus musculature, the left atrial appendage, and the walls of the right and left atria. For these sites, a PV isolation procedure alone would not be expected to prevent recurrences of AF. Although different ablation energies may be used to achieve PV isolation[43,44], the underlying strategy remains the same.

Role of autonomic innervation in AF
Several lines of evidence suggest that the intrinsic autonomic cardiac nervous system may play a role in the initiation and maintenance of atrial fibrillation. Vagal nerve stimulation from either the cervical trunk or the right pulmonary artery shortens the atrial ERP, an effect that can be abolished by catheter ablation of the vagus nerve[45]. In a canine study, injection of acetyl choline or carbamol into the epicardial fat pad at the base of the right superior pulmonary vein resulted in spontaneous premature depolarizations and spontaneous AF was observed in four of 11 dogs. In seven dogs, single premature extrastimuli easily induced AF. AF was sustained for an average of 10 minutes (ACH) and 38 minutes (CARB), with the shortest AF cycle length seen at the PV-atrial junction adjacent to the fat pad[46].

In superfused canine pulmonary veins, norepinephrine combined with acetylcholine enhances the Ca²⁺ transient and Na⁺-Ca²⁺ exchange current resulting in EAD formation and rapid firing within the PV sleeve[47]. In another canine study, autonomic nerve stimulation decreased pulmonary vein sleeve action potential duration from 160 ± 17 to 92 ± 24 ms, p < .01 and initiated rapid (782 ± 158 bpm) firing from early afterdepolarizations in 22 of 28 pulmonary vein preparations. The initial spontaneous beat had a coupling interval of 97 ± 26 msec. Atropine or Ryanodine receptor blockade prevented PV firing[48]. The ligament of Marshall has been shown to be a potential site for the initiation of triggering foci and communicates with the inferior left ganglionated plexus to modulate interactions between extrinsic and intrinsic cardiac autonomic nervous system[49]. Rapid atrial pacing in the rabbit quickly leads to an augmentation of vagal nerve activity and an attenuation of sympathetic nerve activity[50]. Both of these lead to a shortening of the atrial APD and refractory period. The density of growth associated protein-43 (GAP43), choline acetyl transferase (ChAT) and tyrosine hydroxylase (TH) expressing neural elements in the RA and LA becomes progressively higher with rapid atrial pacing induced AF[50]. Thus, a rapid atrial rate results in progressive autonomic remodeling, manifesting as nerve sprouting, sympathetic and vagal hyper-innervation, lending
The mechanisms of initiation and maintenance of atrial fibrillation

G. Neal Kay

Figure 5. Epicardial mapping in a patient with long-standing persistent AF with mitral valve surgery. On the left, 2 snapshots of activation are recorded from the right atrial free wall and the posterior left atrium. Note that there are multiple waves of activation on the epicardium at the same time. On the right is plotted the incidence and spatial occurrence of epicardial breakthrough over the right atrium (top) and left atrium (bottom) with the size of the red markers indicating the frequency of breakthrough recorded over a 12 second window. Reproduced with permission from (51).

Further support that autonomic remodeling may play an important role in sustaining AF. A similar increase in vagal activity with shortening of the atrial APD has been observed in the canine model of pacing induced AF(52). The induction of vagal reflexes during circumferential PV isolation has been reported to result in improved freedom from recurrent AF(53). In a randomized clinical trial of PV isolation versus PV isolation plus targeting of autonomic ganglia, the combined approach significantly improved the long term results of catheter ablation(12).

Mechanisms of more persistent forms of atrial fibrillation

Persistent forms of atrial fibrillation are likely maintained by reentry. Based on the work of Cox and colleagues(3,4), creation of multiple lines of conduction block with a cut and sew technique is a very effective treatment for even the most long-standing forms of AF with a 5-year freedom from AF in 89% of patients without antiarrhythmic medications and 98% when medications were used(4). This technique involves a large encircling incision around all 4 PVs as well as the creation of scars joining the PV barrier to the mitral annulus, across the roof of the left atrium, a line across the interatrial septum, and lines in the right atrium. The strategy is based on results of intraprocedural mapping suggesting that most patients with persistent forms of AF have at least two macroreentrant circuits that conduct simultaneously. By creating lines of conduction block no greater than 6 cm apart, the Maze procedure is designed to prevent large macroreentrant circuits from sustaining(5,53). It must be admitted that this surgery also effectively isolates the PVs and the posterior left atrium. The most effective catheter based technique for ablating persistent AF is still that designed to emulate the Cox Maze procedure with over 70% of patients maintaining sinus rhythm despite the lack of electroanatomic mapping or irrigated RF energy(54). Taken together, these observations strongly suggest that interruption of large macroreentrant circuits is important if persistent forms of AF are to be effectively treated.

So, what is the mechanism by which AF is maintained? Mapping of human AF at the time of cardiac surgery has provided a panoramic view of long-standing persistent AF that strongly supports the concept of multiple waves of reentry involving both the right and the left atria(54,55). Simultaneous endo and epicardial mapping in the goat model of AF shows a high degree of endo-epicardial dissociation(56,57). In another study of 24 patients with long-standing AF and 25 patients with induced AF who were epicardially mapped at the time of cardiac surgery, the incidence of focal fibrillation waves in the right atrium was almost 4-fold higher in patients with longstanding persistent AF than in those in whom AF was acutely induced(58). This finding is consistent with the effects of atrial remodeling that occur in long-standing persistent AF to support slowed conduction and the maintenance of reentry. These studies indicate that a mean number of more than 200 endo and epicardial breakthroughs could be recorded each second in patients with longstanding persistent AF (Figure 5). If AF is maintained by a focal source (driver), then epicardial or endocardial mapping should show repetitive activation at the same site. However, during mapping studies of patients with longstanding persistent AF, the vast majority of epicardial breakthrough sites (90.5%) were not repetitive and occurred as single events (Figure 6). A repeat site of breakthrough (two cycles in a row) was recorded in only 7% with 3 repetitive cycles recorded in only 1.6%(de Groot NM 2010). Thus, these studies do not support the concept that a small driving focus maintains AF(59).

In contrast to these epicardial mapping studies in patients with longstanding persistent AF, there is experimental evidence that one, or a small number of localized drivers may maintain AF (Figure 7)(60,61). This concept suggests that a “mother rotor” rotating with a very high frequency can maintain...
AF while spinning off and break down into multiple waves. In 1992, Schuessler demonstrated that in an isolated canine right atrial preparation, acetylcholine could result in the conversion of induced AF with multiple waves to a single, rapidly rotating focus that was sustained. The concept of rotors is that of spiral waves rotating around a vortex of excitable but unexcited core of cells known as a phase singularity. These spiral waves may be stationary or drift over the myocardium. In the isolated sheep heart with induced AF, a left-to-right gradient of frequencies has been demonstrated suggesting that a rotor rotating at higher (dominant) frequency in the left atrium was driving atrial fibrillation while the slower, right atrium was being passively activated. Based on these observations, the concept of a mother rotor with a dominant frequency driving human AF has been proposed. Using a 64-electrode basket catheter for mapping of both the right and left atria, Narayan and colleagues applied proprietary software to record electrograms from 92 patients with AF in the CONFIRM trial (Figure 6). The patients were randomly assigned to Focal Impulse and Rotor Modulation (FIRM) guided ablation or conventional PV isolation. Focal rotors were recorded in 97% of patients with this software with a mean of 2.1 ± 1 rotors per patient. These rotors were stable for at least 10 minutes or more in each patient. In the FIRM-guided ablation group, catheter ablation of rotors terminated AF in 56% of patients compared with only 20% in the conventional ablation group. In follow-up, 82% of the FIRM guided patients remained free of AF versus 45% in the conventional ablation group.

Several concerns persist regarding the FIRM ablation strategy. First, the 64 pole basket catheter is not well shaped to record activation of the left atrium. Although the maps are displayed as a rectangular 8X8 grid, this presentation greatly distorts and oversimplifies the complex 3-dimensional shape of both atria. In addition, the rotors identified by the proprietary software have been difficult to reproduce. Among 24 patients undergoing FIRM-guided ablation at one center, the basket catheter was found to be within 1 cm of the left atrial wall for only 54% of the left atrial surface area. Offline analysis of the recorded electrograms revealed no difference between the sites of purported rotors identified by the FIRM software and...
The mechanisms of initiation and maintenance of atrial fibrillation

G. Neal Kay

Volúmen 30 | nº 3 | Octubre 2015

The mechanisms of initiation and maintenance of atrial fibrillation

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Volúmen 30 | nº 3 | Octubre 2015

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Volúmen 30 | nº 3 | Octubre 2015

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Volúmen 30 | nº 3 | Octubre 2015

The mechanisms of initiation and maintenance of atrial fibrillation

G. Neal Kay

Volúmen 30 | nº 3 | Octubre 2015

Figure 8. FIRM mapping of the right and left atria using a 64 electrode basket catheter. Activation times are coded red to blue with a rotor rotating in a clockwise direction (white arrow) located in the low left atrium. Catheter ablation at this site terminated atrial fibrillation. Reproduced with permission from (13).

Figure 9. Offline analysis of dominant frequency (upper panel) and Shannon Entropy (lower panel) demonstrate no correlation between the site of a rotor identified by FIRM mapping and surrounding atria. Reproduced with permission from (14).

distant sites in terms of dominant frequency or Shannon entropy (Figure 9)(14). Termination of AF was observed in only 1 of 24 patients with ablation at the site of FIRM identified rotors. The conclusion of this study was that a basket catheter poorly covered the surface of the left atrium, that FIRM maps do not exhibit distinctive electrophysiologic characteristics, and that ablation of FIRM-identified rotors rarely terminates AF(14). Whether further studies will substantiate these observations remains to be seen.

Conclusions

Several mechanisms are probably important for initiating and maintaining atrial fibrillation. Clearly, structural, autonomic, and electrophysiologic remodeling of the atria are important determinants of the progression from paroxysmal to persistent forms of this arrhythmia. The importance of triggering foci within the thoracic veins, including the pulmonary veins, the superior vena cava, the ligament of Marshall, and the coronary sinus musculature which initiate AF is beyond question. The available evidence best supports the multiple wavelet hypothesis for more advanced forms of atrial fibrillation, suggesting that limited ablation of rotors is unlikely to be effective for many patients. The very high success rate of much more aggressive partitioning of the atria which prevents the propagation of larger reentrant circuits also supports the multiple wavelet hypothesis. It is likely that the reason catheter ablation has reached a ceiling of approximately 70% success relates to the multiple mechanisms that may be present in different individuals.
References


